Using fMRI and Behavioural Measures to Investigate Rehabilitation in Post-Stroke Aphasic Deficits

Sonia Leslie Elaine Brownsett

2013

Imperial College London, Department of Medicine

This thesis is submitted for the degree of
Doctor of Philosophy

Acknowledgments

Firstly, I would like to thank all the volunteers that participated in my studies, especially the patients. Thanks also to the C3NL lab (past and present) for their support, especially those that appreciated the trials and tribulations of stroke studies. I would also like to thank David Howard, for his support, sensible perspective and for pointing me in the direction of this PhD. The largest dose of gratitude must go to Professor Wise (honFRCSLT) for his unique supervisory style, which has supported and encouraged throughout many a difficult result. I'm sure the sense of futility was mutual but he did a remarkable job of being optimistic and was, indeed, proved right in the end. I must also thank my family for their obvious contribution, but most importantly Tony and Thomas for their continued unconditional support and patience at many a missed bedtime.

To Hannah, Noah, Joshua, Erin, Niall, Isla, Sophie and Thomas.

Statement of Publications

The results from this thesis have been submitted for publication. The results presented in Chapter Three have been submitted to Brain and Language and are currently under review. The results from Chapters Four and Five have been provisionally accepted for publication in Brain.

Brownsett, S; Wise R; Warren, J, Geranmayeh, F; Parry, A; Howard, D. **Self-administered aphasia therapy- is lesion localisation important?** Under Review.

Brownsett, S; Warren, J; Geranmayeh, F; Woodhead, Z; Leech, R; Wise, R. **Cognitive control and its impact on recovery from aphasic stroke.** Brain. 2013. doi:10.1093/brain/awt289.

Declaration of Originality

Metal Beetle Ltd, who were financially reimbursed for their services, programmed the software described in Chapter Three. Dr. Jane Warren contributed to the design of the experiments in Chapters 4 and 5. I declare that the rest of the work presented in this thesis is my own and conforms to the rules and guidelines set out for PhD theses by Imperial College London and all else is appropriately referenced.

Copyright Declaration

Abbreviations

A1	Primary auditory cortex
ACC	Anterior cingulate cortex
AG	Angular gyrus
aI	Anterior Insula
ANOVA	Analysis of variances
ATL	Anterior temporal lobe
B0	External magnetic field
BET	Brain extraction tool
BKB	Bamford-Kowal-Bench sentences
BOLD	Blood oxygenated haemodynamic response
CEN	Central executive network
CI	Confidence intervals
DAP	Dorsal auditory pathway
DLPFC	Dorsolateral prefrontal cortex
DMN	Default mode network
dof	Degrees of freedom
EPI	Echo-planar imaging
EV	Experimental variable
FEAT	FMRI Expert Analysis Tool
FLAME	FMRIB's Local Analysis of Mixed Effects
FLIRT	FMRIB's Linear Image Registration Tool
fMRI	Functional magnetic resonance imaging
FSL	FMRIB's Software Library
G	Read gradient
GLM	General linear model
Gx	Frequency encoding gradient
Gy	Phase-encoding gradient
Gz	Slice gradient
HRF	Haemodynamic response function
IFG	Inferior frontal gyrus
ListNorm	Listening to normal speech trials

ListVoc	Listening to vocoded speech trials
ListWhite	Listening to white noise
M0	Net magnetisation
MNI	Montreal Neurological Institute
MTG	Middle temporal gyrus
PACE	Promoting Communication Effectiveness in Aphasia
PC	Dorsal inferior parietal cortex and adjacent lateral intraparietal sulcus
pCC	Posterior cingulate cortex
PE	Parameter estimate
PET	Positron emitting tomography
pSTS	Posterior superior temporal gyrus
PT	Planum temporale
QALY	Quality-adjusted life year
rCBF	Regional cerebral blood flow
RCT	Randomised controlled trial
RepNorm	Repeating the ListNorm trials
RepVoc	Repeating the vocoded speech trials
RF	Radiofrequency
ROIs	Regions-of-interest
rTMS	Repetitive transcranial magnetic stimulation
SALT	Speech and Language Therapy
SD	Standard deviation
SFG	Superior frontal gyrus (SFG)
SMA	Supplementary motor area
SN	Saliency network
STC	Superior temporal cortex
STG	Superior temporal gyrus
STP	Superior temporal plane
STS	Superior temporal sulcus
TE	Echo time
TR	Repetition time
TROG	Test of reception of grammar
vACC	Ventral anterior cingulate cortex

Table of Contents

List of Figures

List of Tables

Abstract

In this thesis I investigated whether an intensive computerised, home-based therapy programme could improve phonological discrimination ability in 19 patients with chronic post-stroke aphasia. One skill specifically targeted by the treatment demonstrated an improvement due to the therapy. However, this improvement did not generalise to untreated items, and was only effective for participants without a lesion involving the frontal lobe, indicating a potentially important role for this region in determining outcome of aphasia therapy.

Complementary functional imaging studies investigated activity in domain-general and domain-specific networks in both patients and healthy volunteers during listening and repeating simple sentences. One important consideration when comparing a patient group with a healthy population is the difference in task difficulty encountered by the two groups. Increased cognitive effort can be expected to increase activity in domain-general networks. I minimised the effect of this confound by manipulating task difficulty for the healthy volunteers to reduce their behavioural performance so that it was comparable to that of the patients. By this means I demonstrated that the activation patterns in domain-general regions were very similar in the two groups. Region-of-interest analysis demonstrated that activity within a domain-general network, the salience network, predicted residual language function in the patients with aphasia, even after accounting for lesion volume and their chronological age.

I drew two broad conclusions from these studies. First, that computer-based rehabilitation can improve disordered phonological discrimination in chronic aphasia, but that lesion distribution may influence the response to this training. Second, that the ability to activate domain-general cognitive control regions influences outcome in aphasia. This allows me to propose that in future work, therapeutic strategies, pharmacological or behavioural, targeting domain-general brain systems, may benefit aphasic stroke rehabilitation.

1. Introduction

1.1 Speech Comprehension

In normally developing humans, the ability to understand speech is acquired effortlessly and once established, this ability demonstrates remarkable resilience to distortion and interference. However, a sudden injury to the brain, such as a stroke, can lead to aphasia, a devastating inability to comprehend and produce spoken language. It is primarily through lesion-based studies that our knowledge about the complexity of language has developed: understanding how language breaks down after an aphasic stroke is essential to shaping appropriate intervention. Decades of research have been devoted to understanding, from both a neurological and a neuropsychological perspective, how language is organised and how deficits due to acquired lesions may manifest. Despite this, there is very little evidence for therapeutic interventions targeting speech perception deficits in aphasia.

This thesis uses functional magnetic resonance imaging and neuropsychological assessments to investigate the rehabilitation of speech perception deficits in chronic post-stroke aphasia. Firstly, this introduction presents the neural mechanisms involved in both the understanding and production of speech in healthy brains. I then review the literature relevant to the breakdown of speech comprehension in aphasia from both a neurological and neuropsychological perspective, including both domain-specific and domain-general mechanisms. Finally, the literature pertinent to the study of the recovery and rehabilitation of aphasia, from both a behavioural and imaging perspective is presented.

1.1.1 The Auditory Pathway

Once speech is produced it is transmitted through the air in the form of pressure waves that are directed by the outer ear to the tympanic membrane. These pressure waves cause the tympanic membrane to vibrate. This vibration, in turn, causes the ossicular chain (consisting of the malleus, incus and stapes bones) within the middle ear to move. The stapes bone then presses against the oval window (a membrane-covered opening leading from the middle ear to the inner ear) causing it to vibrate.

These vibrations transmit movement into the fluid-filled inner ear cavity that contains the basilar membrane along the length of the cochlea (Rhodes and Pflanzer, 1996).

The basilar membrane vibrates in the form of travelling waves. The amplitude of these waves diminishes the further along the membrane they travel and the location of the peak amplitude of the wave is determined by the frequency of the sounds. Hair cells along the basilar membrane contain stereocilia (an organelle responsive to fluid motion). The vibrations of the basilar membrane cause these stereocilia to bend, which allows a flow of ions into the hair cell. This leads to a depolarisation of the hair cell, which in turn initiates an action potential in the dendrites of the auditory nerve. This transmits a signal to the cochlear nucleus in the brainstem and then on to bilateral primary auditory cortex via the inferior colliculi and the medial geniculate nuclei of the thalamus (Rhodes and Pflanzer, 1996).

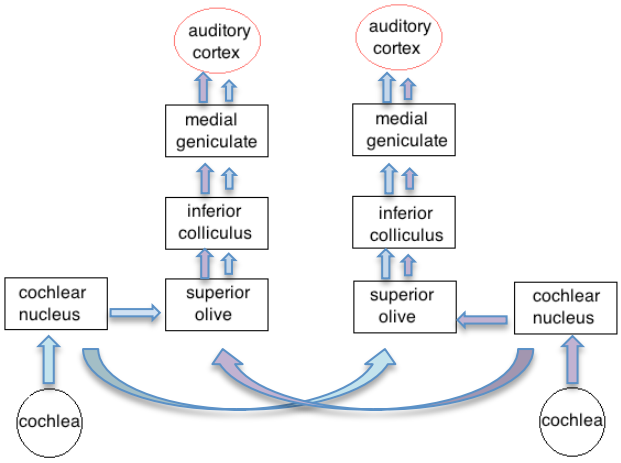


Figure 1.1 *Diagram depicting the auditory pathway from the cochlea to the auditory cortex.*

A lesion or tumour along any length of the auditory pathway can cause a central hearing loss. In contrast, a lesion at the level of the cortex of one hemisphere does not typically impact on hearing as each auditory cortex receives input from both ears; although there is dominance of crossed projections. However, lesions to the primary and secondary auditory cortex are known to produce aphasic deficits in speech comprehension (see Bogen and Bogen, 1976).

1.1.2 Primary Auditory Cortex

The auditory cortex in primates can be subdivided into the hierarchically organised primary area, or 'core', belt and parabelt cortices (for a review see Rauscheker and Scott, 2009). Primary auditory cortex (A1) is located in the superior temporal plane within Heschl's gyrus. An ubiquitous property of the auditory pathway, including A1, is that it is organised tonotopically, with A1 neurons being most responsive to pure tones (Kaas *et al.,* 1999) (see *Figure 1.2*).

The auditory information is distributed from A1 to the adjacent belt area of the auditory cortex, where tonotopy is still present but the neurones respond more strongly to complex sounds than pure tones (Kaas *et al.,* 1999). Belt regions then project in turn to parabelt regions, which have been shown to be the location of multisensory convergence in macaques (Smiley *et al*., 2007). From these parabelt regions auditory information can be integrated with other sensory information in widely distributed cortical areas in the parietal and frontal lobes. This hierarchical organisation (core→ belt→ parabelt), with information proceeding to more distal regions as the perceptual information becomes more complex (see Rauschecker, 1998), has been demonstrated in functional imaging studies on humans using both pure tones (Hall *et al.,* 2002) and speech sounds (Davis and Johnsrude, 2003).

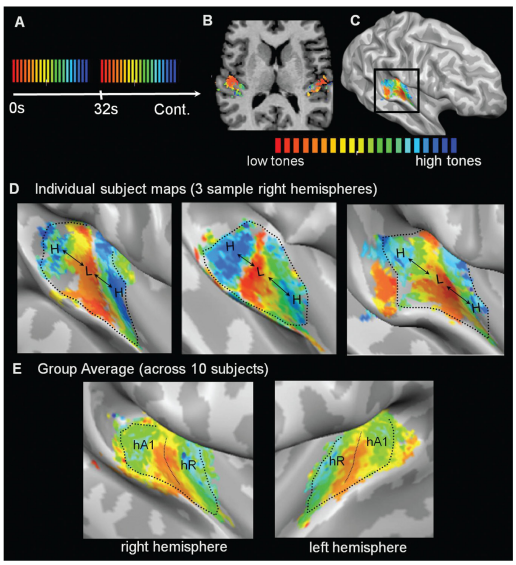


Figure 1.2 *Tonotopic maps in auditory cortex.* ***Panel A:*** *Sound stimuli from low to high frequencies: 88 to 8000 Hz (red-to-blue scale).* ***Panel B:*** *Analyses were performed in each individual subject's (n= 10) volumetric space.* ***Panel C****: Color-coded frequency maps were projected onto each subject's cortical surface meshes.* ***Panel D:*** *Three sample right hemispheres are shown with a voxelwise*

threshold of P < 0.05 (FDR corrected). Dotted lines indicate how surface containing the two maps were defined for the next step. ***Panel E:*** *Group tonotopic maps across all 10 subjects.* ***Reproduced from DaCosta and colleagues (2011), with kind permission from Journal of Neuroscience.***

Imaging studies in healthy volunteers have contributed significantly to our understanding of the neurological basis of speech comprehension, which has been shown to involve a complex network of neural 'auditory' regions, these classically include Heschl's gyrus (A1 in humans) and the posteriorly adjacent planum temporale (PT), and extending out into the superior and middle temporal gyri (Davis and Johnsrude, 2003). In the left cerebral hemisphere these regions correspond, to a greater or lesser extent, with the anatomical localisation of 'Wernicke's' area (Bogen and Bogen, 1976). Posterior temporo-parietal cortex is considered important for speech sound and lexical analysis (Hickok and Poeppel, 2007; Rauscheker and Scott, 2009). However other areas, in addition to these 'classical' areas not typically considered as part of primary or secondary auditory cortex, have been shown to be involved in language comprehension and include the anterior and ventral temporal regions, and the supramarginal and angular gyri (AG) in the inferior parietal lobe (for an overview, see Price, 2010).

1.1.3 Dual Stream Processing

Building on Ungerleider's and Mishkin's (1982) original work on dual stream processing in the visual system, Rauschecker and Tian (2000) used data from both humans and non-human primates to suggest that the primate cortical auditory system, like the visual system, is divided into: a ventral object/pattern processing stream, projecting to the anterior superior temporal cortex; and a dorsal spatial information processing stream, projecting to the posterior part of the superior temporal gyrus (STG) and on to parietal cortex. In non-human primates the anterior lateral belt region of the auditory cortex has been shown to be more active in response to the identity of a conspecific call than the caudal lateral belt region, which responds preferentially to the spatial location of a conspecific call irrespective of its identity (Tian *et al.,* 2001; Rauscheker and Scott, 2009), indicating a distinction between a ventral 'what' stream, and a dorsal 'where' stream. There is a plethora of evidence that has emerged suggesting that processing speech sounds in humans also engages distinct anterior and posterior auditory processing pathways within the language dominant hemisphere (Scott *et al*., 2000; Warren *et al*., 2002; Scott & Johnsrude, 2003).

In humans, the ventral auditory processing stream, originating in the anterior superior temporal plane (STP), projects ventrally along the temporal plane towards the anterior (Scott *et al*., 2000; Narain *et al*., 2003) and the inferior temporal regions and also the inferior frontal regions (Hickok and Poeppel, 2000; Scott & Wise, 2004). This view has developed from functional imaging studies in humans that have shown that comprehending intelligible sentences activates the left superior temporal sulcus (STS) (such as Scott *et al*., 2000; Narain *et al*., 2003). This stream also projects to the semantic system within the ventral and anterior temporal lobes. In semantic dementia, patients have a progressive impairment of semantic knowledge that correlates with the degree of atrophy of the anterior temporal lobes (see Mummery *et al.,* 2000; Lambon Ralph & Patterson, 2008), in particular, in the anterior fusiform gyrus (*e.g.* Acosta-Cabronero *et al.,* 2011). This ventral stream is involved in the extraction of meaning from input where it converges in the ATL with conceptual knowledge from other sensory domains (Patterson *et al*., 2007). These regions have been activated in numerous functional imaging studies of language, demonstrating the prominence of semantics in language (Scott *et al*., 2000; Spitsyna *et al*., 2006; Awad *et al*., 2008,

Brownsett &Wise, 2009). Possible divisions of the ATL region has been specifically investigated in terms of their contribution to comprehension. In a study by Visser and Lambon Ralph (2011) they used a novel fMRI technique that corrected for the susceptibility artefact in this region to investigate differential patterns of activation bilaterally during semantic decision tasks. They found that the left superior ATL was specialised for auditory processing and the ventral ATL was activated in response to semantic processing, similar to those finding by Sharp and colleagues (2004*b*).

The dorsal auditory pathway (DAP) was originally thought to be involved in the processing of auditory spatial information and so form a 'where-in-space' identification pathway. This pathway projects from the STP to prefrontal cortex directly, and indirectly via inferior parietal regions (Rauscheker and Scott, 2009; Hickok and Poeppel, 2007). However, in humans it has been suggested (see Warren *et al*., 2005), that labelling this dorsal pathway a 'where' pathway is an inadequate description due to findings in humans that link the PT, within posterior STP, to sound identification (see Belin *&* Zatorre 2000; Wise *et al*., 2001), localisation (Warren *et al*., 2002; Deouell *et al*., 2007) and production (silent and covert) (Wise *et al*., 2001; Hickok *et al*., 2009), as well as sensorimotor control of speech production (Dhanjal *et al*., 2008; Brownsett and Wise, 2009). Griffiths and Warren (2002) proposed that these differing roles could be explained by the functional and anatomical heterogeneity of the PT. They suggest that the PT acts as a 'computational hub' that segregates incoming auditory components and matches them with learned spectrotemporal representations before projecting the encoded information on to higher order areas for further analysis. Similarly, Warren and colleagues (2005) propose that within the posterior STP, sequential auditory information is matched to pre-exiting templates (or memories) of those sequences. They further suggest that these templates constrain motor responses to such an extent that the DAP essentially acts as a pathway involved in planning 'how' to produce speech. Other authors have suggested that this mechanism of informing and constraining both speech production and perception through comparing sensory experiences with pre-existing motor templates of sound production (including speech) occurs when the dorsal stream interfaces with premotor areas via the inferior parietal cortex (Rauschecker and Scott, 2009; Rauschecker, 2011).

1.1.4 Neurological basis of Speech Production

Producing speech requires the control of multiple muscles including: the intercostal muscles and diaphragm, for a controlled exhalation; the larynx, to produce the vocal fold vibration that defines many speech sounds and the 'articulators', namely the pharynx, uvula, hard and soft palates, tongue, alveolar ridge and lips. Rapid fine motor control of these many muscle groups is required to produce the stream of distinct phonemes and allophones that form a simple utterance. As this stream is produced so rapidly, co-articulation and assimilation of phonemes is common. Feedback and feedforward information is essential to shape succeeding phonemes based on the position of the articulators during the previous phoneme (*i.e.* the final /l/ sound in /pull/ and /pill/ differ due to the shape of the mouth during the preceding vowel). Sensory feedback provides a speaker with information about how to adapt speech to account for errors in production, such as those made developmentally. As the speaker becomes more skilled this auditory feedback becomes less important (see Price, 2012). Guenther (2006) describes how this feedback mechanism operates in order to control speech production. He describes a feedforward system during the production of speech, the output of which is compared to actual auditory and somatosensory feedback, in order to permit subsequent corrections after speech errors. This occurs though the rapid transmission of neural signals between pre-motor/primary motor cortex directed to sensory regions (*i.e.* PT and parietal operculum). Therefore, the complex act of producing speech involves frontal regions (including premotor and primary motor cortex), the parietal regions (somatosensory cortex) and auditory temporal regions (STP) (see Rauscheker and Scott, 2009). Subcortical areas include the basal ganglia and cerebellum (Guenter, 2006). It is through the repeated use of this system that phonology develops in young children. As an infant the production of early babbling is reinforced in a language specific nature by both these feedforward and feedback mechanisms. The positive reinforcement from the parent/carer of approximations to local linguistic tokens refines the target speech token and provides a comparison by which to evaluate previous productions. As the child learns to re-attempt specific speech 'tokens', their somatosensory and auditory feedback is compared to that modeled by the parent/carer further, until a pattern is established.

1.1.5 Compensatory Mechanisms in Healthy Volunteers

1.1.5.1 Compensatory Speech Comprehension Mechanisms in Healthy Volunteers

In normal, everyday communication multiple distortions of an incoming speech signal occur. Speech is a complex sound that is typically produced rapidly, often in the presence of background environmental noise. Multiple speakers, unfamiliar accents, inter-speaker variability, assimilation of phonemes and allophones, novel words and age-related hearing loss all contribute to a degraded incoming speech signal. Despite this degradation in signal, humans are remarkably good at inferring meaning from everyday communicative speech (Shannon *et al*., 1995; Davis and Johnsrude, 2003). Much research has focused on understanding the mechanisms by which healthy subjects can understand such distorted speech, often in the endeavour to provide insights into the damaged brain (McGuire *et al*., 1996; Scott *et al*., 2000; Davis and Johnsrude, 2003; Sharp *et al*., 2004*a*; Zheng *et al*., 2009; Eisner *et al*., 2010).

Noise-vocoded speech simulates the signal heard by patients with cochlear implants, and has proved useful in studies on healthy subjects to investigate the effectiveness of auditory training regimes that can be used in cochlear implant rehabilitation programmes (such as Stacey & Summerfield, 2007). Functional imaging researchers have used noise-vocoded speech to experimentally degrade the incoming speech signal for a variety of reasons. Thus, Scott and colleagues (2000) investigated auditory processing streams by varying the intelligibility of the speech stimuli and Davis and Johnsrude (2003) determined compensatory brain mechanisms as subjects listened to noise-vocoded speech. Others have also used noise-vocoded speech in a healthy control group to approximate comprehension difficulty with that experienced by chronic aphasic patients as they listened to undistorted speech (Sharp *et al*., 2004 *a, b*). Many of these studies demonstrated that the task difficulty associated with understanding noise-vocoded speech resulted in increased activity in frontal cortex, interpreted as the engagement of 'top-down' linguistic control.

Sharp and colleagues (2004*a*) found that completing semantic tasks in which stimuli had been noise-vocoded resulted in an increased activation of the right dorsolateral prefrontal cortex (DLPFC) and right insula. This activity was inversely correlated with task accuracy in healthy volunteers. They attributed this activation to the

increased monitoring demands associated with items held in working memory. They then found that the level of activation within the left fusiform gyrus in patients was similar to that observed when healthy volunteers completed the same task with vocoded stimuli (Sharp *et al*., 2004*b*), but much greater activation was observed when healthy volunteers completed the same task with clear speech stimuli. They attributed this to the availability of increased semantic information from the clear speech. A subsequent reanalysis (Sharp *et al*., 2010) of the same patient and control data demonstrated that functional connectivity between the left superior frontal gyrus (SFG) and left angular gyrus (AG) was significantly increased in patients compared to healthy controls when both groups were listening to undistorted speech. However, the strength of this functional connectivity significantly increased in healthy controls when they attempted semantic tasks on verbal stimuli that were presented as noise-vocoded speech. The authors interpreted these findings as increased integration across regions that control the language network, and they were among the first to suggest explicitly, using functional imaging, that this top-down control is important for language recovery after stroke.

Similarly, Obleser and colleagues (2007) found that by varying the number of frequency channels in noise-vocoded sentences and the semantic predictability of the sentence completion, activity in bilateral STS and the left inferior frontal gyrus (IFG) correlated with the amount of spectral detail in the speech signal regardless of the semantic predictability. They concluded that engaging higher-order cognitive subsystems remote from auditory cortex supported speech perception under adverse conditions. Similarly, Eisner and colleagues (2010) found that in healthy volunteers learning to understand noise-vocoded speech, and analysing only left hemisphere regions-of-interest (ROIs), the recruitment of higher-level prefrontal cortex and the left IFG correlated with accuracy of task performance, which was also reflected in the strength of the functional connection between the left IFG and the AG. The authors concluded that these responses outside auditory cortex explain, in part, the variable ability of patients with cochlear implants to make effective use of their devices.

These studies suggest that top-down mechanisms, in addition to those domain-specific processes traditionally associated with speech comprehension, are crucial to aiding comprehension of degraded speech in healthy volunteers. This distinction between

domain-general cognitive control systems, which respond to task irrespective of modality, and domain-specific processes has not always been discussed explicitly in these previous publications. Many of the same regions have been shown to be part of separate non-linguistic, domain- general networks. This is discussed in section 1.3.

1.1.5.2 Compensatory Speech Production Mechanisms in Healthy Volunteers

It can be predicted that the top-down mechanisms used in order to aid the perception of degraded stimuli must also be implicated in speech production as the two are intimately linked in the dorsal auditory processing stream. Distortions in vocalisations rarely affect a speaker's ability to convey a message, despite common speech errors such as spoonerisms, mis-articulations, mispronunciations and normal dysfluencies. This is thought to be due to our ability to use auditory and somatosensory feedback to rapidly detect errors and modify speech accordingly (Guenter *et al*., 2006). Functional imaging studies suggest that this mechanism is reflected in increased activation of the auditory cortex when feedback is distorted. Elides and Wang (2008) found that in nonhumans, the auditory cortex is suppressed during normal vocalisation but becomes more activated during distorted vocalisation. Similarly, Tourville and colleagues (2008) found that distorting speech in humans enhances bilateral STC. McGuire and colleagues (1996) report findings from a positron emitting tomography (PET) study which showed increased activation during masked feedback within the left insula and frontal operculum in addition to the posterior part of the left STG and right middle, transverse and STG. The authors suggest that this was a consequence of greater conflict between the actual and the expected auditory inputs and consider their activations to be part of a self-monitoring network operating during both covert and overt speech production. Similarly, Zheng and colleagues (2009) suggest that the activation of the posterior STG/PT during perturbed auditory feedback may be part of a system critical for maintaining fluency on-line. However, a recent study that I was involved in failed to find any effect of impeding somatosensory feedback by applying a small dose of lignocaine to the tongue using both univariate and multivariate analyses (Geranmayeh *et al*., 2012).

Both the additional recruitment of domain-general regions to aid comprehension, and the increased activation in domain-specific regions when self-monitoring becomes

difficult, are two mechanisms that one could anticipate when studying the responses to comprehension of normal language in patients with aphasia. Both top-down and bottom-up processes are likely to be disturbed in aphasia and so result in a degraded stimulus, either at the level of perception or comprehension, or at the level of self-monitoring of distorted feedback.

1.2 Speech Comprehension Deficits in Aphasia

1.2.1 The Neurological Basis of Comprehension Deficits in Post-Stroke Aphasia

Two 19th century neuropsychiatrists, Broca and Wernicke, published seminal studies on patients with lesions in the frontal lobe and posterior temporal lobe, respectively, that resulted in language deficits. Their publications have formed the basis of many models of language processing and neuroanatomical models of language organisation across a range of disciplines. Broca presented patient 'Tan' who had reportedly good comprehension but no spoken output except for two automatic phrases. At post-mortem, Broca identified a lesion in the third convolution of the left frontal lobe. This region, now eponymously known as Broca's area, has become synonymous with nonfluent language production, or expressive, deficits in aphasia. A few years after Broca, in 1874, Wernicke presented a series of patients in his thesis with what he termed 'sensory aphasia'. These patients had intact speech production but poor comprehension of language, and all had lesions affecting the temporal lobe, which, he suggested, was where 'memory images' of speech were stored. Wernicke used the findings of 'sensory aphasia' along with Broca's 'motor aphasia' to develop the first suggestion of how language comprehension and production were linked. He predicted that a link between his posterior region and that described by Broca was needed to explain how language is initially acquired and then maintained throughout life. This model formed the basis for the later Wernicke-Lichtheim-Geschwind model, partly evolving from Lichtheim's presentation of a patient with damage to the connection between Broca's and Wernicke's areas manifesting, as predicted by Wernicke, in intact comprehension but poor production of speech. Lichtheim named this 'conduction aphasia', a label that remains today. This basic nineteenth century model has remained a consistent diagnostic framework for many medical and allied health professionals and has framed the development of most models of language. However, speech and language therapists, and other aphasia experts with even a limited amount

of clinical experience, soon infer that language deficits do not typically fall neatly into these categories. The term 'Wernicke's' aphasia refers to an aphasic deficit that is characterised by fluent speech with phonological paraphasias and neologisms, severely impaired auditory comprehension at the single word level and impaired repetition (Goodglass, Kaplan, & Barresi, 2001) following a lesion to the left temporo-parietal region. Whilst many syndromes have been described with a varying combination of the comprehension deficits seen in Wernicke's aphasia: for example, global aphasia (Varney, 1984); phonological processing deficit (Caramazza *et al*., 1983); conduction aphasia (Bartha and Benke, 2003; Leeper *et al*., 1986); transcortical sensory aphasia (Boatmann *et al*., 2000); word deafness (Franklin, 1989); and even Broca's aphasia (Basso *et al*., 1977), many medical professionals continue to categorise patients with any type of receptive aphasia as 'a Wernicke's aphasic', regardless of the specific level of breakdown. It has been suggested that up to 70% of people with aphasia have some degree of comprehension impairment at the sentence level (Boller, Kim, & Mack, 1977) but not all of these have the additional diagnostic criteria of Wernicke's aphasia. Nevertheless, comprehension disorders are still the most common deficit observed in patients with a posterior temporal lesion (Kertesz *et al*., 1993; Kreisler *et al*., 2000). The extent to which different patients with aphasia exhibit comprehension impairments is clearly ambiguous, this partly arises from the lack of distinction between receptive acoustic-phonological impairment and an impairment in multimodal processes/representations which underpin comprehension, such as semantics. Whilst the impact of such multimodal deficits is likely to play a significant role in any comprehension impairment as comprehension of any auditory stimulus, over an above pure auditory discrimination, necessitates the use of semantics. Most studies have failed to separate these different components and therefore specify the exact nature of the comprehension impairment, however the work by Robson and colleagues (2012), clearly demonstrates the presence and impact of these two distinct impairments.

Perhaps the first to explore the breakdown of specific deficits and therefore provide a more detailed description of the breakdown in language was Luria. In 1970, Luria described a series of tasks in which patients with aphasia, following traumatic brain injury, were required to conduct discrimination tasks. He found that those patients with a lesion excluding the temporal lobe were able to perform these discrimination

tasks. In contrast, patients with a lesion involving the temporal lobe consistently failed, even after training. Luria suggested that the lateral surfaces of the temporal lobe (Brodmann areas 42 and 22) permit the 'secondary organisation of auditory perception', and that 'whilst damage to Heschl's gyrus leads to a hearing impairment, damage to more lateral parts leads to defects of auditory analysis.' He noted that in 48 patients, fewer patients with anterior temporal lesions had a severe deficit in auditory analysis than those with posterior temporal ones. Although Luria's anatomical localisation is even less precise than the original cases of Wernicke and Broca, his assessment on this large group of patients was targeted to investigate a specific deficit, and so his functional descriptions were better elaborated even though the anatomical localisations of lesions remained vague. Only a few lesion studies specifically investigating auditory discrimination deficits (Tallal and Newcombe, 1978; Caplan *et al*., 1995; Blumstein, 1998; Robson *et al*., 2012*b*) have corroborated Luria's localisation. This is partly because the precise localisation of the lesion in studies describing these deficits is typically not reported (Franklin, 1989, Gielewski *et al*., 1989; Morris *et al*., 1996; Maneta *et al*., 2001), but also because lesions are rarely localised exclusively to the posterior temporal region and typically involve parietal and middle temporal regions (Grayson *et al*., 1997; Francis *et al*., 2001; Robson *et al*., 2012*b*). They also, inevitably, involve underlying white matter tracts, which will mean that a much wider region of impaired function is causing the observed behavioural deficit, and determining the boundaries of the lesion underestimates the mapping of anatomy to function (Catani and ffytche, 2005). Significant speech comprehension deficits rather than speech perception alone, are most likely found when the damage extends beyond Wernicke's area and includes the middle and inferior temporal gyri, parietal cortex and underlying white matter (Kertesz *et al*., 1983; Hart and Gordon, 1990; Kreisler *et al*., 2000; see also a review by Price, 2010).

In addition to these lesion studies, much has been learnt in the field by comparing comprehension impairments between different patient groups (both stroke and non-stroke). Jefferies and Lambon Ralph (2006) compared semantic abilities between patients with semantic dementia (SD) and patients with comprehension-impaired post-stroke aphasia. These authors found that despite similar scores the two groups demonstrated very different semantic deficits. The SD patients were very consistent across testing sessions and showed a similar performance across a range of semantic tasks regardless of modality whereas the aphasic patients demonstrated an

inconsistent performance across different semantic tasks, insensitivity to frequency and made semantic errors in naming. They also benefitted from phonemic cues unlike the SD patients. The authors demonstrate through comparing these two patient groups that there are two distinct semantic processes that can be differentially diagnosed, a degradation of amodal representations and poor control of semantic activation. Similarly Robson and colleagues (2012) also used data from the patients in the Jeffries and Lambon Ralph (2006) study combined with patients with Wernicke's aphasia to specifically investigate differential patterns of comprehension impairments across the three patient groups. These authors found that the Wernicke's aphasia patients were impaired on both nonverbal and verbal comprehension assessments consistent with a generalized semantic impairment. Their deficit was most similar to that seen in the semantic aphasia patients. Importantly, there was a strong effect of input modality on comprehension only in the Wernicke's aphasia group. The authors suggest that their data differentiates two different disorders from a previously considered unitary one.

There has been discussion in the literature pertaining to the extent to which phonemic level skills are bilaterally organised in the brain (Hickok *et al*., 2008; Rogalsky *et al*., 2008; Teki *et al.,* 2013). Some authors have shown that the perception and discrimination of speech sounds was not affected by lesions to the right hemisphere (Blumstein *et al*., 1977; Basso *et al*., 1977, Tallal and Newcome, 1978; Baker *et al*., 1981). Other studies arguing that this skill is bilaterally supported were insufficient to demonstrate that the right hemisphere alone is capable of auditory discrimination (Hickok *et al*., 2008; Rogalsky *et al.,* 2008). Rogalsky and colleagues (2008) studied a large group of patients with unspecified unilateral left lesions and completed a simple auditory word to picture same/different task, with both semantic and phonological foils. Their conclusion of bilateral organisation is based on the finding that patients with left hemisphere lesions presented with a significantly higher number of semantic errors than phonological errors, and so concluded that phonemic level aspects of auditory word comprehension must be bilaterally organised. However, these conclusions are somewhat tenuous, as phonemic level errors were still evident across the group and its subdivisions, and it is well established that most patients will present with some degree of anomia, which would explain the semantic errors.

Anomia is often the only deficit that persists in the milder cases of aphasia (*i.e.* Dronkers *et al*., 2004; Bakheit *et al*., 2007), and the inclusion of a large heterogeneous population of patients most likely confounded the finding of more semantic than phonemic deficits in the entire group.

In addition, Price (2010), in a review of the literature, examined studies that demonstrated the influence of top-down predictions on cortical involvement of auditory discrimination of vowels. She reported two studies (Myers *et al*., 2009; Leff *et al*., 2009), in which additional activations in the left dorsal *pars opercularis* (Myers *et al*., 2009) and in the left anterior superior temporal lobe (Leff *et al*., 2009) were observed when unexpected stimuli were introduced to subjects. These studies showed that pre-lexical processing of speech results in bilateral superior temporal gyral activation, which becomes left lateralised when there is an incongruent stimulus. A more recent study by Leff and colleagues (Teki *et al.,* 2013), demonstrated, using dynamic causal modelling, that patients' behavioural performance on auditory comprehension tasks correlated with disparate connections: there was a positive correlation between semantic tasks and the connection strength between right STG and right A1, and there was a negative correlation between phonemic perception and the inter-hemispheric connection between left and right STG. They concluded that aphasic patients with more impaired comprehension have less speech representations (by which presumably was meant auditory prelexical templates) in both temporal lobes, and so they rely more on the right hemisphere auditory regions than healthy controls and aphasic patients who present with less impairment. Price (2010) suggested that top-down predictions from prior experience might drive the left lateralisation frequently observed, but the evidence from Leff and colleagues suggests that in the presence of a significant lesion, this lateralisation may be less apparent as the patient makes use of both temporal lobes to aid their impaired speech processing.

In addition to deficits in comprehension and discrimination, patients with lesions to Wernicke's area have also been reported to present with repetition deficits (Selnes *et al*., 1985). Repetition deficits have traditionally been observed as a defining feature of both Wernicke's and conduction aphasia (traditionally thought to occur following a lesion to the arcuate fasciculus). More recent research, discussed above, implicates cortical regions of the dorsal auditory pathway (DAP) in speech repetition (see

Hickok and Poeppel, 2007; Rauscheker and Scott, 2009). The PT, which constitutes a major part of Wernicke's area, has been shown to be active during both overt and covert repetition (Wise *et al.,* 2001; Hickok *et al.,* 2003). The task of repetition involves both accurately perceiving an incoming auditory stimulus and producing the motor plans for that same stimulus. Warren and colleagues (2003) suggest that this component of the DAP is specifically involved in matching incoming auditory information with pre-existing templates that constrain motor responses. Rauschecker and Scott (2009) expanded this to suggest that this mechanism was bi-directional, and so the DAP both informs and constrains speech production and perception. Damage to the PT would presumably result in a loss or weakening of 'templates' that in turn impedes repetition, even if the underling white matter remains intact. However, a patient with a lesion confined to the PT alone has not been described in the literature.

To summarise these anatomical contributions to language various authors have developed neuroanatomical models of speech production (Guenther 2006; Hickok and Poeppel 2007, Rauscheker and Scott, 2009). All these models agree that the posterior temporal cortex and/or the inferior parietal regions support the completion of tasks that involve both auditory perceptual skills and the motor preparation of speech. However, the other route for language is from perception to meaning. Therefore, humans can both repeat pronounceable non-words that convey no meaning, but they can also understand real-words even if they are congenitally unable to produce them (Bishop *et al.,* 1990). This route by which auditory perception maps to meaning is a source of considerable controversy, depending on the patient population studied and the interpretation of results from functional imaging studies on healthy subjects. The two contending sites for amodally representing concepts of objects are the inferior parietal cortex (predominantly the angular gyrus) and the ventral and inferior temporal lobe (Binder & Desai, 2011; Patterson et al., 2007). How much semantics is represented bilaterally is another unresolved issue, although it is plausibly argued that, like autobiographical (episodic) memory, only bilateral pathology results in the most profound semantic-level impairments (Lambon Ralph *et al*., 2010*a*).

1.2.2 Linguistic Basis of Speech Comprehension Deficits

Speech perception is thought to differ from auditory perception in a number of ways. Language is spoken at a rate of up to ten phonemes per second (Liberman *et al*., 1967), which results in both the merging of one phoneme with another and the generation of allophones rather than pure phonemes due to the articulatory effects of preceding phonemes with subsequent ones. Known as co-articulation, this affects both the production of phonemes and also the segmentation of speech. Speech is a continuous stream of merging phonemes, not a series of connected individual phonemes with gaps of silence between to mark onset and offset. The listener must be able to both segment the sound pattern and also map these sounds onto their own representation of phonemes – although many now consider that speech perception is based at the level of the syllable (Greenberg *et al.,* 2003). Mattingly and Lieberman (1990) proposed that these differences demonstrate that speech perception involves a special module, innate and independent of other modules, and presumably unique to humans, and this notion is what most models have been based upon.

The notion that the mechanism of language comprehension can be explained in terms of information processing has influenced the development of numerous prominent information-processing models that have endeavoured to describe the human ability to comprehend speech (*e.g*. Morton, 1969; Marslen-Wilson & Tyler, 1980). Whilst these models could be supported by evidence from normal processing, they often failed to account for the deficits observed in patients. The field of cognitive neuropsychology developed from Marshall and Newcombe's (1966, 1973) seminal work on dyslexia, in an attempt to understand how the deficits observed in abnormal language could be explained. The authors presented two patients with dyslexia who demonstrated very different deficits (deep and surface dyslexia) that were only revealed through individual treatment and the analysis of the errors they produced. They also showed that their deficits could be interpreted using the 'dual route' model of reading, developed to account for normal reading performance, and described how reading could break down with a lesion that was confined to either route. Subsequently, a series of models incorporating processing components and relationships between components were developed to account for reading errors

(Morton and Patterson, 1980) and other domains of language (Patterson and Shewell, 1987; Ellis and Young, 1988).

Ellis and Young (1988) developed a model based on the deficits seen by those with word repetition deficits. The model was composed of an auditory analysis system (extraction of phonemes from a speech wave), an auditory input lexicon (containing information about known words but not about their meaning), a semantic system (the meaning of words) that was bi-directionally linked to the auditory input system, and a speech output lexicon (spoken forms of the word). They presented patients with deficits that demonstrate three possible means of word repetition: first, from auditory analysis→ auditory input→ semantic system→ speech output lexicon→ phoneme level; second, the same route but bypassing the semantic system; and third, a direct route from auditory analysis→ phoneme level output which allows nonword repetition. This model was developed further by Kay and colleagues (1992) to account for a range of deficits seen in patients with aphasia at the single word level and including auditory and written inputs, and to develop a battery of standardised assessments to detect deficits at any of the different levels of breakdown.

Most models described are based on multiple subsequent stages influencing each other consecutively. This implies that the quality of initial input must be crucial to the end result of comprehension (Blumstein, 2009). Auditory single–word comprehension deficits, typically associated with Wernicke's aphasia, have been shown in a range of aphasic syndromes, including Broca's aphasia, conduction aphasia and global aphasia (Basso *et al*., 1977; Varney 1984). Franklin (1989) suggests that cognitive neuropsychological models (Ellis & Young, 1988; Kay *et al*., 1992), unlike more traditional lesion based classifications (*i.e.* Wernicke- Lichtheim models), allow the deficit to be separated into a range of disorders in order to explain different patterns of impairment in individual patients, and therefore aid planning of more directed intervention.

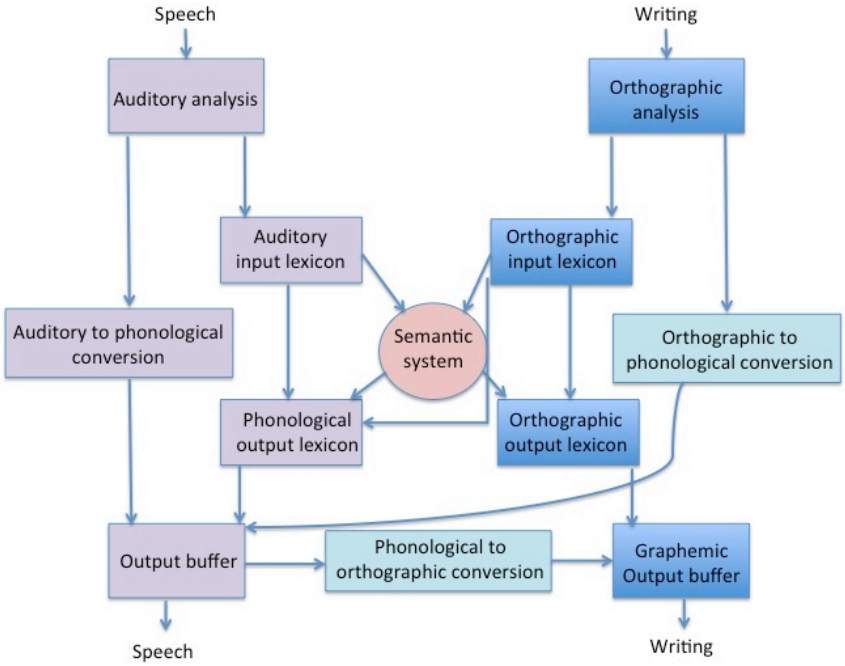


Figure 1.3 *A cognitive neuropsychological model of single word language processing (adapted from Kay et al., 1992) composed of: an auditory and orthographic analysis system (extraction of phonemes and graphemes, respectively, from an input); an auditory input and orthographic lexicon (containing information about known words but not about their meaning); a semantic system (the meaning of words) that is bi-directionally linked to the auditory and orthographic input system; a phonological and orthographic output lexicon (spoken and written forms of the word); an output buffer for the temporary storage of phonological and graphemic items to be produced; an auditory to phonological conversion route, allowing the repetition of word or non-words without accessing the semantic meaning of the item and an Orthographic to phonological conversion route, allowing the reading of novel or nonsense words without accessing the semantic meaning of the item.*

Franklin suggested that by using such a model, at least five types of auditory comprehension impairment could be predicted. Firstly, word-sound deafness (which she suggests will impair all tasks that require accurate phonology, even if social context is still available to aid comprehension). She suggests that impairment at this level would manifest in an inability to discriminate phonemes and because of this there would be impaired repetition. Secondly, word-form deafness, where the patient can detect that two similar, but not identical, auditory words are different but may not be able to determine their meaning. Thirdly, word-meaning deafness, where the patient can accurately differentiate between real and non-words, but cannot access the meaning. This can be considered an access problem because semantic representations remain intact. The fourth and fifth levels relate to semantic impairments, one where

the representations are degraded and the other where task- and context-dependent access to specific aspects of semantic information is abnormal even through the representations themselves are largely preserved. Auditory discrimination deficits, encompassing the first three levels of breakdown, as described by Franklin, have been reported in a variety of aphasia types including: Broca's aphasia (Basso *et al*., 1977); Wernicke's aphasia proper (Blumstein *et al*., 1977; Robson *et al*., 2012*b*); variants of Wernicke's aphasia (Gainotti *et al*., 1982; Caramazza *et al*., 1983); aphasia following a parietal lesion (Caplan *et al*., 1996); conduction aphasia (Leeper *et al*., 1986); global aphasia (Varney, 1984) and jargon aphasia (Maneta *et al*., 2001). However the extent to which these auditory discrimination deficits impact on auditory comprehension has been subject to considerable debate in the literature.

It is important to note that whilst this type of cognitive neuropsychological model continues to play an important role in clinical practice, both in terms of assessment and planning therapy, at the level of impairment, the move towards a network-based understanding of cognitive function within the field of neuroscience cannot be easily explained using such models alone. Recent computational models (*e.g.* Welbourne and Lambon Ralph, 2007; Ueno *et al.,* 2011) have described the interaction of clinical deficits with different brain regions, incorporating both the knowledge from cognitive neuropsychology, mainly derived from lesion studies, and more recent neuroimaging research demonstrating the interplay and connectivity of multiple regions throughout the brain in complex functions such as language or semantics. This is discussed further in section 1.3.

1.2.3 Auditory Discrimination Deficits and Comprehension

Auditory comprehension impairments, as discussed above and illustrated in figure 1.3 can occur due to a breakdown at multiple linguistic levels including at the level of: the extraction of phonemes from an input; the auditory input lexicon (information about known words but not about their meaning); access to, or storage of the semantic system (knowledge about the meaning of words). A breakdown at any of these levels, not just auditory discrimination can result in a significant impairment of comprehension. For example, using neuropsychological approaches in a variety of diseases, including semantic aphasia, semantic dementia, transcortical sensory aphasia

and herpes simplex virus encephalitis has taught us about the important contribution of both access to and storage of semantic knowledge to comprehension impairments (*e.g.* Butterworth *et al.,* 1984; Boatmann *et al.,* 2000; Jefferies and Lambon Ralph, 2006, Noppeney *et al*., 2007; Robson *et al*., 2012*a*). Similarly, neuroimaging studies of these diseases have shown that the neural regions supporting comprehension at the level of semantics incorporates multiple regions within distributed network (Whitney *et al.,* 2011).

In addition to the contribution of semantic deficits to a breakdown in comprehension, much historical work has focused on comprehension impairment due to a breakdown at the level of decoding the incoming auditory signal. As described in section 1.2.1, Luria (1976) localised phonological analysis, or 'a disturbance of complex discriminative hearing' to secondary auditory cortex. He argued that despite intact hearing a patient could have specific difficulty discriminating speech sounds, which, he claimed, would lead to a disturbance in every function reliant on it. Critics of Luria's hypothesis argue that the discrimination tests used by Luria demanded a response in a different domain *i.e.* raising a hand, writing or repetition, and so his results could simply reflect the deficit within that domain. Whilst there is a considerable body of evidence confirming the type of impairments described by Luria, highlighting impairments of both phonological discrimination and phonological identification in aphasia (Basso *et al*., 1977; Blumstein *et al*., 1977; Miceli *et al*., 1977; Tallal & Newcombe 1978; Miceli *et al*., 1980; Baker *et al*., 1981; Gainotti *et al*., 1982; Varney, 1984; Morris *et al*., 1996; Maneta *et al*., 2001; Robson *et al*., 2012*b*), his suggestion that phonological analysis deficits lead to a deficit in comprehension skills has been widely contested. Assuming a hierarchical model of language comprehension, it seems intuitive that a deficit at this lower level will impact on all subsequent levels of comprehension, ultimately leading to a degraded message being incompletely understood (Schuell *et al*., 1964; Luria, 1976; Tallal and Newcombe, 1978; Varney, 1984; Robson *et al*., 2012*a,b*). However numerous studies have suggested that the two skills can doubly dissociate and have failed to find a link between deficits in phonological processing and language comprehension (Blumstein *et al*., 1977; Basso *et al*., 1977; Baker *et al*., 1981).

Tallal and Newcombe (1978) suggest that a reason for the discrepancy is in the

auditory comprehension assessments used. They suggest that many comprehension tests used allow adults with aphasia who have retained knowledge about non-linguistic aspects of language *i.e.* prosody, to use these residual skills in order to appear less functionally impaired. Varney (1984) also suggests that the null results in the influential study by Basso and colleagues (1977) are due to the lenient criteria of a deficit (*i.e.* less than 50% correct), which may have influenced the absence of a correlation in their study.

In a series of three studies (discussed in detail below), Robson and colleagues (2012) tackle the ambiguity in the literature regarding the link between discrimination and comprehension. They highlight that the null results obtained when investigating a link between auditory discrimination and comprehension by some authors (Blumstein *et al.,* 1977; Baker *et al*., 1981; Gainotti *et al.,* 1982) have been cited as evidence of absence of a link. This led to conclusions that the main impairment in patients with Wernicke's aphasia is in the mapping between sound and meaning rather than at the level of discrimination (Hickok, 2000; Rogalsky *et al*., 2008) which has, in turn, influenced controversial neurobiological models of language and interpretation of the role of Wernicke's area in speech perception (Hickok, 2000; Hickok & Poeppel, 2004, 2007, see Robson *et al*., 2012*b*). In the study by Rogalsky and colleagues (2008), reviewed in section 1.2.1, the authors also found that the semantic errors were more prevalent than phonemic errors, which they suggested provided evidence for the deficit being at the level of mapping from sound to semantics rather than discrimination itself. However, in this study and that by Baker and colleagues (1981), the heterogeneous groups studied were likely to have combined patients with variable impairments from the lexical level to semantics, with or without additional impaired phonological discrimination (Dronkers *et al*., 2004; Bakheit *et al*., 2007). The fact that phonemic errors were present suggests that there was also breakdown at this level.

Whilst investigating the laterality of phonological deficits, Hickok and colleagues (2008) suggested further evidence to support their claim that semantic deficits explain the deficit seen in posterior temporal lesions. Using the intracarotid sodium amobarbital test, they assessed 20 subjects ability to perform auditory comprehension tests with both semantic and phonemic foils whilst either the left or right hemisphere was anaesthetised. They found that the right hemisphere was capable of carrying out

the task but also that there were greater semantic than phonemic errors. They concluded that auditory comprehension deficits in aphasia are therefore predominantly semantic. However, these conclusions are tenuous for the following reasons: first, it failed to recognise that semantics is thought to be widely distributed in the brain (Jefferies and Lambon Ralph, 2006), and lesions typically include additional perisylvian regions that may store lexical and semantic representations, or involve executive processes that direct and control semantic activation; and second, the study by Hickok and colleagues (2008) found that in their pre-surgical patients there was no difference between early-diagnosed patients and later diagnosed ones, which they argued was against a notion of atypical organisation as the result of chronic epilepsy. This conclusion ignores the fact that 15 of the patients had refractory temporal lobe epilepsy. This diagnosis may not be determined before early adulthood, but on careful examination of the clinical history most patients describe symptoms of temporal lobe epilepsy throughout their childhood (French *et al*., 1993), making a division based on formal diagnosis somewhat arbitrary.

Robson and colleagues (2012) conclude from their studies in patients with Wernicke's aphasia, that a small degree of semantic impairment (typically when the lesion involves the MTG or AG) is likely to have a disproportionate impact on comprehension as the two weakened systems have reduced capacity to support each other. Under these circumstances semantic deficits play a contributory role to the overall deficit but acoustic–phonological deficits are predominant. The authors demonstrated this in a study that used a case-series comparison methodology to investigate performance on a range of comprehension and semantic tasks across three groups of patients: post-stroke Wernicke's aphasia and semantic aphasia, and neurodegenerative semantic dementia. The purpose was to determine the extent to which the deficit seen in Wernicke's aphasia can be accounted for by an acoustic-phonological deficit, a semantic deficit, or a dual deficit hypothesis. They found, not surprisingly, that the patients with Wernicke's aphasia did present with impaired verbal and nonverbal comprehension abilities consistent with a semantic deficit, similar to the semantic control deficits observed in the patients with semantic aphasia. In addition, they also showed an effect of input modality that revealed an additional specific deficit in auditory processing. The same group also directly investigated the

link between phonological discrimination and auditory comprehension in eleven patients with well-defined Wernicke's aphasia (Robson *et al*., 2012*b*). They developed a sensitive test, which involved ascertaining auditory discrimination thresholds by using phoneme confusability measures, to capture the extent of the deficit in the patients who they report as performing at floor on the standard tests. A strong correlation between auditory discrimination thresholds and comprehension impairment, at both the single word and sentence level, was found.

Traditionally, the deficits associated with damage to this level of processing are that of pure word deafness, auditory verbal agnosia or word sound deafness. In reality the deficit is rarely 'pure', but manifests as a severe comprehension disorder for spoken words but with other modalities intact, such as intact auditory analysis of prosody and other non-speech sounds (Franklin, 1989). This can lead to the phenomenon, frequently observed in patients, where they are able to communicate reasonably well in everyday contexts by using a combination of non-verbal communicative skills; yet, in formal testing situations, typically with no prosodic information provided, the extent of their deficit is revealed (Franklin, 1989).

1.2.4 Summary of Speech Perception in Aphasia

The evidence presented so far remains ambiguous about the precise mechanism by which speech perception can break down in aphasia. The PT appears to play an important role in matching the incoming auditory signal to existing representations or 'templates' of speech segments. These may then be combined at the word level to form lexical representations that can be comprehended through access to a widely distributed semantic system, via the ventral processing stream. Domain-general mechanisms are likely to play an important role in the presence of a functional lesion anywhere along this processing 'stream', and the extent to which connections between the domain-specific and domain-general systems are damaged will influence the degree of comprehension impairment. However, aphasic strokes are typically large, and a single insult to the brain can have drastic consequences on both domain-general and domain-specific systems. Multiple connected and disparate regions can be damaged, which usually leads to multiple levels of linguistic deficits. This makes the understanding of the neural systems involved in comprehension of language difficult

to isolate in patient populations. Our understanding of normal brain function has moved away from localising individual cognitive components to recognising the interplay of different functionally specialised regions connected across large distributed networks. It is now widely accepted that interactions within and between multiple large-scale neural networks are essential for effective domain-specific behaviour (Mesulam, 2009; Bonnelle *et al*., 2012). Yet the models proposed to account for a deficit in single word comprehension do not incorporate these additional domain–general components of comprehension, over and above semantics.

1.3 Domain General Networks in Language

Evidence for the role of top-down processing in speech discrimination was initiated by Warren (1970), who showed that subjects were unable to recognise the absence of a word medial phoneme in the context of a sentence. He also found that listener perception was dictated by the semantic context of a sentence when presented with sentences containing possible 'minimal-pairs' words with an omitted phonemes: so the initial phoneme in the '*eel' in the sentence 'the *eel was on the *' was either /h/ or /wh/ depending on the use of the word final: floor or axel. Warren termed this the phoneme restoration effect. In contrast, the importance of bottom-up processes was demonstrated by Miller and Nicely (1955), who showed that when presented with phonemes in noise the most difficult words to understand were those that differed by only one phonetic feature, *i.e.* place or manner of articulation. Remez and colleagues (1981) demonstrated that listener expectations of the sounds they heard played an important role in determining their discrimination ability. In their study, two groups of subjects were exposed to a series of tones. One group was informed that they were listening to synthetic speech and asked to describe what they heard, whilst the other was only asked to describe what they heard and not informed that it was speech. The former were able to perceive speech within the tones and transcribe accurately, the latter heard only electronic sounds and other such noises. Knowledge of the involvement of these top-down behavioural phenomena in speech comprehension indicates that any discussion pertaining to the neural underpinnings of speech comprehension also necessitates mention of non-linguistic influences on performance. Whilst the contribution of 'top-down', domain-general mechanisms to language comprehension has been well established (Miller and Nicely, 1955; Warren, 1970 and

Remez *et al*., 1981), the specific anatomical and functional contributions to the language system have only recently begun to be understood.

Typically, functional imaging studies investigate neural activity in response to a task. However, it has been recognised in numerous studies that the use of a baseline that eliminates 'mind wandering' is required to eliminate 'language' related activity within the baseline condition (Binder *et al.,* 1999; Spitsyna *et al*., 2006; Awad *et al*., 2007; Brownsett and Wise, 2009). The default mode network is typically active during 'rest' or 'passive' states, and is thought to reflect 'self-referential' or 'stimulus-independent' thoughts (Raichle *et al*., 2001; Greicus *et al*., 2002) that rely on declarative (semantic and episodic) memories and possibly covert language systems (Brownsett and Wise, 2009). The DMN includes the posterior cingulate cortex (pCC), precuneus, bilateral AG and ventral anterior cingulate cortex (vACC). Effective deactivation of this network has been linked to better task performance in healthy volunteers relative to patients with structural damage to part of the network as the result of diffuse axonal injury after traumatic brain injury (Bonnelle *et al*., 2012).

The ability to flexibly switch between thoughts and actions is loosely termed cognitive control. This ability is essential to processing incoming information when learning. Over and above the linguistic difficulties associated with aphasia, it is not uncommon for patients to concomitantly report and demonstrate cognitive control deficits including, but not limited to, attention deficits, interference of unwanted stimuli, production of unintended responses and poor self-monitoring. For example, when participating in aphasia therapy for auditory comprehension deficits, the patient needs to be able to attend to the task, the therapist and the stimuli, eliminate unwanted noise, visual motion and thoughts, and, whilst completing the task, they must be able to attend to their response in order to monitor their success. All of these components require identifying the most salient information from a continuous stream of intra- and extra-personal stimuli in order to guide behaviour.

This skill is thought to be supported by two independent, but interacting, neural networks: the salience (cingulo-opercular) and central executive (fronto-parietal) networks (SN and CEN, respectively). These networks are active during attention to both external stimuli and task-related performance. The SN comprises the IFG/

anterior insula (aI), dorsal anterior cingulate cortex (dACC), anterior lateral prefrontal cortex and thalamus. It is known as the 'salience network' due to its role in identifying the most salient stimuli in the environment (Seeley *et al*., 2007, Menon *et al*., 2010). The fronto-parietal network includes the dorsolateral prefrontal cortex, inferior parietal lobule, and the intraparietal sulcus and is thought to be involved in initiating and adjusting control by maintaining task relevant information to allow rapid adjustment of performance. These two networks are functionally linked through the cerebellar cortex. It has been proposed that the SN may rapidly manipulate changes of activity in other networks (Sridharan *et al*., 2008, Menon *et al*., 2010, Bonnelle *et al*., 2012), which has been supported by the recent discovery of the presence of 'Von Economo' neurones in the aI and the dACC. These neurones have large axons that are thought to facilitate the rapid relay of aI and ACC signals to other cortical regions (Butti *et al*., 2013).

The dACC region of the SN has been proposed to exert top-down control over sensory and limbic regions during both task preparation and maintenance (Dosenbach *et al*., 2007). In a review of the function of the ACC in general, Paus (2001) suggests that this region is engaged when willed control of behaviour is important and when rehearsed actions are not sufficient to guide behaviour (Raichle *et al.,* 1994; Paus, 2001). The opercular component of the SN is located in the bilateral IFG/aI (Menon and Uddin, 2010). These are areas frequently implicated in domain-specific language networks, such as Broca's area and its homologue in the right cerebral hemisphere. The frontal operculum is also reciprocally connected to auditory belt and parabelt areas (Hackett *et al*., 1999). Davis and Johnsrude (2003) suggest that this connection may enable high-order areas to manipulate low-level auditory cortical areas during effortful comprehension. Menon and colleagues (2010) propose that the aI is specifically sensitive to transient salient environmental events, and its function is to mark salient events for additional processing. An alternative suggestion by Dosenbach and colleagues (2008) suggests that this component is involved in task maintenance and strategy. Many studies have demonstrated that activity in the DMN and the SN/CEN are anti-correlated (Raichle *et al*., 2001; Greicius *et al*., 2003; Greicius and Menon, 2004), which some have suggested demonstrates a switching between internal and external stimuli (Sridharen *et al*., 2006). In addition pathological states have been

shown to interfere with the balance between the interoceptive (DMN) and exteroceptive (SN/CEN) networks (Anticevic *et al*., 2012; Bonnelle *et al*., 2012).

1.3.1 Domain General Deficits in Aphasia

Executive control problems are thought to be common in aphasia (Murray, 2012), yet assessing these domain general abilities is not routinely carried out in these patients. This may be partly because linguistic impairments can impact on the accuracy of completing and interpreting formal assessments of cognitive control and *vice versa* (Fridriksson *et al*., 2006). However, most experienced clinicians make subjective observations about many of these features from conversations with the patient and objective examples are frequently captured by picture description tasks. Fridriksson and colleagues (2006) noted that if executive functioning is impaired in aphasia, functional communication ability might be more impaired than the severity of the language deficit may suggest. Similarly, it is a frequent pragmatic and reliable clinical observation that impaired attention and executive function skills interfere with the effective rehabilitation of aphasia. Earlier studies in aphasia demonstrated an absence of a link between general cognitive abilities and language performance in aphasia (Basso *et al.,* 1973; Baker *et al.,* 1975). However, more recently executive dysfunction has been shown to correlate with communication deficits (Coelho *et al*., 1995; Purdy *et al*., 2002; Coelho, 2002; Fridriksson *et al*., 2006), and communication deficits have been shown to reduce speed, but not accuracy, of processing in nonverbal executive functioning tests (Purdy, 2002). In addition to this direct relationship between residual skills, 'frontal executive skills' have been shown to be predictors of success of post-stroke rehabilitation (Robertson & Murre, 1999, Fillingham *et al.,* 2006: Lambon Ralph *et al*, 2010*b*).

Murray and colleagues used a picture description task to investigate the effects of varying attention demands on speech production. Picture description requires attention to the task but a complex picture can divide attention in a way that a single item in a naming task does not. The patient must 'wander' around the picture and select the salient components to describe, but they can be easily distracted by another component in the picture, or even semantic associations of a component. This division

of attention can increase word retrieval deficits even in mildly aphasic patients, and so can provide a useful insight into functional communication (Murray *et al*., 1998).

Sustained attention becomes even more relevant when participating in therapy, which typically relies on a stimulus-response mechanism, involving attending to the stimulus, identifying the salient features of both the stimulus and task, modulating other cognitive networks such as working memory and semantics, preparing a response, initiating the response and modulating the response depending on both the auditory and somatosensory feedback received. As such various authors have emphasised the need to consider non-verbal cognitive function when planning intervention in aphasia (Kinsella 1998; Hinckley *et al*., 2001; Helm-Estabrooks, 2002; Murray 2012; Jefferies and Lambon Ralph 2006; Corbett *et al*., 2009).

Lesion studies in monkeys have shown that damage to the dACC can lead to an impaired ability to both sustain correct behaviour (Kennerly *et al*., 2006) and sustain attention to task and responses (Laplane *et al*., 1981; Rushworth *et al*., 2003). In humans, lesions have been linked to domain-general deficits, including response monitoring and error detection (Løvstad *et al*., 2012) and initiating and sustaining speech production (Nemeth *et al.,* 1988; Paus, 2001). However, lesion studies alone make it difficult to determine the exact role of the dACC in language, as the lesion is not isolated to the dACC and often encroaches on adjacent structures.

Functional imaging of language has not typically included possible domain-general interpretations of activations. However, this new knowledge of the SN and DMN, for example, complicates previous interpretations of functional imaging results in aphasia, many of which have found activity increases in IFG/aI bilaterally in relation to task performance. Whilst some have suggested this correlation may reflect domain–general processes, such as increased task difficulty due to greater working memory load (Fridriksson and Morrow, 2005), others have linked task-related right IFG activation to the loss of transcallosal inhibition of the contralateral homologous region (Chrysikou and Hamilton, 2011). This has led to some authors suggesting that activity in the right hemisphere, particularly when located in the homologue of Broca's area (in the right inferior frontal gyrus), should be suppressed with inhibitory transcranial magnetic or direct current stimulation (Heiss and Thiel, 2006; Turkeltaub

et al., 2011). If this is indeed a compensatory mechanism, although not language-specific and a reflection of the extra effort essential for patients with aphasia to complete a language task, inhibition could instead result in poorer task performance. Comparative studies demonstrating that these systems respond to task difficulty both in healthy volunteers and patients are difficult to design due to the need to ensure tasks are easy enough for patients to complete within a scanning environment (Price and Friston, 1999). Nevertheless, differentiating the role of these domain-general 'effort' systems and the regions within them, from the abnormal activation associated with structural damage to a domain-specific system is essential before therapeutic interventions are used to either inhibit or excite a shared neural region.

1.4 Mechanisms of Recovery in Aphasia

Evidence from various disciplines has contributed to identifying numerous mechanisms by which the brain recovers both spontaneously and in response to intervention, but the field is beset by speculations and potential misinterpretations of data. There is no unified systems-level theory about how recovery after aphasic stroke occurs. An almost universal belief, backed by limited evidence, is the right hemisphere 'takes over' language functions that have been lost in the damaged left hemisphere (the 'relateralisation' hypothesis). Too often, as in studies investigating the basis for comprehension deficits discussed above, behavioural studies neglect the underlying neural changes taking place and neurological studies neglect the intricate behavioural contributions to the observed neural responses.

1.4.1 Neural Mechanisms of Spontaneous Improvement in Humans

There is a large literature on changes at the physiological and cellular level that may support recovery from a focal brain lesion. One example is the study by Nudo and colleagues (1996) of synaptic reorganisation in perilesional tissue in the primary motor cortex of a squirrel monkey. Reorganisation only occurred if the monkey was encouraged to use its paretic forepaw. This led to the notion of constraint induced therapy in the rehabilitation of motor stroke, which has been extended to the design of studies investigating the rehabilitation of aphasia, such as those by Pulvermuller and colleagues (2001).

Studies investigating stroke recovery in humans suggest that multiple factors contribute to the extent of recovery. This introduces additional confounds to research, but also provides multiple possibilities to investigate. In the acute stage, Berthier and colleagues (2011) review data from recovery and conclude that spontaneous recovery after aphasic stroke depends on three possible spontaneous restorative mechanisms: reperfusion of the ischemic penumbra (perilesional tissue); resolution of focal oedema and regression of diaschisis, and the reorganisation of the relationship between structure and function.

Hillis (2006) describes how tissue reperfusion can be enhanced using thrombolysis, stenting, endarterectomy and pharmacologically-induced blood pressure elevation. In the UK thrombolysis has become standard treatment during the hyper-acute stage and works by dissolving the thrombus and in so doing re-establishes blood flow. The use of thrombolysis has resulted in net reduction in death and improvement in functional outcomes but only when administered within 4.5 hours (Mitchell *et al*., 2011). Aphasic symptoms are often the first clinical sign that patients both report and act upon, which means they are more likely to receive thrombolysis than those without aphasia (Engelter *et al.,* 2006). A recent study demonstrated that the volume of the lesion both before and after thrombolysis was the biggest predictor of aphasia outcome (Kremer *et al*., 2013).

Soon after the onset of stroke oedema can develop around the lesion, which may in itself lead to disruption of the perilesional neuronal activity. The presence of the oedema is the marker of severe cellular metabolic disruption and failure of membrane ion channels. Post-stroke oedema declines over eight weeks and functional recovery has been linked, at least in part, to the resolution of this oedema (Inoue *et al*., 1980). The effect of the lesion, and possibly the oedema, can affect remote but anatomically and functionally connected regions to the lesion site. This so-called diaschisis may decline over the first three months post-stroke, thereby resulting; it has been claimed, in some recovery of function (Demeurisse *et al.,* 1991; Cappa, 1997). Diaschisis is a variant of disconnection, and the impact of disconnection syndromes on behaviour was 'rediscovered' by Geschwind (1966*a,b*). Once it became possible to image white matter tracts with diffusion tensor imaging the impact of disconnection on clinical syndromes has received considerable interest (Catani & ffytche, 2005), and diffusion

tensor imaging studies are now being combined with functional magnetic imaging (fMRI) studies. There is now little doubt that remote cortical dysfunction as the result of lesions within long white matter tracts contributes to the behavioural deficits in stroke patients. The impact of these lesions on intact grey matter activation patterns in fMRI studies on stroke patients can impact on both task performance and patterns of activation observed in imaging studies, and so needs to be considered when comparing between groups of patients and healthy volunteers.

One problem with inferring recovery mechanisms from functional imaging results is the lack of agreement as to what a pattern of activity, or perhaps more importantly, an absence of apparent activation, actually represents. In functional imaging an absence of activation, or more accurately an inability to reject the null hypothesis, can be due to: insufficient power (particularly an issue with patient populations, where inter-subject heterogeneity increases the signal to noise ratio); loss of function due to the lesion; and loss of function due to the effects of diaschisis and due to a reduced or delayed blood oxygen level dependency (BOLD) response. The canonical BOLD response used in functional imaging assumes that increased blood flow and volume rises after a stimulus has been presented and peaks at around 6 seconds post onset of the stimulus. However the presence of cerebrovascular disease can alter this blood flow and result in either a delayed or reduced BOLD response (Bonakdarpour *et al.*, 2007) (see also Methods section).

Changes in activation patterns observed in longitudinal functional imaging studies are typically reported as decreases, increase and shifts in activation. In healthy subjects, the interpretation of decreases in the extent of activity have included a sharpening of responses reflecting increased expertise (or experience) so that a minority of neurones fire more rigorously, whereas the majority of neurones show decreased firing (Raichle *et al*., 1994; Poldrack, 2000). Increases in the extent of activity have been interpreted as an expansion of cortical representations, as observed in monkeys in response to auditory frequency discrimination training (Recanzone, 2000). In humans, a similar expansion is thought to reflect the adaptive representation of motor function in adjacent, intact cortex after motor stroke (Nudo *et al.,* 1996). Shifts in activation, such as suggested by ‘re-lateralisation’ hypotheses or perilesional ‘take-over’, are thought to reflect the functional reorganisation of representation through using new, additional

and also maladaptive neural processes (Callan *et al*., 2003; Turkeltaub *et al.,* 2011; Kiran *et al.,* 2012).

1.4.2 Mechanisms of Recovery in Aphasia Using Functional Imaging

Functional imaging affords the investigation of the neural mechanisms of recovery in aphasia by investigating patients' neural responses to tasks, spontaneous response changes over time and changes due to intervention (Musso *et al*., 1999, Abo *et al*., 2004; Fernandez *et al*., 2004; Naeser *et al*., 2004; Fridriksson *et al*., 2006; Meinzer *et al*., 2006; Xu *et al*., 2006). Some studies have suggested that successful rehabilitation is due to dominant intact perisylvian activation (Heiss *et al*., 1993; Warburton *et al*., 1999; Meizner *et al*., 2008). Others have related recovery to an increase in bilateral activation (de Boissezon *et al*., 2005). The most widely reported and controversial phenomena in this literature are the activations observed within the contralateral hemisphere. Some authors suggest that these activations demonstrate that the reorganisation of language function to the contralateral hemisphere is essential for successful rehabilitation (Musso *et al*., 1999; Thulborn *et al*., 1999; Abo *et al*., 2004; Winhuisen *et al*., 2005; 2007; Raboyeau *et al*., 2008; Turkeltaub *et al*., 2012). Others argue that the reorganisation of language function to contralateral regions represents a maladaptive response (Belin *et al*., 1996; Rosen *et al.,* 2000; Blank *et al*., 2003; Naeser *et al*., 2005; Thiel *et al.,* 2006; Turkeltaub *et al.,* 2011). A recent study with a larger cohort of 14 mildly aphasic patients by Saur and colleagues (2006) interpreted their results as indicating that the brain recovers in two phases, subacute and chronic, with a shift of activity from left to right Broca's area and then back again.

Musso and colleagues (1999) used PET in the first functional imaging study of therapy of four patients with Wernicke's aphasia. Between scans the patients participated in brief, intense language comprehension training. Token test scores improved in all patients and activation in the posterior part of the right superior temporal gyrus and left precuneus correlated with the training-induced improvement in verbal comprehension. The authors conclude that training induced improvement occurs due to the functional take-over of the homologous area. Thulborn and colleagues (1999) found a similar rightward shift to the homologous areas in one patient with Broca's aphasia and one with Wernicke's aphasia - this was evident in

both the acute and the chronic stage. A passive listening task by Leff and colleagues (2002) found that chronic patients, with a lesion involving the left pSTS and with poorer performance on auditory discrimination tasks, showed activity in the right pSTS. However no such activation was evident in either healthy volunteers or patients without a lesion affecting the pSTS. The authors do not draw conclusions about the role of this change in physiological responsiveness of the right STG - merely note that it is abnormal.

The majority of imaging studies investigating mechanisms of recovery have focused on the IFG, perhaps because it is so often damaged in patients with aphasia (Pedersen *et al*., 2004). Some authors have interpreted activation observed in the right IFG as maladaptive due to reduced transcollasal inhibition from the lesioned left IFG. In patients, Naeser and colleagues (2005) found that inhibitory rTMS applied to the right IFG actually resulted in an improvement in naming performance in a single subject. This suggested that the right IFG activity was somehow maladaptive to performance in aphasia - a suggestion also put forward by Belin and colleagues (1996). They examined mechanisms of recovery from aphasia in seven nonfluent aphasic patients who they report had received successful melodic intonation therapy. Using PET to measure changes during hearing and repetition of simple words and 'Melodic intonation therapy loaded' words they found that repetition of normal words activated right homologue regions, but when repeating words using melodic intonation therapy there was activation in left Broca's area and prefrontal cortex and a deactivation of right posterior STC. They conclude that this deactivation of homologue regions in response to therapy provides evidence that they are abnormal activations, and successful recovery requires language processes to shift back to the left hemisphere. Similarly, in healthy volunteers, Thiel and colleagues (2006) simulated a lesion by applying inhibitory rTMS over the left IFG and investigated neural activity using PET. This resulted in decreased activity within the left IFG and increased on the right in all subjects. The authors suggested that this rightward shift of language-related activity was the result of reduced transcallosal inhibition.

However, Winhuisen and colleagues (2007) combined rTMS and $H_2{}^{15}O$-PET to inhibit right IFG activation in nine patients. They found that when rTMS was applied to the left IFG, verb generation ability was reduced in all patients at both two weeks

post-onset and at eight weeks post-onset. When applied to the right, only four patients in the acute stage demonstrated a reduced ability to perform a verb generation tasks, but this only occurred in two patients at eight weeks. They concluded that the right IFG activation is likely to play a role in residual language function but its compensatory potential seems to be less effective than in patients who recover left IFG function. This view is in accord with a study by Saur and colleagues (2006) which suggested that better outcome after aphasic stroke occurs when the contralateral IFG activation observed in the sub-acute stage is diminished and perilsional IFG activation is upregulated in the chronic stage.

In contrast to these domain-specific perspectives, Rosen and colleagues (2000) used a word stem completion task in PET and fMRI in six patients with left IFG damage who were impaired on attention-demanding lexical tasks. They found task related right IFG activity; to a large extent in patients and a lesser extent in healthy volunteers. They suggest this could either represent the recruitment of existing pathways through alternative behavioural strategies or an anomalous response due to the presence of the left hemisphere lesion. A greater extent of activity was observed in perilesional tissue compared to the extent of left frontal cortical activity observed in healthy controls. This activity correlated with verbal performance whereas the extent of activity on the right did not. They proposed that the anomalous right activation probably reflects the extra effort required by the patients rather than a new language pathway *per se*. This possibility, they suggested, was supported by other studies that have shown the right IFG to be active within just 24 hours of stroke, when it would seem implausible for a new language pathway to have appeared. They concluded that the right IFG activation must reflect a loss of normal regulation of the activity in homologous regions rather than a domain-general mechanism.

Other authors have suggested that these right activations may reflect activation of systems supporting language rather than language shifts or disinhibition. Raboyeau and colleagues (2008) used foreign language learning in healthy volunteers to compare directly difficulties in naming between 22 patients performing a naming task in their native language and ten healthy volunteers completing the same task in a foreign language. They found that rCBF increased in the right IFG/aI regions after training in both groups, and this correlated with behavioural improvement in patients.

In healthy volunteers, activity in the right dACC correlated with improvement. They also found that regions associated with the DMN were deactivated after training, suggesting that all participants were engaging more in the task. They interpret this activation as a neural correlate of lexical learning and suggest that it 'illustrates the specific monitoring role of the attention network in resolving verbal conflict'.

Van Oers and colleagues (2010) used fMRI to investigate the contributions of both hemispheres in thirteen aphasic stroke patients and thirteen healthy subjects. Severity of aphasia was examined at two months and twelve months post-stroke. Language performance in the chronic phase correlated with higher relative activation of left compared to right perisylvian areas. Naming ability and token test scores were positively correlated with activation during semantic tasks in the left IFG and bilateral IFG respectively, with the latter requiring additional working memory and executive functioning skills. They therefore conclude that in the chronic stage after stroke left IFG activity is associated with improvement of picture naming and sentence comprehension, whereas activity in the right IFG may reflect up-regulation of non-linguistic cognitive processing. Similarly, Baumgartner and colleagues (2013) found that in 14 healthy volunteers performing perceptual, semantic and phonological decisions on auditory and visual stimuli in fMRI, the right IFG (and also anterior insula and dACC) showed modality independent activation during perceptual processing of more difficult manipulated items (evidenced by increased error rates). They extrapolated from their findings to suggest that homologous activations in patients may be due to increased attentional focus on the non-linguistic perceptual features of language, such as prosody.

Functional imaging has also been used to assess neurological responses to therapeutic intervention rather than spontaneous mechanisms (for example, Musso *et al*., 1999; Fridriksson *et al.,* 2006; Cherney and Small, 2006) but these have often been in very few numbers of patients (*i.e.* < 4) (Cherney and Small, 2006; Fridriksson *et al*., 2006, Meizner *et al*., 2007, Vitali *et al*., 2007). As in the Belin (1996) study these studies often suggest that therapy induced improvement corresponds with left prefrontal activation whereas the right activations reflect abnormal activation due to persisting aphasia and not related to recovery as previously suggested.

Thompson and colleagues (2010) used fMRI to investigate patterns of neural activation associated with treatment-induced improvement of complex sentence production (and comprehension) in six patients. Aphasic participants performed an auditory syntactic verification fMRI task prior to, and following, a course of syntax therapy. Region-of-interest (ROI) analyses were conducted in bilateral middle and IFG, precentral gyrus, MTG, STG and insula, and additional regions associated with complex syntactic processing, including the posterior perisylvian and superior parietal cortices. Therapy induced a general shift in activation to more posterior perisylvian and superior parietal cortices bilaterally, which were areas not activated by healthy controls. The authors suggest this implies that their therapy stimulated the 'recruitment of alternative cortical areas for processing complex syntactic material'. Conversely, Meizner and colleagues (2008) suggested that in 11 chronic aphasia patients short-term intensive language training to improve language functions induced changes of activation, which correlated with improvement, within the perilesional region. They suggest that their results provide evidence for the importance of 'treatment-induced functional reintegration of perilesional areas'.

In summary, there is little evidence to suggest that a better outcome can be expected for patients who show activity in the right homologous cortex early after the stroke, with a subsequent shift back to the left in the chronic stage, once the effects of diaschisis have reduced, as suggested by Saur and colleagues (2006). However, better recovery resulting from a shift back to the left hemisphere (*i.e.* Rosen *et al*., 2000; Saur *et al*., 2006) may simply be a reflection of the fact that most patients who recover have smaller strokes and therefore they have more intact left hemisphere cortex remaining that is capable of being activated (Hillis, 2006). Alternatively, if the left hemisphere does normally inhibit the right then smaller lesions are less likely to result in homologous activations as residual left cortex can continue to function and inhibit the right (Thompson, 2000).

1.4.3 Behavioural Approaches to Recovery in Aphasia

Decades of research has been undertaken to investigate if patients with aphasia can improve through behavioural intervention. Howard and Hatfield (1987) provide a comprehensive introduction into the different schools of aphasia therapy including:

the didactic (re-teaching language); behavioural modification (re-teaching language, but based on principles coming out of behavioural psychology); the stimulation school (re-accessing intact language by providing plenty of stimulation); pragmatics (optimal use of unimpaired skills to promote communication by any strategy possible); and cognitive neuropsychology (theories of language based on comparisons between healthy participants and patients with aphasia). In practice aphasia therapy typically incorporates some aspects of many of these schools.

The behavioural modification approach, largely based around Skinner's (1957) operant conditioning work, aimed to eliminate an undesirable behaviour by removing the reinforcement that came with it. Skinner argued that if a stimulus is not reinforced positively then there is a decreased probability of it occurring again. An important part of behaviour modification is the reinforcer to be used. Holland (1970) argues that a simple response is sufficient as a reinforcer, whilst Howard and Hatfield (1987) argue that patients' desire to communicate more effectively should be sufficient.

The stimulation approach emphasised that procedures were not lost but were inaccessible to the patient (Howard and Hatfield, 1987). This method, developed mainly by Wepman and Schuell, aimed to stimulate access to the language skills that are inaccessible rather than lost. Importantly, Schuell believed that diagnosis should come from objective test results. She used principles of intelligence testing to assess large numbers of patients and formed a standardised continuum of severity along which all patients could be placed. She developed an intensive auditory stimulation programme based on her experience that auditory comprehension deficits, at some level, were common to all patients with aphasia. Her programme adopted many aspects of the behaviour modification approach, such as producing as many correct responses as possible whilst minimising incorrect responses (errorless learning) and the use of appropriate reinforcers in order to promote Hebbian learning of useful items (Schuell, 1953; 1965; see Howard and Hatfield, 1987). Errorless learning, originally developed for memory disorders, has been specifically investigated in aphasia, and whilst there was no difference found in the effectiveness of the treatment of anomia using either errorless or errorfull methods, the patients preferred errorless learning (Fillingham *et al*., 2006).

In contrast to these deficit-reducing schools, the pragmatic school emphasised functional communication rather than recovery of language skills, and was based around the common observation that patients often demonstrate better performance in the real world rather than during formal testing, due to residual non-verbal skills. Pragmatic approaches use social interaction to improve the communication abilities of aphasic patients such as PACE (Promoting Communication Effectiveness in Aphasia). PACE is based on the pragmatic rule of reciprocity of communicative messages (Davis and Wilcox, 1981). However, a more recent therapy, known as constraint-induced aphasia therapy, suggests that pragmatic schools of therapy increase the linguistic impairment through non-usage. Constraint-induced aphasia therapy is based on principles that experience (or 'use') enhances a system but lack of experience (or 'non-use') can cause it to atrophy (Pulvermuller *et al.,* 2001).

The cognitive neuropsychological approach to aphasia therapy, arguably the most dominant approach to aphasia therapy in the United Kingdom, is based upon evidence that aphasic performance can be understood in terms of information models of language processing rather than lesion location (Whitworth *et al*., 2005). This approach usually targets deficits based on their hierarchy within a model of language processing (for example, treating the earliest point of breakdown or that which impacts most on other components). These models are frequently used in the planning of assessment in aphasia and ultimately planning of therapy. This school of therapy is based on the idea that clearer understanding of the underlying nature of the disorder better enables the clinician to determine which kind of treatment might be appropriate (for further discussion see, Howard & Hatfield, 1987; Hillis, 1993; Nickels, 2002).

Although cognitive neuropsychology remains the dominant approach, in reality most therapies based on it also incorporate components of other schools. The Royal College of Speech and Language Therapists clinical guidelines state that a framework for intervention should include reduction of the impairment and the disability and limiting the handicap (RCLST, 1998). Typically, reduction of impairment is based on the identification of the precise level of breakdown, which it is argued, benefits from a neuropsychological approach to both assessments and therapy planning. However the use of drill and practice in these therapies, very much stimulation school methods, are often coupled with behavioural modification principles. Reducing the disability

aims to find alternative communication methods. This is often simultaneous to reducing the impairment, in-line with pragmatic schools of therapy. Limiting the handicap typically involves both educating family members about the impact of aphasia and the techniques that can be employed to aid communication outside the clinical setting, and also ensuring that gains made in the clinic are transferred to the real word setting.

1.4.4 The Evidence Base for Aphasia Therapy

Despite a plethora of single case and case series purporting to demonstrate the effectiveness of aphasia therapy, there remains much scepticism in the scientific-medical community with regards to its clinical and cost effectiveness. This notion is supported by Cochrane reviews suggesting limited evidence for its effectiveness (Greener *et al*., 2000). Since Cochrane (1972) first suggested that treatment should be restricted to techniques which have been proven to work in a randomised controlled trial (RCT), the RCT has been seen as the gold standard by which to judge effectiveness of an intervention (Concanto, 2013). Yet many neuropsychologists, regardless of specialty, would argue that it is not plausible or informative, for both clinical and empirical reasons, to do large clinical trials on complex interventions. Complex interventions are defined as those that have several interacting components, as typically used in the rehabilitation of aphasia. The aphasic population is functionally heterogeneous, which necessitates tailored therapy based on knowledge about the deficit, patient priorities and capabilities, pre-morbid history and potential for improvement. Empirically these variations in patients and disease characteristics produce difficulties in blinding studies, in identifying control interventions and in ensuring interventions are standardised (Rudd and Wolfe, 2012). Howard (1986) listed the main features of a good RCT - that the subjects and the treatment are homogenous, differences between treatments can be precisely specified, and that there is low spontaneous recovery in the disease being investigated – features that cannot be fulfilled in trials of aphasia therapy. He suggested that when a RCT of aphasia therapy has reported a null result, most have also administered an inadequate dose (for example, Lincoln *et al.,* 1984) and therefore '*a priori*, one would expect inadequate treatment to have no effect'. He emphasised the statistical issues associated with inferring negative results from a study that has failed to reject the null hypothesis

statistically. Unfortunately, in a recent review of an influential RCT of aphasia and dysarthria therapy (Bowen *et al*., 2012), it was once again necessary to highlight similar points (Leff and Howard, 2012).

A series of influential Cochrane reviews have been conducted to investigate the effectiveness of aphasia therapy as measured by the outcomes of RCTs. Greener and colleagues (2000) concluded that that SALT 'for people with aphasia after a stroke has not been shown either to be clearly effective or clearly ineffective' and that 'decisions about the management of patients must therefore be based on other forms of evidence'. Ten years later the review was updated (Kelly *et al*., 2010) to conclude that 'some indication of the effectiveness of SALT for people with aphasia following stroke was evident'. In the most recent update of this review, this finding has become a little more specific and suggests that 'some evidence of the effectiveness of SALT for people with aphasia following stroke in terms of improved functional communication, receptive and expressive language' (Brady *et al*., 2012). These reviews have caused considerable turmoil in aphasia research departments. Some feel the pressure to balance good clinical research with the need to refute claims about ineffectiveness of intervention. The improvement of outcomes in the Cochrane review most likely reflects an (somewhat reluctant) increased use of RCTs in order to effectively disseminate positive findings to non-specialists. This reflects an engagement in public relations within the clinical community more than a change in the attitude towards the value of RCTs in assessing aphasia therapy.

In small trials, the data collected need to be of sufficient quality and quantity to allow the investigator to be sure that improvement was a consequence of the therapy alone. Crossover designs provide an excellent opportunity to investigate single case studies. If the rate of improvement is greater during the treatment phase than the non-treatment phase then improvement is likely to be due to therapy (Byng and Coltheart, 1986). Single cases are important if a novel therapy approach is used in order to develop a hypothesis that can be tested further (Robey and Schultz, 1988). If a positive effect of therapy is found then the next step should be replication within a group of similar patients. Case series studies afford the opportunity to begin to make generalisations about the suitability of an intervention for different patients.

In the most recent Cochrane review, Brady and colleagues (2012) identified 39 RCTs that were of suitable quality for their review. They concluded that 'there is evidence from randomised trials to suggest there may be a benefit from speech and language therapy but there was insufficient evidence to indicate the best approach to delivering speech and language therapy'. In addition to the overall review, language was broken down into receptive and expressive outcomes. Particularly pertinent to the present thesis was the fact that the results from the 'receptive language' outcomes (encompassing all modalities and various levels) were disappointing. In trials reviewing a novel therapy versus no therapy, and a novel therapy versus social 'support and stimulation', they found some evidence of benefit of SALT. However, reviewing studies comparing one type of therapy against another they found no evidence of benefit of the intervention being evaluated.

Of the studies that contributed to this disappointing conclusion, many were clearly problematic. For example, Lincoln and colleagues (1984) conducted a RCT of the effects of therapy versus no therapy and found no significant difference. However, in this study only two hours of therapy per week were administered, and so the only valid conclusion is that two hours of therapy per week results in no difference between the two groups. Similarly Marshall and colleagues (1989) found an effect of treatment, but no difference between therapist and volunteer administered treatment. This is not surprising given that theories of therapy state that the procedures used in therapy are important and not who is administering them, especially when the volunteers were initially trained by a therapist (Howard, 1986).

In a recent RCT (Bowen *et al*., 2012), included in this most recent update of the Cochrane review, the authors overcame many of the issues oft cited as reasons for lack of feasibility of conducting such studies in aphasia. However, methodological concerns within this RCT cast doubts on their conclusions that 'communication therapy had no added benefit beyond that from everyday communication in the first four months after stroke' and that 'future research should evaluate reorganised services that support functional communication practice early in the stroke pathway' (Bowen *et al*., 2012). Leff and Howard (2012) highlight the main issues with the study in terms of controlling for dosage and type of therapy as well as the problems associated with interpreting a null result. However an additional concern with this

study is the outcome measure used. Whilst ultimately the goal of any intervention should be to improve functional communication, using a sample of 'conversational' speech as a measure of improvement at such an acute stage is controversial. Therapy typically begins by determining which component or components of a favoured model of language have broken down, followed by intervention to improve that deficit. Vague functional outcome measures are clearly subject to spontaneous improvement across the spectrum of disorders common in the sub-acute period (first four months) after a stroke. As previously discussed by Howard (1986), global non-specific tests are not suitable for assessing the effects of a specific treatment which, although not specified in the therapy arm of the RCT, would presumably be more specific than 'conversation development'. Secondary outcome measures of the study used supported communication analysis to investigate improvement. This acts as an excellent assessment of what was 'treated' in the non-therapist's arm of the study but not the therapist's arm. Unfortunately, the results of this trial have been interpreted as suggesting that current SALT resources are being inappropriately allocated to this acute stage (Rudd and Wolfe, 2012) and has even been incorporated into draft NICE clinical guidelines to suggest that intervention in the acute stage should not take place over and above assessment (Royal College of Physicians, 2012).

1.5 Therapy for Speech Comprehension Deficits in Aphasia

Patients with auditory comprehension deficits have a poorer prognosis than those without (Bakheit *et al*., 2007). Many therapy studies aimed at improving auditory comprehension deficits have been reported. These typically target general, all-encompassing levels of auditory comprehension (Schuell *et al*., 1964; Prins *et al*., 1989); sentence level comprehension (Naeser *et al*., 1986, Byng *et al*., 1994; Mitchem *et al*., 1995; Musso *et al*., 1999; Thompson *et al*., 2005) or auditory access to semantics (Behrmann and Lieberthal, 1989). Yet, despite a large amount of research defining deficits at the single word level of comprehension, and, more specifically, phonological discrimination deficits (see section 1.2.3), very little research investigating the rehabilitation of these deficits in aphasia has been published. Possible reasons for this paucity of therapy studies include:

- Most patients with a single-word deficit make substantial recovery over the first few months, and so there are few candidates to recruit

- Those with residual single word deficits are likely to be more severe and may not be suitable for the study
- Therapy typically draws on intact systems to support the treatment of impaired processes, and as patients with word comprehension deficits typically also have impaired output, intervention strategies available are limited (Whitworth *et al*., 2005)
- Ambiguity in the literature regarding the underlying nature of this deficit that makes planning suitably targeted therapy problematic; and, given the need to control for non-specific therapy effects, few tasks are available to improve discrimination without incorporating other linguistic skills such as semantics and speech production

However the motivations for researching this area are equally as compelling:

- First, these patients do exist, as demonstrated by the wealth of literature investigating the precise level of breakdown.
- Second, given the insensitivity of the standardised assessments available (see Robson *et al*., 2012*b*), combined with the knowledge that most patients with aphasia have additional confounding deficits, the number of patients with such a deficit, to some degree, is likely to be underestimated.
- Third, whilst intervention targeting auditory discrimination deficits are likely to impact on the efficacy of the entire process of language comprehension, speech production may also benefit from intervention aimed at improving the access to the auditory-motor 'templates' that may support speech perception (Rauscheker & Scott, 2009).

Schuell and colleagues (1964) developed an intensive auditory stimulation approach to rehabilitating aphasia. Although it was not specifically aimed at phonological discrimination deficits, they would almost certainly have expected such a breakdown to benefit from their approach. As language is typically acquired through the auditory modality and auditory feedback allows a speaker to monitor responses whilst developing language, Schuell (1954) considered auditory comprehension to be the most important component of language, as it provides the crucial link between both input and output modalities and the language system (see Howard and Hatfield,

1979). Aphasia, in Schuell's view, is an interference of language processes but not a loss of them. In her view, therapy should not consist of didactic teaching but instead should stimulate adequate functioning of these disrupted processes (Schuell *et al*., 1964). She emphasised that therapy should be flexible, should follow an accurate diagnosis (which necessitated a thorough language assessment), be relevant to the patient, and every stimulus should elicit a response and errors should not be corrected.

Whilst Schuell never submitted her approach to a formal trial, it has formed the basis of many approaches to therapy reported in the literature (see Robey, 1998). Prins and colleagues (1989) found no effect of therapy in a RCT of auditory comprehension therapy, 'conventional' stimulation therapy and no therapy. They also cited reasons for the inadequacy of previous trials. Amongst many flaws, the lack of a control group, the heterogeneity of the functional impairment, the questionable validity of the outcome measures, and the lack of control over 'dosage' (the frequency and duration of therapy) are factors that they proposed rendered many trials inadequate to answer whether an intervention is effective or not. However, in their study their lesion localisation was no more precise than localised to the left hemisphere and, although they used standardised tests, they reported scores as an overall 'combined comprehension score'. This included tests assessing a range of comprehension skills, which made inferences about the heterogeneity of functional deficits impossible. The therapy, which was based on Schuell's theory that auditory comprehension disorders are always present in aphasia, consisted of 28 tasks at nonverbal, phonological, lexical semantic and morphosyntactic levels, and covered a wide range of linguistic elements known to be problematic in aphasia. The training included perceptual training (through environmental sound recognition and matching two pictures), auditory discrimination and comprehension (using word-to-picture matching tasks with minimal pairs), semantic judgements (including synonym identification and single word-to-picture matching) and comprehension of syntax (sentence-to-picture matching, in which tense, gender and word order were varied). Patients completed two sessions per week for five months. The authors reported a non-significant improvement on treated items, and acknowledge that the very broad scope of the therapy and assessment was the most likely cause of their null result as no treated element received a useful dose of therapy.

1.5.1 Therapy for phonological discrimination deficits

All of the phonological discrimination therapy studies that have been published are restricted to single subjects (Gielewski *et al*., 1989; Morris *et al*., 1996; Grayson *et al*., 1997; Wee and Menard, 1999; Maneta *et al*., 2001; Teisser *et al*., 2007). Although they typically follow a cognitive neuropsychological approach to therapy, most of them also incorporated many of Schuell's interventional components into their therapy. These studies comprise the current evidence base for the treatment of phonological discrimination deficits and their techniques are presented below. However, one study did not provide sufficient detail to attribute any reported improvement to therapy, especially as it was completed within the first two months post-stroke, at a time when spontaneous recovery is maximal (Gielewski *et al*., 1989).

Grayson and colleagues (1997) present a single case study of a patient with a large temporo-parietal infarct, diagnosed as globally aphasic. It was considered that the impaired auditory comprehension was at a pre-lexical level of processing, but also involved an unspecified semantic deficit. The authors used a crossover design that first provided semantic therapy one-month post onset (one hour, five times a week), which involved spoken word-to-object matching. After four weeks additional but less intensive (three 15 minute sessions for three weeks) auditory therapy was introduced, which involved spoken word-to-picture matching tasks with rhyming foils. They found an improvement on a minimal pair discrimination test only after the period of auditory therapy, and concluded that this specificity demonstrates that improvement was not due to spontaneous recovery but the intervention itself. However, it is possible that the intensive 'semantic' therapy that preceded the 'semantic-plus-auditory' therapy may have also had a positive impact on the second stage of therapy, and so the specificity of the auditory component of therapy is less clear.

Perhaps the most influential therapy study in this field is that described by Morris and colleagues (1996), who provided single-case evidence that a minimal pairs training approach could improve auditory discrimination in chronic post-stroke aphasia. These authors described a patient with a deficit at the level of auditory phonological analysis. He had poor auditory discrimination of minimal pairs, written comprehension and pre-phonetic auditory processing. The patient's scan was reported

to show 'low attenuation in both hemispheres, especially the left basal ganglia'. Twelve sessions of therapy over six weeks were completed with the aim to improve phonological discrimination. Therapy consisted of a variety of tasks, including phoneme-to-grapheme matching, same/different phoneme discrimination, spoken word-to-picture matching with minimal pair distractors (also used in Giewlski *et al*., 1989; Grayson *et al*., 1997), written word-to-picture matching, spoken word-to-single picture matching judgement and same/different judgement of non-words. Feedback regarding accuracy was given after each trial. The hierarchy of stimuli included increases and decreases in the number of distinctive features, providing lip reading, and progressing from free voice to recorded voice. Lip reading is thought to aid comprehension in two ways. First, for some phonemes, the shape of the lips and position of the tongue can give a cue to the phoneme about to be produced. Second, the lips provide a timing cue that allows the listener to know that something is about to be produced. The authors reported a significant improvement in minimal and maximal pair discrimination, a trend for improvement in auditory lexical decision, improved repetition but no improvement in naming and written synonym judgement. They report that the lack of generalisation demonstrates the specificity of the therapy.

The therapy programme described by Morris and colleagues (1996) has been used as a method for investigating improvement with other therapies (Grawemeyer *et al*., 2000; Maneta *et al*., 2001; Teisser *et al*., 2007). For example, Maneta and colleagues (2001) used a similar approach in a more severe patient with a left temporal-parietal lesion and predominantly jargon output, but found no significant improvement despite a trend towards improvement. Both studies completed a similar amount of therapy (i.e. twelve ~30-40 minutes therapy sessions over 6 weeks). Maneta and colleagues (2001) suggest that more extensive therapy may have resulted in a greater improvement but add that 'clinicians need therapies that work within the reality of limited clinical time'. The authors also evaluated a training programme aimed at promoting communicating effectiveness between the patient and his wife. This involved explicit teaching of strategies to the wife in addition to education about aphasia. They used conversational analysis to demonstrate a significant improvement in interactions made by the patient and conclude that this arm of therapy was more beneficial than the impairment-based auditory discrimination therapy. An important difference between this study and that by Morris and colleagues is the severity of the

patient. It is likely that the additional severe deficits in this former patient, such as poor semantic skills, required some improvement before he was able to focus on impairment-based therapy.

Teisser and colleagues (2007) also based their rehabilitation programme for a patient with word deafness on Morris and colleagues' (1996) therapy. These authors used a computer to deliver the therapy and found that the patient improved, not only on the phonological discrimination and recognition targeted by the therapy but also on other auditory comprehension domains and even improved everyday disability ratings. The authors note that there were differences between their therapy and that of Morris and colleagues (1996), which may account for the generalised improvement in their study not observed in that by Morris and colleagues. First, their therapy used CV phoneme discrimination rather than the lexical level discrimination used by Morris and colleagues (1996), and they used errorless learning. Secondly their patient had no additional aphasic deficits, which would inevitably impact on generalisation.

The few therapy studies investigating phonological discrimination have used minimal and/or maximal pairs as their main stimulus (Morris *et al.,* 1996; Maneta *et al.,* 2001). Minimal pairs consist of two phoneme strings that differ in a minimal number of distinctive features such as manner, place of articulation or voicing. Maximal pairs differ on many dimensions. Barlow & Geirut (2002) highlighted the difference between major and non-major distinctions of sound classes. The former differing between main groupings of sounds (*i.e.* vowels versus consonants), and the latter where the pair is from the same group but differ in the method of articulation (*i.e.* place, manner, voicing). These, and other authors, have suggested that the contrasts with the maximal number of differences are known to form the most salient speech sound differences in a language and are therefore easier to differentiate (Baker et al, 1981; Barlow & Geirut, 2002). Robson and colleagues (2012*b*) used phonological confusability (Miller & Nicely, 1954) measures to vary the perceptual distance between the target and reference stimuli. They suggest that their measure, used for assessment of a phonological discrimination deficit, was similar to the minimal/maximal pairs approach used by Morris and colleagues (1996). They argue that their approach permits a finer classification of phonemes. However, unlike the minimal pairs approach, the use of perceptual distance has not been used in a

published intervention for aphasia therapy. Minimal pairs have an established evidence-base for use in both paediatric therapy and pedagogy (Blache and Parsons 1980; Gierut 1991; Crosbie *et al.,* 2005; Dodd *et al.,* 2008). Dodd and colleagues (2008) directly compared the use of both minimal and maximal paired approaches in a paediatric population and found that both approaches improved outcome, but with no difference between the two approaches. The same authors also compared a minimal pairs approach with a 'core vocabulary' approach and found that the former was more effective for children who made consistent speech errors (Crosbie *et al.,* 2005), whilst the 'core vocabulary' approach was best for those with inconsistent speech patterns. The rationale for using minimal pairs to treat disordered phonological skills was that, by introducing a featural contrast to a sound system, the child would be able to apply this contrast to similar featural differences. So generalisation to untreated phonemes should be expected (Weiner *et al.,* 1981; Barlow & Geirut, 2002). Often discrimination therapy in children is provided as an initial stage of therapy, ultimately aimed at improving the child's intelligibility during speech production. However in adults the distinctive features are typically well established, and it is damage to this phonological analysis system through brain injury that can produce a deficit of both discrimination and production of speech sounds.

The production deficit in adult acquired aphasia is not the same as that seen in phonological disorders in children. Children with phonological disorders are typically not able to discriminate between two non-established phonemes until they are explicitly taught to attend to the difference. This is similar to foreign language learning, when explicit teaching of a novel contrast is required before the non-native speaker is able to detect the differences between them (Callan *et al.,* 2004). Adults with acquired aphasia are typically, although not always, more aware of their production error than children from the onset, even if they are unable to correct it or recognise what the error was. Typically a mixture of allophones of a particular phoneme may be produced by the adult speaker with evidence of *conduit d' approache*[1]. Nevertheless, although perceptual training has been shown to facilitate production in children (Crosbie *et al., 2005*), to date this has not been shown in adults (Morris *et al.,* 1996; Maneta *et al*., 2001).

[1] The term *conduit d' approache* refers to increasingly closer approximations to the correct form of the item being attempted.

1.5.2 Dosage in Aphasia Therapy

Broca, after using pedagogical materials aimed at children's reading to improve his patients with aphasia language abilities, questioned the wisdom of expecting children to make progress with just a few minutes training per day (Howard and Hatfield, 1987). Although aphasiology has largely moved away from relying on mainstream pedagogical materials, the question of dose remains both relevant and unanswered. In response to ambiguity about the effectiveness of SALT, Bhogal and colleagues (2003) reviewed ten studies that compared 'conventional SALT' for people with post-stroke aphasia with treatment of a comparative control group, either completing the same SALT or an altered version with the same duration. They concluded that therapy was effective in studies that provided a mean of nine hours of therapy per week for eleven weeks, a total of 98 hours, compared to trials that only provided approximately two hours per week for 23 weeks, a total of 44 hours. Bakheit and colleagues (2007b) found that intensive therapy (~five hours per week) did not result in greater improvement than standard therapy (~two hours per week) after a twelve-week period in the sub-acute period post-stroke. However, a third group who received a statistically different amount (mean 0.6 hours per week) improved least. They also found that in the sub-acute stage many aphasic patients were not able to tolerate intensive treatment. These studies highlight the need to consider dose when designing and implementing studies investigating the efficacy of intervention. Rarely, do behavioural studies consider the likelihood of neural re-organisation occurring after their prescribed dose. The exact dose required to improve outcome is likely to vary between patients and interventions and probably requires specific investigation once efficacy has been established.

1.5.3 Computer-Based Rehabilitation in Aphasia

Most patients receive less than three hours therapy per week as an outpatient from the National Health Service (Code and Heron, 2003). In an attempt to provide more intensive intervention than is typically available when delivered solely by a speech and language therapist, the use of computer-based therapy has been advocated as a means of providing a sufficient dose of therapy (see Varley, 2011). Numerous authors have developed computer-based therapies for a range of linguistic deficits in aphasia including; reading disorders (Katz & Wertz, 1997; Cherney, 2012); writing disorders

(Seron *et al*., 1980; Mortley *et al*., 2001); naming therapy and/word-finding (Pederson *et al*., 2001; Doesburgh *et al*., 2004; Mortley *et al*., 2004; Lagarno *et al*., 2006; Ramsberger & Marie, 2007; Palmer *et al*., 2012); production of speech sounds (Reeves *et al*., 2007; Lee *et al*., 2010) and sentences (Linebarger *et al*., 2001); script-training for personalised situations (Cherney *et al*., 2008); sentence comprehension (Crerar *et al*., 1996); and multiple domains of language (Archibald *et al*., 2009). Only one reports using any tasks that target the auditory discrimination level of comprehension (Archibald *et al*., 2009). These authors used a comprehensive computer-based therapy programme with eight patients with aphasia that targeted various domains of language, including auditory comprehension. Auditory comprehension tasks included matching environmental sounds and minimal pair same/different judgement. The authors found that subjects spent most time on these tasks (mean = 6.2 hours from a total mean of 21.5 hours spent on therapy) rather than tasks targeting other areas of language, and they reported an improvement on a standardised auditory comprehension subtest only (Z = -2.18, P = 0.03). Considering the patients were simultaneously receiving regular SALT it is not possible to conclude, without a control period, that these improvements were due to the intervention itself. The null result of the other domains is likely reflected in the lack of specificity of their therapy programme. Unlike the other studies mentioned, (*i.e.* Pederson *et al*., 2001; Doesburgh *et al*., 2004; Mortley *et al*., 2004; Lagarno *et al*., 2006; Ramsberger & Marie, 2007; Palmer *et al*., 2012) which targeted a specific deficit, this study targeted a broad spectrum of deficits in a very heterogeneous population both in terms of lesion localisation and behavioural deficits. The authors suggest that this general approach is justified rather than a more precisely defined therapy programme as there is a lack of evidence as to which deficits should be prioritised. They also suggest that assessments are not subtle enough to differentially diagnose discrete deficits. Speech and language therapists are highly trained to conduct in-depth detailed examinations in order to pinpoint the exact level of breakdown and so better target therapy. No test in itself is likely to be conclusive but, in a battery of assessments, a carefully chosen hypothesis about a level of breakdown can be tested.

Generalisation of improvement following computer-based therapy has been reported both in terms of improvement of untreated test modalities (Seron *et al*., 1980; Crerar *et al*., 1996; Katz and Wertz, 1997) and generalisation to functional communication

(Mortley *et al*., 2001, 2004; Wade *et al*., 2003). Others have reported limited or no generalisation to untreated items (Pederson *et al*., 2001; Doesburgh *et al*., 2004; Fink *et al*., 2005; Lagarno *et al*., 2006; Ramsberger & Marie, 2007). Obviously the best outcome for any intervention is that the patient is able to generalise to different stimuli and situations. However failure to demonstrate generalisation may be due to the specificity of the therapy. In research conditions this can be an advantage when interpreting a positive finding, but it could also reflect a delayed integration of the participants' newly acquired skills or, despite the motivation to provide more therapy, an inadequate dose. Indeed most of the studies reported do not deliver the intensity and amount of therapy recommended for generalisation to functional communication (Bhogal *et al*., 2003).

Whilst some studies have been completed on large groups (*i.e*. Katz and Wertz; Cherney *et al*., 2010) most have been conducted on single-cases series or small groups with no reference to the lesion localisation (Crerar *et al*., 1996; Pederson *et al*., 2001; Mortley *et al*., 2001; 2004; Wade *et al*., 2003; Doesburgh *et al*., 2004; Fink *et al.,* 2005; Lagarno *et al*., 2006; Ramsberger & Marie, 2007; Cherney *et al*., 2008). An important aspect of developing multiple interventions for different aphasic deficits is knowledge about who benefits from the intervention. One can envisage a series of 'off-the shelf' programmes that can be prescribed for a range of deficits, but in order to get to this stage clear evidence about who will benefit is required.

Despite concerns about using computers with an older population (Varley, 2011), patients have responded positively to the use of such service delivery models (Wade *et al*., 2003; Cherney *et al*., 2008). As the newer stroke population becomes more confident in IT usage this concern will not be an issue. Many therapists have been concerned that the use of computer-based therapy may impact on the quality of the therapy given whilst also reducing the need for therapists and therefore undervaluing their skills. In reality this has not proved to be the case. All of the interventions mentioned above report at least weekly intervention with a speech and language therapist. Computer-based therapy is often seen as an adjunct to traditional therapy, in that it offers the same additional work as a 'pen and paper' homework type exercise frequently offered by therapists to 'top up' or 'carry-over' the therapy provided in a clinical setting (*i.e.* Dosenborgh *et al*., 2004). Most studies demonstrating positive

results of using computer-based rehabilitation recognise the essential role of the speech and language therapist in assessing the patient, 'prescribing' therapy, developing the therapy programme and monitoring and evaluating progress of the therapy. They emphasise that a real advantage of computer-based therapy over individual one-to-one therapy is that it enables the therapist to provide a sufficient dose of practice.

Another significant advantage to home-based computer rehabilitation programmes is that control of dosage compliance is handed to the participants in the same way as treatment for non-complex medical interventions. Once the professional has prescribed a dose the patient is given the 'medication' and then chooses to adhere to the recommended dosage regimentally or skip a dose here or there. The obvious clinical advantage here is that a missed session ('dose'), such as due to illness or holiday, does not necessarily result in an extended period of time between intervention sessions.

Ong and colleagues (2012) using a computer-based therapy for patients with hemianopia, found that dose correlated with the amount of improvement in their study. They found that after five hours training a 10% improvement in reading speed was achieved, but after 20 hours there was a 46% improvement. This is impressive, as the amount of improvement in the studies of aphasia discussed above is typically between 5 to 25%. This suggests that when allowing the patient to 'self-administer' it is essential to ensure that the therapy is sufficiently appealing and engaging in order to maximise dose.

1.6 Main Aims and Hypothesis of the Thesis

The results in this thesis are described in three chapters, a behavioural study, an imaging study in healthy volunteers and an imaging study in patients. They investigate three main aims:

First, in Chapter Three, the aim was to develop and investigate the effectiveness of a computer-based therapy programme, one designed to improve phonological

discrimination in patients with post-stroke aphasia. The impact of a temporal-parietal lesion, with and without additional involvement of the frontal lobe, on this deficit was investigated. A subsidiary aim was to investigate how effective a noise-vocoded version of this training programme was at improving healthy volunteers ability to decode noise-vocoded speech.

The hypotheses were that this therapy would result in improved phonological discrimination, and auditory comprehension, if patients self-administered a sufficient 'dose', but would not improve other skills that were not targeted directly by the therapy. In addition, this programme was expected to simulate this behavioural performance in healthy volunteers by using noise-vocoded stimuli rather than clear speech. It was anticipated that the outcome in both groups would depend on the dose of therapy/training taken.

Second, in Chapter Four, my aim was to investigate the neural systems engaged when understanding and repeating both normal and distorted sentences in healthy volunteers. Specifically, it was to investigate activity in both perisylvian domain-specific language regions and higher-order, fronto-parietal, domain-general systems associated with cognitive control and attention. It seemed plausible that changes with training, described in Chapter Three, would be observed as much, or more, in the domain-general systems than in language regions.

It was expected that both normal and noise-vocoded conditions would engage language-specific systems, but that listening to vocoded speech would also engage domain-general systems associated with the additional cognitive effort required. The prediction was that a positive response to therapy would result in changes in activation of these systems, with a greater engagement of domain-general systems during the noise-vocoded condition.

Third, in Chapter Five, the aim was to investigate the systems that patients with aphasia recruited during listening to and preparing to repeat normal sentences in the presence of a comprehension deficit. As with healthy volunteers, it was also to investigate the changes in activations in both perisylvian and domain-general regions

associated with a behavioural response to the training described in Chapter Three, and the extent to which activation in these regions could predict residual language skills.

It was expected that the patients would recruit similar, domain-specific and domain-general, regions to those used by healthy volunteers under the distorted speech conditions in Chapter Four. Additionally, it was expected that the between-subject variability of this activation would reflect the heterogeneity of both residual functional language skills and behavioural changes observed as a response to the therapy presented in Chapter Three.

1.7 Outline of the Thesis

Chapter Two introduces the neuroimaging data acquisition and analysis techniques used throughout this thesis. Methods specific to a particular chapter are discussed within that chapter.

Chapter Three describes the development and effectiveness of a self-administered computer-based rehabilitation programme. In post-stroke aphasic patients this was aimed at improving phonological discrimination. In healthy volunteers, the training was designed to improve the perception and comprehension of three-channel, noise-vocoded speech. Therapy involved the use of an intensive home-based computerised therapy programme with weekly support from myself. I investigated the extent to which improvement depended on a number of factors, including: the amount of therapy the patients and healthy volunteers completed, the location of the patients' lesions, and the impact of their lesion on their ability to engage domain-general networks in order to complete the tasks. Importantly, this study allowed me to investigate the generalisation, if any, of therapeutic improvements to untreated domains and items. It was predicted and shown that improvement would not generalise to untreated domains of language - such as picture description. I interpreted this as evidence that improvements on the targeted areas were as a result of therapy, and not a non-specific training effect. However, given a sufficient dose, it was also expected that skills that were not targeted by the therapy but that directly rely on intact phonological discrimination skills, such as single word comprehension, might

also improve. However, only one linguistic skill, same-different auditory discrimination of real words, a function specifically targeted by the therapy, demonstrated a significant improvement due to the therapy and this was only in participants without frontal lobe involvement. When scores were separated into treated versus untreated items, patients showed an improvement in response to therapy on treated items only. Whilst standardised behavioural testing was not carried out with the healthy volunteers, their response to therapy was measured using the in-scanner behavioural data collected during the study presented in Chapter Four, both before and after the training. Using noise-vocoded stimuli, the healthy volunteers performance was similar to that in patients listening to normal speech, demonstrating that the tasks were well matched in terms of difficulty across the two groups. The extent of improvement in healthy volunteers, in the absence of domain-general deficits, correlated with the amount of therapy the volunteers completed. I demonstrate that targeting a single component of language with prolonged self-administered therapy and time-limited clinical supervision can make improvements in patients with chronic post-stroke aphasia. My results suggest that using this approach, tailored to specific linguistic functions and taking into account lesion distribution, programmes could be developed to provide an adequate dose of therapy specifically targeted for a range of predefined language impairments in order to result in behavioural improvement.

Chapter Four describes the use of fMRI to explore both the language-specific and domain-general neural systems used by the healthy volunteers during listening to and repeating simple sentences. This was done both before and after training to improve auditory discrimination of three-channel, noise-vocoded speech. During scanning, participants heard simple sentences that were presented to them normally, and as noise-vocoded speech, thereby impairing speech perception and increasing the non-linguistic cognitive effort required. Each listening trial was followed immediately by a trial on which they repeated back the previous sentence. I predicted that listening to sentences in the context of this listen-repeat task would activate both language-specific regions (including speech perception and comprehension, verbal working memory and pre-articulatory rehearsal), whilst repeating them would activate similar regions but with additional involvement of sensorimotor regions associated with producing speech. In addition, activations in domain-general networks (including

networks involved in attention to utterances and decision uncertainty during impaired speech perception) were expected during the listening phase of the task. Interestingly, all of the motor activation expected during repetition trials occurred during the listening trials, suggesting that covert rehearsal was also taking place during the listening tasks. When contrasting the more difficult task of perceiving and preparing to repeat noise-vocoded speech with the same task on clear speech, increased activity in the midline frontal cortex was demonstrated. The reverse contrast demonstrated activity in the default mode network. However, there were no effects of session (*i.e*. changes due to the behavioural training) on brain activity in either domain-general or domain-specific regions.

As in that on healthy volunteers described in Chapter Four, Chapter Five used fMRI to explore both the language-specific and domain-general neural systems used by patients with chronic post-stroke aphasia during listening to and repeating simple sentences. This was done at three time points, twice before and once after phonological discrimination therapy. Listening to sentences in the context of a listen-repeat task was expected to activate regions, excluding the infarcted regions, involved in both language-specific processes (speech perception and comprehension, verbal working memory and pre-articulatory rehearsal) and a number of domain-general processes (including attention to utterances and attempts to overcome pre-response conflict and decision uncertainty during impaired speech perception and production). As in the healthy volunteers, the listening trials compared to the repeat trials revealed extensive activation in bilateral premotor and primary somatosensory-motor cortex, in addition to the saliency and central executive networks. In the reverse contrast components of the DMN were activated. This demonstrates that sub-vocal rehearsal in the listening trials was taking place, in addition to activation of high-order cognitive control networks, similar to those activated when healthy volunteers listened to noise-vocoded stimuli. There were no session effects observed (*i.e.* no changes as a response to therapy).

Using a region of interest analysis, a correlation between activation in the midline frontal region and performance on a picture description task was demonstrated using a region based on the same activation as shown in healthy volunteers. This correlation was not influenced by the sizes of the lesion or the patients' chronological ages. I

interpreted these findings as direct evidence in support of the clinical intuition that domain-general cognitive control is an essential factor contributing to the potential for recovery from aphasic stroke.

In Chapter Six I discuss the findings of the entire thesis, including the results form chapters three, four and five.

Finally, Chapter Seven discusses the future implications of the findings throughout my thesis, with a particular emphasis on how my results might inform the design of future studies.

2 Methods

In this Chapter the general functional magnetic resonance imaging methods used in the imaging experiments of the thesis are presented. This includes a brief introduction to the mechanisms by which the data was acquired and the scanning protocols used.

2.1 Introduction to Nuclear Magnetic Resonance

Magnetic resonance imaging (MRI) is an imaging technique that can be used to produce internal images of the body. MRI uses nuclear magnetic resonance, which combines knowledge about a proton's spin properties with the use of changing magnetic gradients to create an image without the use of ionising radiation.

2.1.1 Principles of MRI

MRI technology uses the basic properties of magnetism (*i.e.* polarity), combined with the reaction of hydrogen protons to a magnetic field, to create a signal that is detectable. Hydrogen protons are widely distributed in water - a major component of blood and all soft tissues. These protons are normally orientated in random directions. However, when an external magnetic field (B_0) is applied to a tissue containing hydrogen, such as blood, the protons within its nuclei precess or 'spin' around the direction of this external field's axis, either in parallel or anti-parallel to the magnetic field.

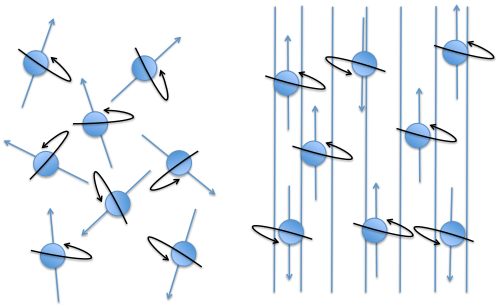


Figure 2.1 *In the absence of a magnetic field hydrogen protons spin in random directions (left panel), when an external magnetic field (B0) is applied the protons spin either in parallel or anti parallel around the direction of the external fields axis (right panel).*

The frequency of spin precession when this external magnetic field is applied is known as the 'Larmor frequency'. Due to the north-south magnetic effect, most parallel and anti-parallel 'precessions' cancel out each others' magnetisation effect, but there is a small preference for 'spins' to assume parallel alignment which produces a net magnetisation (M_0) (Blink, 2010; Jezzard & Clare, 2001).

If a short radiofrequency (RF) pulse, tuned to the Larmor frequency, is applied the hydrogen protons change orientation. Energy is transferred to the protons spinning at the same frequency as the RF pulse and this transfer is termed 'resonance'. This transfer of energy causes some spins to flip from a low (in parallel) to high-energy (anti-parallel) alignment (excitation). When the RF pulse is removed the excited spins begin to return to their original orientation and low energy state (T1 recovery) and so lose energy. The time it takes to relax from the higher energy state to the lower energy state is the relaxation time (TR) (Blink, 2010; Jezzard & Clare, 2001).

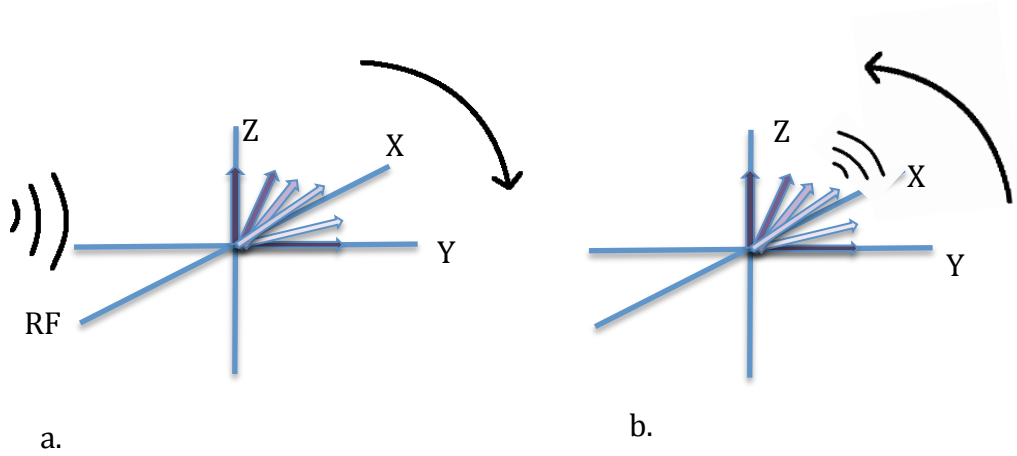


Figure 2.2 *a. When a short RF pulse (RF) is applied, the protons orientation is tilted down to the XY plane. b. When the pulse is removed they relax back to the original direction, releasing detectable energy as they do so. Adapted from Blink, 2010*

2.1.2 T1 Relaxation

When the spinning protons begin to relax back to their original direction, due to the removal of the RF pulse, they release energy in the form of a faint RF signal that is detected by a RF detector coil tuned to the Larmor frequency. This loss of energy and relaxation back to the original state is known as T1 relaxation and describes what happens in the Z plane (*Figure 2.2*). The decay in amplitude of the RF signal emitted

as spins relax back to M_0 is unique to each tissue type, and so permits differentiation of tissues on an image.

2.1.3 T2 and T2* Relaxation

Prior to the RF pulse being applied, the protons aligned along the Z–axis are not in-phase, *i.e.* they are precessing at different speeds. When a spin is first flipped to the XY plane they become in-phase, *i.e.* they are all rotating round the Z- axis in the XY plane. However, they also all have their own magnetic field (much smaller than B_0) and as their magnetic fields also begin to interact (by repelling or attracting each other), this increases or decreases the precession, which causes them to become out of phase as they relax. This is known as T2 or spin-spin relaxation and occurs due to the loss of signal resulting from the random spin-spin interactions in the XY plane (Blink, 2010; Savoy, 2001).

In addition to the spin-spin interactions additional factors can affect the dephasing of spins. The magnetic field may be inhomegeneous, different tissues have differing magnetic susceptibility, which distorts the field at tissue borders (i.e. air/bone interface), and subjects may have different magnetic susceptibility i.e. due to dental work etc. The sum of all these spin-spin interactions and additional factors is called T2* (Blink, 2010; Savoy, 2001).

During gradient echo planar imaging T2* images are acquired. These are not especially useful clinically as the resolution is not sufficient to identify some pathological processes and considerable signal dropout is observed at the interface between brain and sinus areas such as in the frontal and temporal regions. However, T2* contrast is caused by the small field gradients around blood vessels, and this is what underlies the blood oxygen level dependence (BOLD) response used in functional magnetic resonance imaging (fMRI).

2.1.4 Signal Localisation

In order to localise the source of the signal additional magnetic coils (known as gradient coils) are used to cause the B_0 field to vary slightly along each of the X, Y

and Z planes. This variation can be used to calculate where the signal has originated from spatially. The gradient that is switched on during acquisition is the '**read gradient'** (G). This is on during acquisition only and not during the initial RF pulse.

A **slice gradient** (Gz) is switched on at the start and remains on during the transmission of the RF pulse. When this gradient is switched on the B_0 field changes slightly depending on how much Gz is superimposed onto B_0, *i.e.* depending on its relative position. If an RF pulse is sent and matches the Larmour frequency in a slice it will tilt the magnetisation within this slice only. This is known as slice-encoding and allows us to locate the signal along the Z plane, or along the body (Blink, 2010).

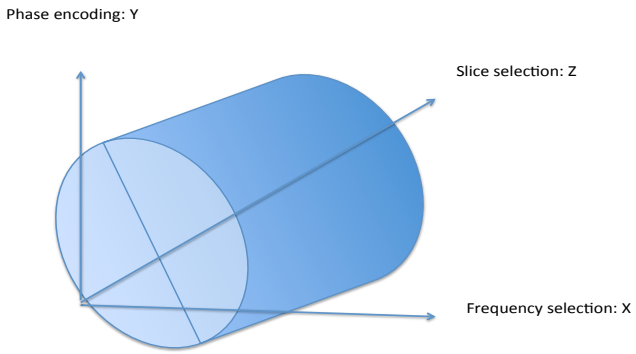


Figure 2.3 *Representation of an MR scanner bore with the gradient direction superimposed.*

In addition to Gz, a **phase-encoding gradient** (Gy), which is perpendicular to Gz, is switched on (i.e. in the anterior-posterior direction). While Gy is switched on, the protons in the anterior Gy direction have a higher Larmor frequency than the posterior ones and so spin slightly faster and are out of phase. When Gy is switched off they spin at the same frequency but in different phases. The position of the signal in the left-right direction is deduced from the signal frequency and is termed the **frequency encoding gradient** (Gx) (Blink, 2010).

Frequency-encoding, slice-encoding and phase-encoding ultimately create a grid in K-space (the raw, unprocessed representation of MRI data) where the entire brain is divided into small volumes (voxels), each with an individual phase, frequency and slice. The number of protons in a voxel determines the amplitude of the RF pulse emitted, and therefore its intensity. A transformation, the Fourier transformation, is

used to decompose all the information of frequency, phase, amplitude and slice to calculate the exact location and intensity of each voxel (Blink, 2010).

2.1.5 Echo-planar Imaging

Echo planar imaging (EPI) is a fast MR imaging technique which can be acquired very rapidly, which makes it ideal for imaging BOLD responses and therefore fMRI experiments. In spin-echo acquisition K-space is gradually filled, one line at a time, after each RF pulse. However in EPI, K- space is filled much more quickly by acquiring multiple slices of phase encoding data after each RF pulse. Thus a complete image can be formed after a single RF pulse. This is achieved in EPI through rapidly changing the sign of a continuous readout gradient (*i.e.* negative to positive back to negative and so on), rather than using consecutive 180 degree refocusing pulses as in Spin echo. Two trade-offs for this additional speed of acquisition in EPI include a poorer spatial resolution and increased distortion susceptibility than in spin echo (DeLapaz, 1994, Blink, 2010).

2.2 Introduction to Functional Magnetic Resonance Imaging

2.2.1 Neurovascular Coupling

Activated areas of the brain require more blood. An increase in blood flow leads to an increase in blood volume to the activated region. MRI can be used to detect this blood flow as new blood will not have been affected by the RF pulse and so will have a different spin history and so will be more aligned to B0. When another RF pulse is applied, this new blood will have a larger nuclear magnetic resonance signal due to the greater number of aligned protons to be flipped.

2.2.2 Blood-oxygen Level Dependent (BOLD) fMRI

The oxygen content of venous blood increases during brain activity and so the concentration of deoxyhaemoglobin decreases. This is because when active neural regions utilise slightly more oxygen, the blood flow increases disproportionally, and so the venous compartment of the cerebral circulation contains an increased amount of oxygenated haemoglobin. Oxygenated haemoglobin is diamagnetic whereas deoxygenated haemoglobin is paramagnetic, which distorts the magnetic field and

dephases the signal. Therefore the decrease in deoxygenated haemoglobin results in a more uniform magnetic field, less dephasing and a stronger MR signal (Blink, 2010; Savoy, 2001).

2.2.3 The Haemodynamic Response Function

In order to complete statistical analysis of the imaging data to determine which voxels contained activated neural tissue, the estimated BOLD signal is calculated. The haemodynamic response is temporally extended compared to the actual neural response, typically peaking 5-8 seconds after the onset of a burst of neural activity. During analysis the shape of the haemodynamic response function (HRF) is assumed to be fit a canonical shape *Figure 2.4*).

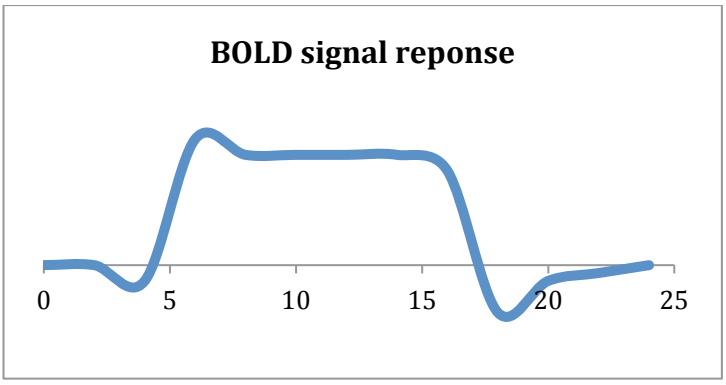


Figure 2.4 *A typical HRF response with a peak around 5-8 seconds and taking up to 25 seconds to return to baseline.*

The timecourse of each explanatory variable is convolved with a canonical HRF in order to simulate how the BOLD response is predicted to change over time. This assumes similar neurovascular coupling and therefore similar rates of BOLD signal change. However, it is important to note that normal aging is associated with reduced vascular reactivity - reduced resting cerebral blood flow and thickening the blood vessels which could all contribute to a non-typical HRF (Desposito *et al,* 2003). Patients with cardiovascular disease and stroke, most prevalent in the older population, have been shown to have a delayed HRF resulting in a reduced BOLD signal (Fridriksson *et al,* 2006; Bonakdarpour *et al,* 2007).

The use of temporal derivatives, as used in FSL can minimise the impact of variation in HRFs between patients and across brain regions with slightly different HRFs.

Temporal derivatives work by detecting differences in BOLD signal at each voxel compared to the changes expected within a modelled experimental variable. This difference is then incorporated into the general linear model, thus improving the statistical strength and sensitivity of analyses (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). However, as SPARSE data is normally treated as temporally independent, temporal derivatives are unlikely to be advantageous in this study and so were not included.

2.3 Acquisition Parameters

All the scanning parameters were the same for all the scans presented in this thesis. They were all acquired on a Philips Intera 3.0 Tesla scanner using dual gradients and a phased array head coil.

A high-resolution two mm T1-weighted image was acquired for each subject with a matrix size of 208 x 208, slice thickness of 1.2mm, 150 slices, TR 9.6 ms, TE 4.5 ms and a flip angle of eight degrees. Functional MR images were collected using a T2*-weighted, gradient echo EPI sequence with whole brain coverage. The total repetition time was 8 seconds, acquisition time was two seconds, echo time 30 ms and with a flip angle of 90 degrees. Thirty-two axial slices with a slice thickness of 3.25 mm and an interslice gap of 0.75 mm were acquired in ascending order (resolution: 2.19, 2.19, 4.0 mm; field of view: 280, 224, 128 mm). Quadratic shim gradients were used to correct for any magnetic field inhomogeneity within the brain.

2.3.1 'Sparse' Scanning

In all the functional MRI data acquired for this thesis, 'sparse' scanning was used (Hall *et al.,* 1999). This method reduces movement and respiratory-related artifact associated with speech production and also permits an auditory stimulus to be presented without the presence of background scanner noise. During sparse scanning only one volume is acquired during each TR, which reduces the power of any individual study as less than half the number of volumes are acquired per unit time compared to continuous acquisition. Data acquisition is programmed to occur close to the peak of the BOLD response to the stimulus (*i.e.* three to five seconds after

stimulus onset), and then the signal is allowed to return to close to baseline after each excitation. One disadvantage of continuous data acquisition is that the BOLD does not return back to this baseline before the following excitation and so the magnitude of each individual MR signal change is reduced. BOLD responses in the auditory cortex are thought to peak at around eight to twelve seconds after the stimulus onset (Hall *et al.,* 1999) and perhaps as early as five seconds in other cortices. In the studies presented here, scanning was timed to occur six seconds after the stimulus onset. Whilst this means that the BOLD signal had not completely returned to equilibrium in auditory cortices, it had declined close to baseline sufficiently enough to permit a measurable signal change during the following stimulus acquisition and also ensured that activations in other cortices, that might have peaked earlier, were also captured.

2.4 Analysis of Functional Magnetic Resonance Imaging Data

Before the statistical analysis could take place the following pre-processing steps were completed: realignment; brain extraction; spatial smoothing; intensity normalisation and high pass temporal filtering.

2.4.1 Pre-processing of Functional Magnetic Resonance Imaging Data

2.4.1.1 Brain Extraction

Whereas functional MRI images do not contain many non-brain structures, structural images include eyes, skull, air in the sinuses, tongue, etc. Normalisation of functional images into standard space is based on these structural images. Therefore non-brain regions need to be removed so that areas of the brain can be accurately aligned and subsequently normalised. FSLs Brain extraction tool (BET) was used to remove non-brain structures. BET uses a surface model approach to achieve this, which fits a tessellated mesh of triangles onto the brain's surface (Smith, 2002).

2.4.1.2 Realignment

During one hour of scanning, and despite the use of immobilising padding, some head movement, usually in the form of gradual drift, is unavoidable. However registering functional scans into standard space necessitates that the voxels are located in the same place throughout the experiment (Smith, 2002). In order to remove the effect of

subject head motion, EPI images were realigned for motion correction using FSLs MCFLIRT. This tool realigns the data to a common reference point by selecting one volume in the dataset that all other volumes are realigned to using a rigid body (six degrees of freedom) transformation. In addition to this, motion outliers are created, which identify points within a time series that have a high amount of signal intensity change once motion correction has taken place. These outliers are included in the design matrix as an additional confound.

2.4.1.3 Spatial Smoothing

Smoothing reduces the between-subject variations in anatomical structures and within-subject high-frequency noise, which improves the signal-to-noise ratio. Larger structures are likely to benefit from smoothing, whereas smaller structures may require smoothing to be turned off or reduced. Spatial smoothing was carried out on this data using 5mm full-width half-maximum Gaussian kernel. This was carried out on each volume of the fMRI data set separately (Friston, 2003; Worsley, 2001).

2.4.1.4 Registration and Normalisation

Before any multi-session or multi-subject analyses can be carried out, the different runs within-subject need to be registered to each other and then all subject data needs to be registered into a standard space in order to make comparisons and inferences between groups. FMRIB's Linear Image Registration Tool (FLIRT) was used to complete this affine registration in each subject. In FLIRT an example functional image is first registered to the same subject's structural scan to produce a transformation matrix. Then the structural image is registered to a standard image - in this study a two mm T1 image was used - to produce another transformation matrix. These two transformations are then combined at a third group analysis stage that registers the functional data into standard space. In all of the studies reported in this thesis affine transformation has been used, utilising twelve degrees of freedom (linear, scaling and skew transformations) (Jenkinson, 2001; Jenkinson and Smith, 2001).

2.4.1.5 Lesion Masking in Patients

In patients, the presence of a lesion can cause serious distortions during the registration process due to the attempts by the software to reduce image mismatch between the standard template and structural image at the site of the lesion. The linear transformations that occur during registration (translations, rotations, zooms, and shears) assume that all images can be matched and so registration acts by attempting to fit unmatched areas of intensity (*i.e.* lesions). If the difference between regions to be matched is large then further transformations will be done in order to minimise this difference. This is typically done at the expense of well-matched areas, such that minimising differences between lesioned and non-lesioned areas are likely to cause distortions in the rest of the brain (Brett *et al.,* 2001). In order to avoid this, cost-function masking can be used to exclude the lesion from the registration process. In this thesis, individual three-dimensional lesions were hand drawn on T1-weighted templates for each slice using FMRIB Software Library image viewer (FSLView). A lesion mask was then created by binarising the image and then inverting it. The patients' fMRI scans were registered to their structural T1 using FLIRT with 6 degrees of freedom. Next, the patient's structural image was registered to the standard MNI anatomical template using FLIRT with twelve degrees of freedom. The binary inverted lesion image was used as an input-weighting mask to reduce the influence of the damaged area on the registration solution and so avoid the distortion associated with normalisation of brains with sizeable infarcts. The two resulting transformation matrices (functional to structural and structural to standard) were then concatenated and applied to the functional data to achieve functional to standard registration (Brett *et al.,* 2001).

2.4.2 Statistical Analysis of Functional Magnetic Resonance Imaging

Univariate analyses are typically carried out in order to subtract the neural activity associated with one task from that of another in order to conclude that the remaining actions reflect the difference between the two tasks. There are various automated software programmes available to analyse functional imaging data. I have carried out univariate analyses within the framework of the general linear model using FEAT (FMRI Expert Analysis Tool) Version 5.98, which is part of FSL. This, like most other software available, requires all explanatory variables to be entered into a design

matrix which is then compared to the dependent variable to investigate how well the variables explain the observed response. At each level of analysis the general linear model was used to produce summary statistics that were passed onto the next level.

2.4.2.1 The Design Matrix

When using the general linear model in FSL explanatory variables (or independent variables) are defined within a design matrix and then a linear combination of how these variables explain the dependent variable, the HRF response, is calculated at each voxel separately at every time point. The design matrix is a description of what would be expected if there were an effect of condition. It assumes that the actual BOLD response equals the modeled response. The basic general linear model assumes that the actual HRF is the modelled response for each event plus some noise. The extent to which these two fit can be calculated using a linear equation. The general linear model is a form of multiple regression and uses the following, somewhat simplified mathematics:

$$Y = X . \beta + \varepsilon$$

Where Y is the dependent variable (*i.e.* observed BOLD signal at a single voxel and a single timepoint), X is the design matrix (explanations of the observed data including modelled HRF response, timing and duration of stimulus), β are the parameters (the estimated contributions of each component in the design matrix to Y) and ε is the error (the difference between the observed data and the predicted model, so the variance in Y is not explained by X) (Friston, 2003).

The different conditions were modeled individually in FSL. An individual experimental variable (EV) was modeled for each condition and for each confound. The timing of these variables were entered in binary code. Every specified EV in the design matrix resulted in a parameter estimate (PE) image. A parameter estimate defines how well the EV's waveform fits the data at each voxel; a higher PE means a better fit. A PE image is equivalent to the "mean difference image". From a PE, a *t*-statistic is then derived by dividing the PE by its standard error (which is calculated

based on noise after the model has been fit). The statistic can then be transformed into a *Z*-statistic.

Additional EV confounds added to the first level models in this thesis, included a time series for the white matter and cerebrospinal fluid. This removed activity associated with these time series and so helped to de-noise the data. In addition, the movement parameters of each patient were entered as an additional EV to remove any residual movement artifact by omitting any activations associated with these movement time-series from the statistical analysis.

2.4.2.2 Modelled HRF

In the analyses described here the default 'Double-Gamma' HRF convolution was used. In addition the temporal derivatives obtained during motion correction of the original waveform are added. This is equivalent to shifting the waveform slightly in time and aims to achieve a better fit of the data. Adding this to the design matrix allows a better fit for the whole model and so reduces the noise and increases statistical significance.

2.4.2.3 First Level Analysis

Each run in each scanning session was analysed at the individual subject level using a fixed-effects model. Fixed-effects models result in statistics that are valid for the population studied but should not be generalised to the wider population. Individual first-level design matrices were created, modelling the different behavioural conditions and timing files for each subject individually. Contrast images of interest were produced from these individual analyses and used in the second-level analysis.

2.4.2.4 Second Level Analysis

At the second level a fixed-effects model was used to combine the two runs in each scanning session for individual subjects. These results were then taken up to the third level for inter-group and intra-group comparisons.

2.4.2.5 Third Level Analysis

Higher level between-subject analyses were carried out using a mixed-effects analysis with the FLAME (FMRIB's Local Analysis of Mixed Effects) tool - part of FSL (Beckmann *et al.,* 2003). Mixed-effects analyses model and estimate the within-subject and between-subject variance and degrees of freedom at every voxel. A group analysis to investigate group level activation was carried out using analysis of variances (ANOVAs) and *post hoc t*-tests. Comparisons between groups can also be made at the higher level using independent sample *t*-tests. A mixed-effects model can be used to make inferences to the wider population.

2.4.2.6 Thresholding and Multiple Comparisons

In the studies presented here a statistical threshold of $Z > 2.3$ and a corrected significance threshold of $P < 0.05$ was used. All imaging results were corrected using a Bonferroni correction to account for multiple comparisons. As functional imaging statistics involve comparisons across 1000's of voxels rather than one, the standard statistical significance threshold of $P < 0.05$ is not suitable. If there was only a single voxel, then $P < 0.05$ would be used to protect against false positives, and false positive conclusion would only be made five in every one hundred times. If this was simultaneously repeated for 20,000 voxels, then there would be approximately 1000 voxels that would be incorrectly reported as significant. Bonferroni correction adjusts the single-voxel threshold, whilst retaining an equivalent error probability of 0.05 across the brain. This can be achieved by dividing the *P*-value by the number of independent tests. Bonferroni correction is often considered too stringent for fMRI as the voxels are not truly independent from each other and adjacent voxels may well respond in a similar pattern and so may result in too may false negatives (Smith, 2002).

2.4.2.7 Region of Interest Analysis

Region of interest (ROI) analyses were carried out where there was a clear hypothesis about a region to investigate the direction of changes in activity and to correlate activity in various regions with patients' and healthy volunteers' performance. Region of interest analyses can boost statistical power by improving the signal to noise ratio and reducing the problems of multiple comparisons by focusing on a small specified

region of the brain rather than the whole brain. Theoretically motivated ROIs were defined by multiplying probabilistic anatomical masks from the FSL Harvard-Oxford Cortical Structural Atlas with functional activity observed in healthy participants. The ROI masks were then re-registered to the same space as individual pre-processed functional data from the univariate analysis. Using FSL FEATQuery (an FSL tool to interrogate univariate data within a defined region) within the ROI, effect sizes for the different conditions and different runs were calculated for each individual. The mean across the two runs was then calculated to provide a mean effect size for each session. Repeated measures ANOVA, bivariate correlations and *t*-tests were used to analyse the ROI data using SPSS (IBM Corp).

3 Auditory Discrimination Training in Healthy Volunteers and Patients with Post- Stroke Aphasia.

3.1 Aims

The aims of this study were to:

1. Develop a computer-based therapy programme to improve phonological discrimination in patients with post-stroke aphasia.
2. Develop a computer-based training programme to improve comprehension of distorted (three-channel, noise-vocoded) speech in healthy volunteers.

and to investigate:

3. The extent to which using distorted stimuli in healthy volunteers simulates the behavioural performance observed in patients with aphasia.
4. The effectiveness of a computer-based therapy programme at improving phonological discrimination in patients with post-stroke aphasia.
5. The extent of generalisation of the therapy programme to untreated domains of language in patients with aphasia.
6. The effectiveness of a computer-based training programme for learning to understand distorted speech in healthy volunteers.

3.2 Material and Methods

3.2.1 Participants

3.2.1.1 Patients

Eighty-eight right-handed patients with persistent post-stroke aphasia were screened for inclusion in the study. Nineteen patients did not wish to be included in the study, a further nineteen had severe co-morbid disease, twelve had English as an additional language (and the software rehabilitation programme was only available in English), seven were unable to give informed consent due to the severity of their impairment and four withdrew from the study after initial inclusion. All participants were required to undergo a MRI study to locate their infarct and to exclude the presence of other lesions (*e.g*. lobar infarcts in the contralateral hemisphere), and so an additional eight patients were excluded due to contraindications to MRI. Therefore, 19 participants with aphasia (seven female, mean age =61, range 37-84 years) completed this study.

This description of the recruitment process highlights the difficulties inherent in recruiting for a trial on behavioural therapy in stroke.

Inclusion criteria for this study were:

- Aged 18-65
- Unilateral lesion following CVA involving the left temporal and/or parietal region
- Auditory comprehension deficit as assessed by a battery of standardised assessments including sections from the comprehensive aphasia test (CAT), Psycholinguistic assessment of language processing in aphasia (PALPA) and the test of reception of grammar (TROG).
- Patient reports difficulty with understanding auditory information
- No significant hearing loss
- Right-handedness
- English as a first language
- Not currently receiving SALT

The mean duration of formal education was 14.1 years (range 10-18). Potential patients were recruited from a variety of sources: during follow-up after initially identifying the patient as an in-patient immediately post-stroke; advertisement; stroke support groups; and outpatient neurology clinics. All patients had a lesion involving the left temporal lobe, in most it extended into the inferior parietal lobe, and six patients had a lesion extending into the frontal lobe (*Figure 3.1*). All patients were at least six months post-stroke (mean four years, range six months to 11 years), at a time when further spontaneous recovery is likely to be negligible (Lendrem & Lincoln 1985; Laska *et al.,* 2001). All patient's comprehension skills were sufficient to give informed consent and production skills were sufficient to allow them to attempt to repeat simple sentences (except two who were only able to repeat single monosyllabic words - both of whom had large lesions including areas of the frontal lobe).

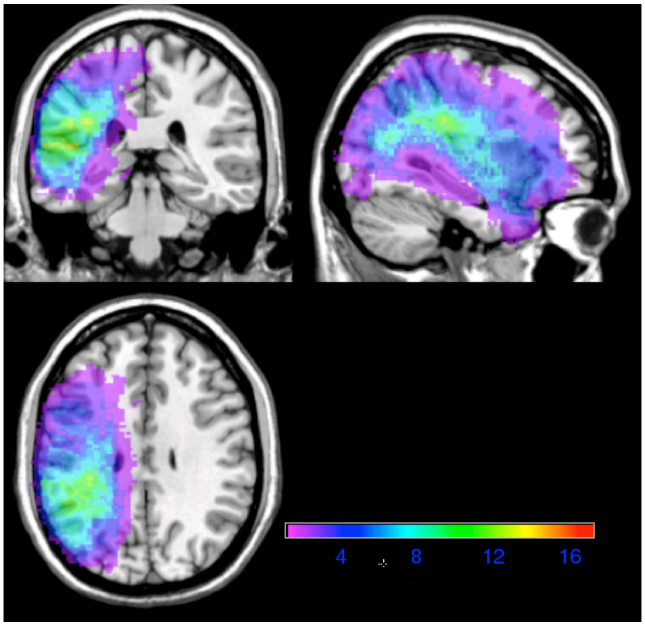


Figure 3.1 *Overlay of lesion distribution in 17 participants with aphasia (two participants scans were not available due to technical difficulties). MRI scans on two of the participants were excluded because of excessive movement artefact, although the distribution of their lesions was evident on visual inspection of clinical scans. Projections are rendered onto a single-subject brain template. The colour code represents the absolute number of participants with a lesion in a given voxel (range: 1 shown in purple to 17 shown in red).*

Patients' vision was normal, or corrected to normal. Patients' hearing using pure tone audiometry was not assessed as part of the study. However, all patients were questioned specifically about this during a detailed case history, and only one patient reported using a hearing aid. This patient (and his wife) reported that he only had a mild impairment. All other patients reported and were observed to have no difficulties in hearing environmental sounds. Nevertheless, the patients were free to adjust the volume of the computer-based therapy to compensate for any peripheral hearing loss.

Patients were primarily recruited on the basis of presenting with both aphasia and a left temporal and/or parietal lesion following a stroke. This was done to reduce the anatomical variability, although lesions were inevitably heterogeneous. The temporal and/or parietal lesion was specified in order to investigate the role of this region in auditory discrimination and repetition, and the therapy was designed with the assumption that a lesion in this region would result in such deficits. All patients presented with aphasia and had a discrimination, comprehension or repetition impairment (see *Table 3.4*), but no patients with an isolated speech apraxia were

included. The patients with lesions extending to the frontal lobe also presented with right limb motor symptoms.

Patient	Age (years) At study	Years post onset of aphasia	Lesion location
CV*	46	11	Left basal ganglia, inferior parietal/superior parietal cortex
CG*	69	4	The length of the MTG and STG and involving the angular gyrus.
DD*	65	3	Left MCA infarct affecting insula, left parietal and posterior temporal lobes and deep white matter, remaining quite posterior.
EJ*	37	7	Left MCA infarct involving the frontal lobe, length of the superior temporal lobe and including the posterior MTG.
FC*	46	8	MCA infarct affecting inferior parietal, and superior temporal gyrus
HV*	59	1	Inferior parietal cortex extending to posterior STG/MTG
HJ	76	1	Left frontal operculum, basal ganglia extending along the length of the STG
KD*	61	11	Large left MCA infarct involving cortex, white matter and deep grey matter of frontal, temporal and parietal lobes. Secondary Wallerian degeneration in the left cerebral peduncle and pons.
LR*	62	4	Large parietal cortical infarct extending to primary motor cortex. There is a little lateral occipital cortex involved on the left.
LR*	46	2	Left parietal cortical infarct. Frontal shunt evident.
MA	61	2	Large MCA infarct involving temporal, parietal and frontal lobes
MJ*	64	0.5	Left deep white matter infarct in lateral lenticulostriate territory and sub-insular cortical and parietal lobe (Angular gyrus)
MT*	78	2	Large MCA infarct involving frontal, parietal and temporal cortices
NG*	48	3	Mature left MCA infarct involving predominantly the frontal cortex but extending to the temporal and parietal regions. The right cerebellar peduncle was reduced in size.
RC*	84	5	Left occipital-temporal-parietal infarct. Mild small vessel disease
SS*	57	3	Lesion involving the inferior parietal lobe extending to post temporal.
TK*	75	3	Small localised left superior temporal gyrus lesion and posterior MTG
TA*	62	1	Inferior/anterior parietal/ temporal lobe intact.
YK*	69	2	Infarct affecting the posterior temporal and parietal cortex

Table 3.1 *Clinical descriptors. Table listing age, time post onset of aphasic stroke (both in years) and description of lesion location. *denotes those patients also participating in the functional imaging element described in Chapter 5.*

3.2.1.2 Healthy Volunteers

Seventeen subjects completed the training programme (five female, Mean age = 59 years, range 25-82). A total of twenty-one healthy volunteers were recruited for the study. Two of these were excluded due to abnormal findings on their anatomical scan (greater than expected age-related diffuse atrophy), and two subjects did not complete the training programme and withdrew from the study. Healthy volunteers were recruited from age-matched spouses and family of the patients with aphasia, and through local advertisement. The inclusion criteria were no history of neurological illness, no sinistrality, no history of dyslexia, no contraindications to MRI and English as their first language. All participants reported normal hearing, apart from two who reported mild hearing the loss for which they had not been prescribed a hearing aid.

3.2.2 Therapy Programme

On inclusion to the study, participants were provided with personal tablet computers to take home. They received instruction in their use. In designing the computer-based programme it was important to consider two confounds not related to the aphasia itself. The first confound was that the programme needed to be user-friendly to a population that was potentially neither comfortable, nor reliably up-to-date, with using computer technology. The second was that some of the patients were reliant on using their non-dominant hand due to their infarct involving some of the motor cortex, so they were less dextrous than a healthy participant. I provided the software developer (Metal Beetle Ltd) with a detailed written specification of the therapy programme required, constraints on its usage and a database of stimuli (both recorded words, phrases and sentences and pictures). I liaised frequently until a suitable programme was developed. Therapy focused on phonological discrimination and repetition skills using both real words and phonologically plausible non-words. A combination of cognitive neuropsychological and repeated stimulation approaches was used (Schuell *et al.,* 1964; Morris *et al.,* 1996). This approach is commonly used in standard SALT and has been shown to be effective in single case studies of patients with auditory discrimination deficits (Morris *et al.,* 1996; Francis *et al.,* 2001; Franklin *et al.,* 2002) but has not been evaluated in a larger group of patients (see section 1.5).

3.2.2.1 Stimuli

Auditory stimuli included both real words and non-word minimal and maximal pairs. Stimuli were used either in isolation, with a short carrier phrase or in a sentence. All stimuli were recorded in an anechoic chamber by a single standard English female accent. The visual stimuli presented alongside the auditory stimuli in some tasks were all photographs depicting either both or one of the minimal word pairs.

3.2.2.2 Real Word Stimuli

Four levels of phonetic difficulty for real words were used, each comprising three stages: single words, short carrier phrases and simple sentences (Subject-Verb-Object or Subject/Object-Verb-Adjective structure). The difficulty was manipulated by increasing the number of phonetic differences present in the pair (as discussed in section 1.5). The phonetic differences consisted of three parameters commonly used by speech and language therapists to distinguish phonemes: the place of articulation (alveolar ridge, lips *etc.*), the manner of articulation (plosive, fricative *etc.*) and voicing (absence or presence of vocal fold vibration). The number of parameters that differ between phonemes increases the perceptual differences between the sounds. The use of minimal pairs (two words where the phoneme string is identical in both words except for one phoneme) permits the manipulation of the parameters of the differing phoneme in order to make the contrast easier or more difficult to discriminate by reducing or increasing the number of differences. The levels of phonetic difficulty applied in this study included maximal pairs where the words had the same initial phoneme only and crossed major[2] classes of phonetic categories, (*e.g*. bat and bone, only have the same initial phoneme), minimal pairs where items had three nonmajor phonetic differences between them (*e.g.* 'pat' and 'rat', which have different voicing, place and manner of articulation), minimal pairs with two nonmajor phonetic differences (*e.g.* 'bat' and 'cat' which have the same manner of articulation (plosive) but different voicing and place of articulation) and minimal pairs with one nonmajor phonetic difference (*e.g.* 'bat' and 'pat', which only differ in their voicing).

[2] See section 3.2.2.2 for examples. Barlow and colleagues (2001) describe nonmajor phonetic class distinctions as the features associated with place, manner, and voice, whereas major phonetic class features differentiate among the main groupings of sounds in language, such as consonants versus vowels, obstruents (stops, fricatives, and affricates) versus sonorants (nasals, liquids, glides, vowels).

Progression from words, to short phrases and then to sentences is used in therapeutic speech comprehension and production tasks in order to gradually generalise newly acquired skills to more functional language use. This inevitably requires additional cognitive processing, such as the increased working memory load associated with sentences compared to single words. The use of sentences meant that stimuli had to be semantically and syntactically valid at a sentence level. There were fifty pairs of words for level one (maximal pairs) and four (minimal pairs with one phonetic difference) and one hundred pairs of words for levels two and three (minimal pairs with three and two phonetic differences respectively). The programme randomly selected items from the appropriate level according to performance.

3.2.2.2 Non-Word Stimuli

The four levels of non-word phonemic difficulty did not include phrase or sentences as a non-word can, by definition, have no semantic meaning. The non-words were used to enhance the skills required to discriminate paired words due to the absence of the top-down semantic processing that can impact on the discrimination of words. The non-words were created in a pseudo-developmental manner, whereby the first level consisted of consonant + vowel and vowel + consonant combinations, such as /ga/. The second level consisted of consonant + vowel +consonant combinations (*e.g.* /gof/) and the third and forth levels were like the second level but with phoneme clusters as the word final (*e.g.* / so**tʃ** /) and word initial sound (/**tʃ**əg/), respectively.

3.2.2.3 Speech Vocoding

In an attempt to simulate the difficulties in auditory discrimination tasks experienced by the patient group, the stimuli used in the training programme for healthy volunteers were noise-vocoded, as described by Shannon and colleagues (1995). Noise-vocoding preserves the syllable structure of speech but removes some of the spectral information, depending on the number of frequency channels, which is replaced with white noise bursts (see Scott *et al.,* 2000; Davis & Johnsrude, 2007). Comprehension of noise-vocoded speech depends largely on the number of frequency channels; the greater the number the easier it is to understand (this is discussed in greater detail in section 1.1.5.1). Noise-vocoded speech is intelligible after some training, and relies on both top-down and bottom-up processes, akin to aphasia

(assuming that a working model of aphasia incorporates some degree of top-down information in order to aid comprehension, such as utilising previous syntactic and semantic information, whilst some models such as that presented in Figure 1.3, do not explicitly state the interaction between these top-down and bottom-up processes they do incorporate such components into their model). Studies have shown that six- and eight-channel noise-vocoded stimuli can be rapidly understood after exposure with feedback in just a single experimental session (Davis & Johnsrude, 2007; Eisner *et al.,* 2010). Davis and Johnsrude (2007) propose that learning to understand noise-vocoded speech involves retuning acoustic-phonetic feature representations that are shared among multiple lexical items, and so permits generalisation to untreated stimuli. Noise-vocoded stimuli have also been shown to produce similar patterns of neural activation in healthy volunteers compared to normal speech stimuli in aphasic patients (Sharp *et al.,* 2004*b*). Finding a simulated deficit to match the auditory deficits experienced by some patients with aphasia is problematic. However, the purpose of this study was not to reproduce the effects of a lesion in controls but to investigate learning when the bottom-up signal was distorted, in a manner that was challenging but responsive to training and approximated task difficulty.

A small study was carried out to investigate the most appropriate number of frequency channels to be used. 20 healthy volunteers were exposed to 15 trials at each of four levels of noise-vocoded speech: two-, three-, four- and five-channels (a total of 60 trials per subject).

Channels of vocoding	Total trials correct	Mean trials correct	Standard deviation	Range
2	1	0.05	2.2	0 to 1
3	145	7.25	4.6	2 to 7
4	257	12.85	2.3	6 to 13
5	288	14.4	0.7	13 to 15

Table 3.2 *Comprehension performance using different degrees of vocoding by 20 healthy volunteers*

Most subjects were able to understand five-channel noise-vocoded stimuli with only a single trial and four-channel noise vocoded speech with no training other than ~two/three exposures to a stimulus. However, they found three-channel noise-

vocoded speech too difficult to understand initially, but with ten or more exposures they learnt to understand the majority of sentences at this level of noise-vocoding.

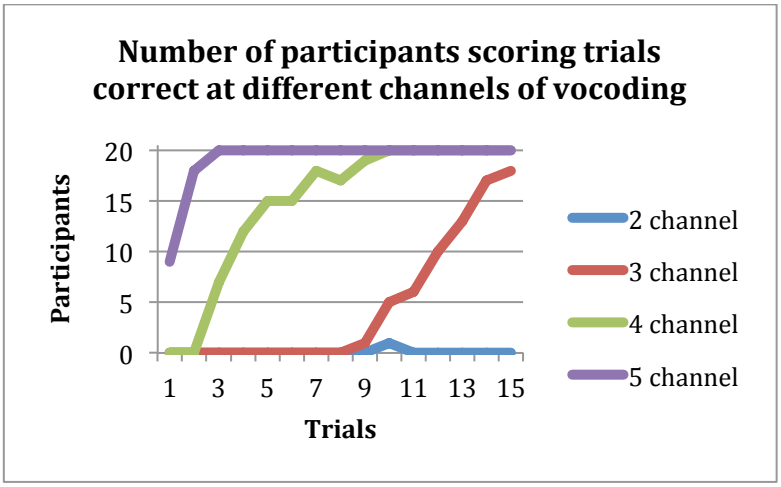


Figure 3.2 *Line graph depicting the number of participants scoring trials correct at the 4 different channels of noise-vocoding. Y-axis shows the number of trials at which participants understood the noise-vocoded sentence. X- axis shows the number of participants understanding the sentence correctly.*

This small study, in the context of other published studies (see Davis & Johnsrude, 2007; Eisner *et al.,* 2010), suggested that three-channel noise-vocoding would prove suitable for investigating the effects of training in the healthy volunteers.

3.2.2.4 Therapy Tasks

There was automatic progression to the next level of difficulty once the patient had attained 90% correct responses on their current level. This programme was supplemented by home visits, at least weekly, by myself in order to ensure the tasks were being carried out appropriately and to provide additional instructions as required. The first seven participants in the study used a slightly different version of the programme. The only difference was that there was a software error on the earlier version that resulted in an error message appearing intermittently at the end of task one and two. This was easily fixed by dismissing the error message and then continuing with the next task. However, three participants required assistance to dismiss the error message, which resulted in additional visits by myself. This was carried out within 24 hours of the message occurring.

Task One: Word to picture matching

The subject heard one item from a pair of words and was presented with two pictures representing each of the two words in the aurally presented minimal pair. The subject was encouraged to repeat the aurally presented word immediately. There was no explicit feedback about the accuracy of each repetition, and these attempts were not recorded. The subject was prompted to make a decision as to which picture matched the heard stimuli (word-picture matching task). Once the decision had been made the subject received immediate feedback. If their response was correct, a large green tick accompanied by a 'cheering' sound was displayed and if incorrect, a large red cross with a disappointed 'oh no' sound was displayed.

Task Two: same/different judgement of two auditory stimuli

The subject was aurally presented with either two identical words or a minimal pair of words. The subject was then prompted to decide if the two auditory stimuli were the same or different. They were requested to press a 'same' or a 'different' symbol. These two symbols consisted of two identical shapes and two different shapes respectively and the subjects practised this before beginning therapy. Once the response was made feedback was given as described in Task one.

Task Three: same/different judgement of spoken word and simultaneous picture

The subject was presented with a single auditory item that they were requested to repeat in the same way as task one. They were then presented with a visual picture either depicting the heard stimuli or its minimal pair. They were required to make a decision about the congruency of the two items and press a 'same' or a 'different' symbol accordingly. Again, feedback was given as described in task one.

Task Four: Repetition of items and self-judgment on accuracy

The subject was presented with a single auditory item that they were instructed to repeat. Once they had repeated the stimulus they were required to make a subjective judgement on the accuracy of their repetition by pressing a 'correct' or 'incorrect' button. The emphasis in this task was on verbal repetition and self-monitoring.

Task Five: Spoken to written nonword matching

In this task the subject was presented with an auditory non-word that they were required to repeat. Then two written non-words were presented, one was congruent with the auditory stimulus and the second was visually very different, with no shared graphemes. The subject was required to choose which written item was congruent with the aurally presented item by pressing the appropriate written non-word. The emphasis on this task was non-word repetition and identification.

Task	Stimulus	Response	Feedback
Word to picture matching	One auditory item	Press one of two pictures	Correct or incorrect
Same/different judgement of two auditory stimuli	Two auditory item consecutively	Press same or different symbol	Correct or incorrect
Same/different judgement of spoken word and simultaneous picture	One auditory item and one picture	Press same or different symbol	Correct or incorrect
Repetition of items and self-judgment of accuracy	One auditory item	Repeat and press correct or incorrect symbol	Identical to response made
Spoken to written nonword matching	One auditory item	Press one of two nonwords	Correct or incorrect

Table 3.3 *Details of the tasks used within the therapy programme, including the stimulus provided, the response required and the feedback given.*

Task difficulty was manipulated in two ways (see Section 3.2.2.1). There were 12 progressive levels of complexity in total. In addition, at each stage the subject had the option to hear auditory stimuli again. This request was recorded but the participant was not penalised in terms of progression to higher levels. However, the subject also had the option to be presented with the written word form of the stimuli. This aid was included so that subjects who found the tasks particularly difficult were able to progress to the next item. Providing this type of maximal cue, in order to maximise the chance of a correct response, is a major advantage to therapist-led therapy. However, as subjects would have been able to progress through levels relying on written word comprehension alone, using this cue resulted in that item being recorded as 'incorrect' for the purposes of progression, the feedback given to the subject was still determined by the accuracy of their response.

3.2.2.5 Feedback

Importantly, the auditory discrimination treatment components provided immediate feedback about the accuracy of responses. However, during the repetition components of tasks One, Two, Three and Five, and the repetition task itself (Task Four), there was no external feedback provided. Feedback has been thought to play an important role in both learning generally, and aphasia rehabilitation specifically (see section 1.4.3). By not providing feedback about the accuracy and quality of the repetition attempts, learning was not expected to take place in this skill. Ideally feedback would have been provided in order to also target this skill, but the speech recognition software available to support this was not sophisticated enough to reliably recognise the distorted speech and errors likely to be produced in this group of patients.

3.2.3 Dose

All patients were requested to complete three 30-minute sessions per day of the rehabilitation programme. Patients were asked to do this for four weeks, giving 42 hours in total on the therapy programme.

Healthy volunteers were asked to complete two 30-minute sessions per day of their training programme for only two weeks, a total of 14 hours. These participants were asked to complete fewer hours training because it was felt unrealistic to request four weeks of intensive participation on a 'therapy programme' that was not useful to the participant, especially when many were still employed full-time.

3.2.4 Assessment of Aphasic Deficits

Patients had three assessment sessions that included a range of speech and language tests. There was a four-week period with no intervention between the first two assessment sessions, and the patients commenced the computer-based therapy in their homes after the second session. A third assessment session was performed after completion of the therapy (see *Figure 3.3*).

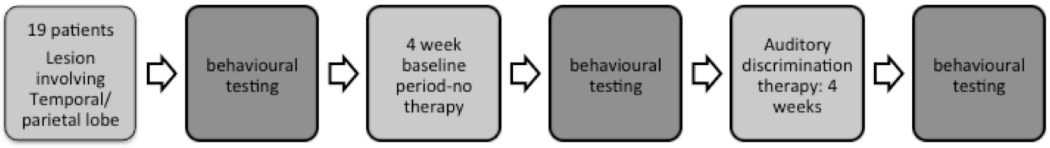


Figure 3.3 *Protocol for patient's participation*

All assessments were attempted on all participants, however, as expected when working with a patient population, completion of the entire battery was not always possible. This was usually due to observed fatigue or requests to cease testing. In the few instances that the entire battery was not completed on the entire group, the numbers are reflected in the Table of results (*Table 3.4*).

The battery of assessments included the following:

PALPA- Minimal pair discrimination: An auditory word to picture matching task. Where the choices include the item, a minimal pair and distractor pictures with phonologically related names. *Normative data: mean=97.5 +/- 1.7.*

PALPA-Same/different word: Two auditory words are presented consecutively and the patient must decide if the items are the same or different. The patient can either verbalise this or point to a figure depicting same and different. *Normative data: mean=97.2 +/- 2.3.*

PALPA- Same/different nonword: Two auditory nonwords are presented consecutively and the patient must decide if the items are the same or different. The patient can either verbalise this or point to a figure depicting same and different. *Normative data: mean=98 +/- 2.6.*

PALPA- Word repetition: A single word, varying in imageability and frequency, is presented aurally and the patient is required to repeat the item. *Normative data: mean=95 +/- 6.72.*

PALPA- Nonword repetition: A single nonword, varying in imageability and frequency, is presented aurally and the patient is required to repeat the item. Normative data was not available for this subtest.

PALPA- Sentence repetition: A range of syntactic structures are presented in sentences and the patient is required to repeat as much of the sentence as possible. *Normative data: mean=100%*

CAT- Single-word comprehension: An auditory word to picture matching task at the single word level. Choice of four pictures, target and phonological, semantic and unrelated distractors.

CAT-Paragraph comprehension: Two short paragraphs are presented and four questions pertaining to each paragraph are asked directly after each paragraph.

CAT- Written word comprehension: A written word to picture matching task at the single word level. Choice of four pictures, target and phonological, semantic and unrelated distractors.

CAT- Single word naming: A single picture is presented and the patient must name. Points deducted if correct but delayed response or phonological and semantic cues given.

CAT- Reading words aloud: The patient is presented with a single written word and must read the word aloud.

CAT-Picture description: A complex picture is presented to the patient who is asked to 'describe what is happening in the picture'.

Sentence comprehension (Test of reception of grammar): Sentences with increasing syntactic complexity are presented individually to a patient. The patient must match the spoken sentence to one of four pictures. *Normative data: less than 80% is clinically significant.*

Maximal Pair same/different discrimination: Two items representing a maximal pair are presented consecutively. The patient must decide if the items were the same or different (previously used in Morris et al., 1996). *Normative data was not available for this subtest.*

Minimal pair sentences: An auditory sentence is presented where one of the key words within the sentence belongs to a minimal pair. The patient must choose from two pictures, each depicting a single item from the minimal pair which picture matches the sentence (unpublished test designed to assess discrimination of minimal pairs at the sentence level). *Normative data was not available for this subtest.*

	Single-word comprehension	Paragraph comprehension	Sentence comprehension	Minimal pair discrimination	Maximal Pair discrimination^	Same/different word	Same/different nonword	Minimal pair sentences	Written word comprehension	Single word naming	Reading words aloud	Picture description	Word repetition	Sentence repetition	Nonword repetition^
CV*	98	**50**	**50**	**85**	83	**89**	**92**	**85**	**80**	**60**	**56**	**17**	**45**	**8**	43
CG*	98	100	**65**	98	83	**94**	**86**	**95**	93	**63**	**65**	**19**	98	**22**	74
DD*	93	**50**	**70**	**68**	69	**68**	**63**	**75**	**60**	**25**	**75**	**-3**	**50**	**25**	49
EJ*	*95*	***50***	***30***	***95***	*81*	***83***	***86***	***85***	***87***	***85***	***38***	***23***	*95*	***6***	*55*
FC*	98	**50**	**25**	**70**	88	100	**50**	**65**	100	**79**	**88**	**26**	**20**	**6**	8
HV*	100	100	80	**90**	100	97	**94**	**80**	100	96	100	51	NT	100	99
KD*	***78***	***50***	***10***	*96*	*73*	***44***	***68***	***75***	***53***	***0***	***0***	***-3***	***8***	***0***	*2*
LaR*	90	75	**70**	**80**	92	**94**	**83**	**75**	97	**88**	100	48	98	**75**	77
LeR*	100	100	**35**	**92**	83	**75**	**80**	**85**	100	**54**	**58**	8	**19**	**0**	5
RC*	**78**	**50**	**25**	**70**	75	**69**	**53**	**55**	**60**	**19**	**54**	**15**	**73**	**6**	38
MJ*	98	75	90	**90**	90	100	**91**	**95**	100	94	100	**28**	90	100	68
MT*	***68***	*75*	***15***	***65***	*73*	***35***	***25***	*NT*	***67***	***0***	***17***	***-3***	***10***	***0***	*19*
NG*	*95*	*NT*	***20***	***90***	*67*	***44***	***63***	***85***	***73***	***38***	*NT*	***0***	***28***	***0***	*29*
SS*	100	**50**	**70**	100	96	97	97	**90**	97	96	98	44	95	**81**	89
TK*	100	100	90	**93**	100	100	**94**	100	100	100	100	78	93	**94**	87
TA*	NT	100	85	**85**	90	**92**	**89**	**90**	100	100	96	46	**83**	**89**	67

YK*	100	100	80	**95**	81	100	**90**	**80**	100	92	100	48	**69**	**19**	47
HJ	***38***	***50***	***5***	***33***	*52*	***47***	*NT*	***60***	***27***	***4***	***17***	***16***	***28***	***0***	*51*
MA	***73***	***50***	*NT*	***80***	*92*	***94***	***80***	***90***	***80***	***17***	***25***	***3***	***40***	***3***	*42*

Table 3.4 *Percentage correct on a range of different assessments at T1. NT= Test not completed. Bold= cut-off for normal performance. ^denotes normative data not available for this test *denotes those patients also participating in the functional imaging element described in Chapter 5. Italics indicates patients with frontal lobe involvement.*

	Ravens Matrices	Pyramids and Palm trees
CV*	83	**85**
CG*	NT	**NT**
DD*	25	**73**
*EJ**	*67*	***96***
FC*	75	**96**
HV*	75	98
*KD**	*42*	***71***
LaR*	67	**87**
LeR*	100	98
RC*	83	**96**
MJ*	83	**56**
*MT**	*83*	***92***
*NG**	*67*	***73***
SS*	75	98
TK*	100	98
TA*	83	100
YK*	100	98
HJ	*NT*	*NT*
MA	*NT*	*NT*

Table 3.5 *Percentage correct on Ravens Matrices and Pyramids and Palm trees assessments at T1. NT= Test not completed. *denotes those patients also participating in the functional imaging element described in Chapter 5. Italics indicates patients with frontal lobe involvement.*

3.2.5 Description of patients

Below is a brief description of the aphasic deficits of the patients presented above.

CV- Expressive and receptive aphasia. Mild semantic impairment with word-finding difficulties evident. Mild-moderate impairment of auditory discrimination and severe

repetition impairment. Poor sentence and paragraph level comprehension. Speech was fluent with frequent semantic and phonological paraphasias.

GC- Expressive and receptive aphasia. Mild semantic impairment with word-finding difficulties evident. Mild-moderate impairment of auditory discrimination, good real word repetition but poor nonword and sentence repetition. Good paragraph level comprehension but poor sentence level comprehension. Speech was fluent with frequent semantic and phonological paraphasias.

DD- Expressive and receptive aphasia. Mild semantic impairment with word-finding difficulties evident. Moderate impairment of auditory discrimination and severe repetition impairment. Poor sentence and paragraph level comprehension. Speech and voice was fluent very dysarthric.

EJ- Expressive and receptive aphasia. Mild semantic impairment with word-finding difficulties evident. Mild-moderate impairment of auditory discrimination, good real word repetition but poor nonword and sentence repetition. Poor paragraph level and sentence level comprehension. Speech was non-fluent with frequent semantic and phonological paraphasias.

FC- Expressive and receptive aphasia. Mild semantic impairment with word-finding difficulties evident. Mild-moderate impairment of auditory discrimination (although excellent same/different words judgement) and severe repetition impairment. Poor sentence and paragraph level comprehension. Speech was fluent with frequent semantic and phonological paraphasias.

HV- Mild receptive aphasia and mild anomia. Mild auditory discrimination impairment. Good repetition. Fluent speech will occasional word finding difficulties and very occasional phonological paraphasias.

KD- Severe expressive and moderate receptive aphasia with semantic impairment. Poor auditory discrimination. Right hemiplegia. Good use of gesture and intonation.

LaR- Expressive and receptive aphasia. Mild semantic impairment with word-finding difficulties evident. Mild-moderate impairment of auditory discrimination, good real word repetition but poor nonword and sentence repetition. Poor paragraph level and sentence level comprehension. Speech was fluent with frequent semantic and phonological paraphasias.

LeR- Expressive and receptive aphasia. Mild semantic impairment with word-finding difficulties evident. Mild-moderate impairment of auditory discrimination, poor real word repetition, nonword and sentence repetition. Poor paragraph level and sentence level comprehension. Speech was fluent with frequent semantic and both phonological paraphasias and mild dyspraxic errors.

GC- Expressive and receptive aphasia. Mild semantic impairment with word-finding difficulties evident. Mild-moderate impairment of auditory discrimination, poor word, nonword and sentence repetition. Poor paragraph level and sentence level comprehension. Speech was fluent with frequent semantic and phonological paraphasias.

MJ- Mild receptive aphasia and mild anomia. Mild speech apraxia. Mild auditory discrimination impairment. Good word and sentence repetition. Fluent speech with very occasional word finding difficulties and phonological paraphasias.

MT- Severe expressive and receptive aphasia with semantic impairment. Poor auditory discrimination. Very limited spoken output. Right hemiplegia. Good use of intonation.

NG- Expressive and receptive aphasia. Moderate semantic impairment with word-finding difficulties evident. Mild-moderate impairment of auditory discrimination, poor real word, nonword and sentence repetition. Poor sentence level comprehension. Speech was non-fluent with limited spoken output, *i.e*. single words and short phrases.

SS- Mild receptive aphasia. Occasional word-finding difficulties evident. Poor paragraph and sentence level comprehension. Poor sentence repetition. Speech was non-fluent with frequent semantic and phonological paraphasias.

TK- Mild receptive aphasia. Occasional word-finding difficulties evident. Mild auditory discrimination deficit. Mild repetition deficit. Speech was fluent with rare semantic and phonological paraphasias.

TA- Mild receptive aphasia. Occasional word-finding difficulties evident. Mild auditory discrimination and repetition deficits. Speech was fluent with occasional semantic and phonological paraphasias.

YK- Expressive and receptive aphasia. Mild semantic impairment with word-finding difficulties evident. Mild-moderate impairment of auditory discrimination, poor word, nonword and sentence repetition. Speech was fluent with frequent semantic and phonological paraphasias. Mild speech apraxia evident.

HJ- Expressive and receptive aphasia. Moderate semantic impairment with word-finding difficulties evident. Moderate-severe impairment of auditory discrimination, poor real word, nonword and sentence repetition. Poor sentence level and paragraph comprehension. Speech was non-fluent with limited spoken output, *i.e.* single words and short phrases.

MA- Expressive and receptive aphasia. Moderate semantic impairment with word-finding difficulties evident. Mild-moderate impairment of auditory discrimination, poor real word, nonword and sentence repetition. Poor sentence level and paragraph comprehension. Speech was non-fluent with very limited spoken output, *i.e.* single words and short phrases.

3.2.6 In-scanner Data Collection

In addition to the assessment data collected for participants with aphasia, a further behavioural measure was available which was perhaps more useful as a measure of change in the healthy volunteers. Further chapters of this thesis present imaging results of fMRI scans that took place before and after training in healthy volunteers and patients, and at an additional time-point four weeks prior to commencing therapy in the patients. These data is discussed primarily in relation to the imaging results. It was also used as a measure of the effectiveness of the therapy in the healthy volunteers, for whom no standardised assessment of noise-vocoded speech comprehension was available.

3.2.7 Data Analysis

3.2.7.1 Patients

The results presented were initially analysed using a standard repeated measures analysis. Three levels were entered for the single within-subject variable- sessions 1, 2 and 3. A between-subject factor of 'lesion' (*i.e.* involving the frontal lobe or not) was also included in the repeated measures analysis. *Post hoc* tests were carried out to compare differences between session 1 and 2, 1 and 3 and 2 and 3. However, as the patient behavioural assessment data in this thesis are from longitudinal assessments from individual patients across time, and so it is difficult to determine the extent to which changes post therapy are significantly different from any changes that may occur before therapy due to autocorrelation, general improvement, placebo, practice effect or regression to the mean. Matthews and colleagues argued that an additional confound when interpreting longitudinal results using *t*-tests (such as used in *post hoc* tests of a repeated measures analysis) is that it ignores the way in which individuals respond over time, which is clinically very useful information. They suggest that by using a summary measure the individual is considered, and the summary measure captures some aspect of that individuals response curve.

In the second analysis method adopted here the one highlighted by Matthews and colleagues (1990) is used. These authors suggest that the problem of autocorrelation can be resolved by reducing (potentially) dependent observations to a single number, to be treated as 'raw' data for further statistical analysis. From each set of individual patients' assessment scores (observations), always over three sessions, two orthogonal components were extracted, each a linear combination of the three observations. The first investigated whether there is an overall trend for improvement, independent of treatment, weighting the three assessments scores (-1, 0, 1), so as to avoid the confound that measurements taken closer in time were likely to be more correlated than those further apart. The second investigated whether there was an effect of treatment, independent of an overall trend for improvement, weighting the assessments (1, -2, 1). Both of these effects have an expected value of zero under their respective null hypotheses, with an unknown standard deviation that depends on the degree of serial dependence/autocorrelation. The significance and effect sizes were calculated from the corresponding one sample *t*-test to investigate an overall linear

improvement (*i.e.* $-1T_1+0T_2+1T_3$) or for greater improvement during the treated than the untreated period (*i.e.* $(T_3-T_2)-(T_2-T_1)$).

3.2.7.2 Healthy Volunteers

To assess the efficacy of the programme in the healthy volunteers the behavioural data from the pre and post training fMRI studies were used. These studies, described in more detail in section 4.4.5, investigated the neural effects of both listening to and learning noise-vocoded speech versus clear speech. As these behavioural measures consisted of two time points, *t*-tests were used to investigate differences. No overt control of the specificity of the therapy was used. However, healthy participants' performance on normal stimuli is also presented, which acted as a pseudo-control as no overt training was carried out using normal speech.

On-line in-scanner behavioural performance was measured using the participant's attempts to repeat sentences in the trial immediately following a listening trial. Three scores (each out of five) for each participants' spoken responses during scanning were calculated: a semantic score; an articulation score and a combined semantic and articulation score. The combined score was used in order to provide a single score that would incorporate both the semantic and articulation accuracy, it was felt that this would be a fairer single score for all patients, given that they had different abilities in both semantics and articulation.

A semantic score of:

- Five points were scored if the whole sentence was repeated correctly;
- Four points if all the content words were produced but one or more function words were omitted;
- Three if greater than 50% of the content words were produced;
- Two if less than 50% of the content words were produced;
- One if a single appropriate word was attempted;
- Zero if there was no response or fillers only.

The same scoring system was used for the articulation score:

- Five points if the whole sentence was correctly articulated;

- Four points if all the content words were correctly articulated but some function words or inflections were incorrect or omitted;
- Three if greater than 50% of the sentence were correctly articulated;
- Two if less than 50% of the content words were produced;
- One if a single appropriate word was attempted;
- Zero if there was no response or fillers only.

The mean of the semantic and articulation score was calculated to produce the combined score. The scoring system was separated in this way in order to allow later comparisons with patients with post- stroke aphasia who may have had additional difficulties articulating the sentences (this is discussed further in Chapter Five).

3.3 Results

3.3.1 Patients: Tolerance and Compliance

The total time the participants were asked to spend on the rehabilitation therapy was 1.5 hours x 28 = 42 hours. The PCs logged the actual time spent, and the mean was considerably less: 20 (± 14.1 standard deviation) hours. As evident from the large standard deviation, the range of compliance was very variable (2.8 - 53.8 hours). The total level reached and the number of trials at each level completed by each patient is shown in *Figure 3.4*. Fourteen participants progressed to the final level, one progressed to the ninth, two to the sixth level, one to the third level and one subject did not move beyond the first level (*Figure 3.4*).

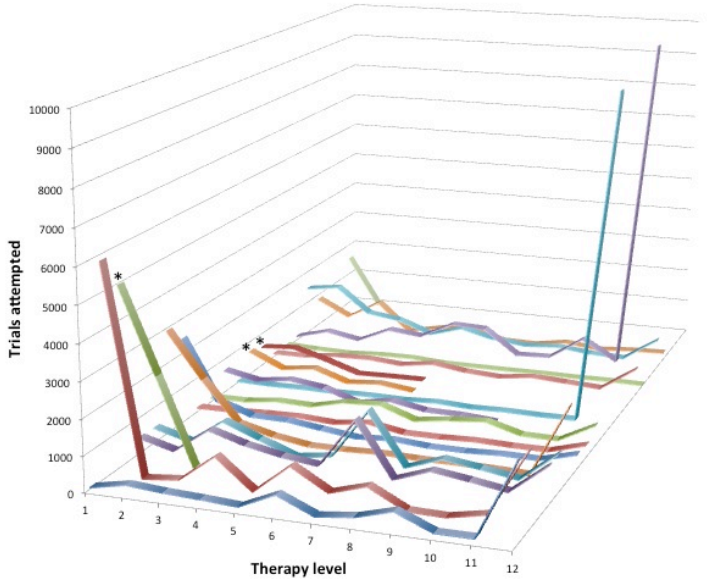


Figure 3.4 *3-D line graphs depicting the variability in the number of trials completed by each participant at each therapy level (1-12). X-axis = therapy levels, Y-axis = number of trials. Lines marked with an * denote participants using the original therapy programme who required additional assistance when an error message appeared.*

Using an independent samples *t*-test, there was no significant difference between the amount of time spent on therapy for those who used the initial programme (M = 21.0, SD = 12.9) and those using the final programme (M = 19.3, SD = 15.3); t (17) = 0. 253, P = 0.803, [95% CI -12.8 to 16.3]. Neither was there a significant difference between those who were unable to dismiss error messages independently (M = 14.1, SD = 12.6) compared either to those with the debugged programme or those who were able to dismiss error messages without assistance (M = 21, SD = 14.5); t (17) = -.767, P=0.453, [95% CI -25.9 to 12.1].

3.3.2 Patients: On-line Behavioural Scores

Despite wide inter-individual variability, the patients' performance on the repeating of normal speech trials (RepNorm) during scanning correlated significantly (using the combined score for articulation and semantics) between scanning sessions one and two (Pearson's r = .88, P < 0.001); between sessions two and three (r = .84, P < 0.001); and between sessions one and three (r = .94, P < 0.001). Similarly, paired *t*-

tests demonstrated no significant differences between any sessions using any of the articulation, semantics or combined scores ($P > 0.1$).

3.3.3 Patients: Outcome of Therapy Repeated measures analysis

Performance across a range of standardised behavioural assessments was analysed in the patients. This was done using two measures, a standard repeated measures analysis and the summary measures method outlined in the methods section (section 3.2.4).

3.3.3.1 Auditory discriminations skills

The results show that the score on the same/different nonword discrimination test was significantly different across sessions F (2,34) = 11.2, $P < 0.001$. There was a significant effect of lesion F (1,17) = 6.5, $P < 0.021$. *Post hoc t*-tests revealed that there was a significant difference between session 1 and 3 ($P < 0.002$) and session 2 and 3 ($P < 0.014$) but not between sessions 1 and 2. This suggested that improvement could be attributed to therapy.

The results show that the score on the same/different nonwords (treated items) test was significantly different across sessions F (2,34) = 6.3, $P < 0.005$. There was a significant effect of lesion F (1,17) = 6.8, $P < 0.02$. *Post hoc t*-tests revealed that there was a significant difference between sessions 1 and 3 ($P < 0.006$) and but not between sessions 1 and 2 and 2 and 3.

The results show that the score on the same/different nonwords (untreated items) test was significantly different across sessions F (2,34) = 11.1, $P < 0.001$. There was no significant effect of lesion F (1,17) = 0.36, $P < 0.6$. *Post hoc t*-tests revealed that there was a significant difference between sessions 1 and 3 ($P < 0.002$) and between sessions 1 and 2 ($P < 0.006$) but not between 2 and 3.

The results show that the score on the same/different words test was significantly different across sessions F (1.5,26)=7.7, $P < 0.005$ using a Greenhouse Geisser correction for non-sphericity. There was a significant effect of lesion F (1,17) = 11, $P < 0.005$. *Post hoc t*-tests revealed that there was a significant difference between

sessions 1 and 3 ($P < 0.019$) but not between sessions 2 and 3 or 1 and 2. This suggested that improvement could not be attributed to therapy.

The results show that the score on the same/different word discrimination test (treated items only) was significantly different across sessions F (2,34) = 8.8, $P < 0.001$. There was a significant effect of lesion F (1,17) = 10, $P < 0.006$. *Post hoc t*-tests revealed that there was a significant difference between session 1 and 3 ($P < 0.006$) and session 2 and 3 ($P < 0.04$) but not between sessions 1 and 2. This suggested that improvement could be attributed to therapy.

The results show that the score on the same/different word discrimination test (untreated items only) was not significantly different across sessions F (2,34) = 1.7, $P < 0.2$. There was no significant effect of lesion, although this was approaching significance F (1,17) = 4.1, $P < 0.06$.

The results show that the score on the minimal pair discrimination test was significantly different across sessions F (2,32) = 5.2, $P < 0.02$. There was no significant effect of lesion F (1,16) = 1, $P < 0.4$. *Post hoc t*-tests revealed that there was a significant difference between sessions 1 and 3 ($P < 0.014$) but not between sessions 1 and 2 or between 2 and 3.

The results show that the score on the minimal pair discrimination (treated items) test was significantly different across sessions F (1.5,24) = 4.2, $P < 0.04$ using a Huyn-Feldt correction for sphericity. There was no significant effect of lesion F (1,16) = 2.2, $P < 0.16$. *Post hoc t*-tests revealed that there was a significant difference between sessions 1 and 3 ($P < 0.02$) but not between sessions 1 and 2 or between 2 and 3.

The results show that the score on the minimal pair discrimination (untreated items) test was significantly different across sessions F (2,32) = 3.9, $P < 0.03$. There was no significant effect of lesion F (1,16) = .04, $P < 0.9$. *Post hoc t*-tests revealed that there were no significant differences between sessions 1 and 3 sessions 1 and 2 or between 2 and 3.

The results show that the score on the maximal pairs same/different discrimination test was significantly different across sessions F (2,32) = 4.4, $P < 0.03$. There was a significant effect of lesion F (1,16) = 5.5, $P < 0.035$. *Post hoc t*-tests revealed that there was a significant difference between sessions 1 and 3 ($P < 0.012$) but not between sessions 2 and 3 or 1 and 2. This suggested that improvement could not be attributed to therapy.

The results show that the score on the maximal pairs same/different discrimination test (treated items only) was not significantly different across sessions F (2,32) = 1.5, $P < 0.3$. There was no significant effect of lesion F (1,17) = 5, $P < 0.06$.

The results show that the score on the maximal pairs same/different discrimination test (untreated items only) was not significantly different across sessions F (2,34) = 2.4, $P < 0.2$. There was a significant effect of lesion F (1,17) = 6.1, $P < 0.03$.

3.3.3.2 Repetition skills

The results show that the score on the word repetition test was significantly different across sessions F (2,30) = 5.2, $P < 0.02$. There was a significant effect of lesion F (1,15) = 12.2, $P < 0.003$. *Post hoc t*-tests revealed that there was a significant difference between session 1 and 3 ($P < 0.024$) but not between sessions 2 and 3 or 1 and 2. This suggested that improvement could not be attributed to therapy.

The results show that the score on the nonword repetition test was significantly different across sessions F (2, 32) = 6.6, $P < 0.004$. There was no significant effect of lesion F (1,16) = 1, $P < 0.6$. *Post hoc t*-tests revealed that there was a significant difference between sessions 1 and 3 ($P < 0.006$) but not sessions 2 and 3 and 1 and 2.

The results show that the score on the nonword repetition test (treated) was significantly different across sessions F (2, 34) = 6.3, $P < 0.005$. There was a significant effect of lesion F (1,17) = 6.8, $P < 0.02$. *Post hoc t*-tests revealed that there was a significant difference between sessions 1 and 3 ($P < 0.006$) but not between sessions 2 and 3 or sessions 1 and 2.

The results show that the score on the nonword repetition (untreated items only) was not significantly different across sessions F (1.3,18) = 0.03, $P < 0.9$, using a Huynh-Feldt correction for non-sphericity. There was no significant effect of lesion F (1,14) = 0.82, $P < 0.4$.

3.3.3.3 Untreated language skills

The results show that the score on the picture description test was not significantly different across sessions F (1.4,21) = 2.8, $P < 0.08$ using a Greenhouse Geisser correction for non-sphericity. There was no significant effect of lesion F (1,15) = 0.6, $P < 0.5$.

The results show that the score on the naming test was significantly different across sessions F (2,32) = 3.6, $P < 0.04$. There was a significant effect of lesion F (1,16) = 15.8, $P < 0.001$. *Post hoc t*-tests revealed that there was no significant difference between session 1 and 3, 2 and 3 or 1 and 2.

The results show that the score on the single word comprehension test was not significantly different across sessions F (2,30) = 1.1, $P < 0.35$. There was no significant effect of lesion F (1,15) = 3.5, $P < 0.08$.

The results show that the score on the written word comprehension test was not significantly different across sessions F (2, 24) = 1.2, $P < 0.4$. There was a significant effect of lesion F (1,12) = 10, $P < 0.009$.

The results show that the score on the TROG was not significantly different across sessions F (1.4,19.6) = 3.3, $P < 0.08$ using a Greenhouse Geisser correction for non-sphericity. There was a significant effect of lesion F (1,14) = 16, $P < 0.001$.

3.3.3.4 Summary of repeated measures analysis

In summary the repeated measures analysis revealed that whilst numerous tests showed a significant improvement across sessions, only same/different nonword discrimination and same/different word (treated items) discrimination showed a significant difference in the *post hoc* tests between sessions two and three and so can

therefore be confidently attributed to the effects of therapy. In addition in same/different nonword and word discrimination, maximal pair same/different discrimination, word repetition, TROG and naming there was a significant effect of lesion (*i.e.* involvement of the frontal lobe in the lesion). However, in picture description, single word comprehension and written word comprehension, minimal pair discrimination and nonword repetition there was no effect of lesion location.

3.3.4 Patients: Outcome of Therapy: Summary measures method

To investigate these findings further, an alternative analysis was carried out described in the methods section as the 'summary measures method'. This was done for two reasons, first, to be sure that any significant change in *post hoc* tests were a positive one, and second, as Matthews and colleagues have argued, an additional confound when interpreting longitudinal results using *t*-tests (such as used in *post hoc* tests of a repeated measures analysis) is that it ignores the way in which individuals respond over time, which is clinically very useful information. They suggest that by using a summary measure the individual is considered, and the summary measure captures some aspect of that individuals response curve. By comparing performance in this way against both 'linear' co-efficients (-1, 0, 1) and 'change due to therapy' co-efficients (1, -2, 1), significant results can be confidently attributed to either a non-specific linear change or a change due to therapy.

Initially all patients were included in the analysis to investigate changes across the entire group of patients regardless of lesion localisation. The assessments were separated into three areas, auditory discrimination (skills targeted directly by the therapy), general language scores (assessments not targeted specifically by the therapy) and repetition (skills implicated in the therapy programme but not expected to change). Then the specificity of the therapy, in terms of lesion localisation, was investigated by separating the group into patients with and without frontal lobe involvement. For assessments that showed a significant improvement, they were further investigated to determine the extent of generalisation from treated items to untreated items.

3.3.4.1 Outcome of Therapy: All Patients (n=19).

3.3.4.1.1 Auditory Discrimination Skills

There were significant linear improvements in performance on maximal and minimal pair discrimination, same/different discrimination nonwords and words. When improvements due to therapy only were considered there were no tests that demonstrated a significant improvement (*Table 3.6*).

3.3.4.1.2 Repetition

There were significant linear improvements in performance on single word and non-word repetition. When improvements due to therapy only were considered there were no tests with significant change, although word repetition was approaching significance.

3.3.4.1.3 Untreated Language Skills

There were significant linear improvements in performance on spoken sentence comprehension (TROG) but not written and spoken word comprehension or picture description. However, when improvements due to therapy only were considered there were no tests that showed significant changes, although written word comprehension was approaching significance (*Table 3.6*).

	Linear improvements						Improvements due to therapy					
Assessment	*Mean*	*SD*	*t*	*dof*	*P*		*Mean*	*SD*	*t*	*dof*	*P*	
Picture Description	4.4	11.9	1.5	16	0.07	~	2.0	13.3	0.6	16	0.3	
Sp. word - picture matching	1.2	8.1	0.6	15	0.3		-1.9	12.6	-0.6	15	0.3	
Written word comprehension	2.6	12.5	0.8	13	0.3		7	16.8	1.6	13	0.07	~
TROG	8.4	12.3	2.7	15	0.008	*	-2.4	15.3	-0.6	15	0.3	
Word repetition	15.4	19.8	3.1	15	0.003	*	20.1	57.3	1.4	15	0.09	~
Nonword repetition	12.6	11.5	4.7	17	0.000	*	4.5	21.3	0.9	17	0.2	
Max. pair same/diff	7.1	8.2	3.7	17	0.000	*	3.7	20.1	0.8	17	0.2	
Minimal pair discrimination	6.9	7.3	4.0	17	0.000	*	-0.3	13.2	-0.1	17	0.5	
Same/diff: Nonwords	12.3	12.2	3.8	18	0.000	*	3.6	17.9	0.9	18	0.2	
Same/diff: Words	9.2	17.4	2.3	18	0.02	*	0.6	8.6	0.2	18	0.4	

Table 3.6 *Linear (left hand column) and treatment (right hand column) effects of therapy for all participants. Assessments are separated in colour bands according to the extent to which they were predicted to be targeted by the therapy; directly targeted by therapy (dark purple), involved in therapy but with no feedback (light purple) and not directly targeted by therapy (grey). * Significance level of P < 0.05, ~ approaching significance. Mean= mean percentage improvement of the group, SD= standard deviation, dof= degrees of freedom used, P= p-value using a one sample t-test (one-tailed).*

Subject	Test 1	Test 2	Test 3
CV	89 (87)	89 (84)	94 (98)
CG	94 (91)	97 (95)	96 (98)
DD	68 (57)	72 (70)	83 (69)
FC	100 (100)	70 (84)	93 (95)
HV	98 (98)	97 (97)	100 (100)
LRa	94 (96)	92 (89)	93 (98)
LR	75 (83)	83 (79)	92 (95)
MJ	100 (100)	97 (98)	94 (93)
RC	69 (61)	64 (63)	89 (90)
SS	97 (100)	97 (95)	100 (100)
TK	100 (100)	97 (100)	94 (98)
TA	92 (95)	94 (100)	99 (100)
YK	100 (100)	97 (100)	99 (100)

Table 3.7*: Raw scores across three sessions on same/different discrimination for patients with a posterior lesion only. Score in brackets are treated items only.*

3.3.4.2 Outcome of Therapy: Patients with only a Posterior Lesion (n=13).

3.3.4.2.1 Auditory Discrimination Skills

There were significant linear improvements in performance on maximal and minimal pair discrimination, same/different discrimination nonwords and words. However, when improvements due to therapy only were considered, only same/different discrimination of words showed a significant improvement t (12) = 1.82, $P < 0.05$. To investigate generalisation of this skill to untreated items, the items were divided into those that had been treated versus those that were untreated. There was a significant improvement in treated items, t (12) = 2.2, $P = 0.02$ but not on untreated items, t (12) = 0.9, $P > 0.2$. There was also no significant difference between the total number of 'same' responses versus the number of 'different' responses using a paired samples t-test (2 tailed): t (12)=0.81, $P > 0.4$.

All the tests were also combined to given a mean 'discrimination' score at each time point. Using this more general score, there were both significant linear (t (12)= 4.9, $P < 0.0001$) and treatment-specific (t (12)= 1.9, $P < 0.04$) improvements.

3.3.4.2.2 Repetition Skills

There were significant linear improvements in performance on single word and non-word repetition. However, when improvements due to therapy only were considered

there were no tests with significant change (*Table 3.6*), although word repetition was approaching significance.

All the tests were also combined to given a mean 'repetition' score at each time point. Using this more general score there were significant linear improvements (t (12)= 5, P < 0.0001) but no treatment specific improvements (t (12)= 1.6, P < 0.1).

3.3.4.2.3 Untreated Language Skills

There were significant linear improvements in performance on the TROG but not spoken and written word comprehension or picture description, although these were approaching significance. However, when improvements due to therapy only were considered there were no tests that showed significant changes (*Table 3.8*), although written word comprehension was approaching significance.

All the tests were also combined to given a mean 'discrimination' score at each time point. Using this general score, linear improvements were approaching significance (t (12)= 1.7, P < 0.06) but not treatment specific improvements (t (12)= 1.3, P < 0.1).

	Linear improvements						Improvements due to therapy					
Assessment	*Mean*	*SD*	*t*	*dof*	*P*		*Mean*	*SD*	*t*	*dof*	*P*	
Picture Description	5.9	13.1	1.6	12	0.07	~	2.4	15.3	0.6	12	0.3	
Sp. word to picture match	-2.0	2.8	-2.3	9	0.02	*	1.2	7.3	0.5	9	0.3	
Writ. word comprehension	2.6	5.9	1.4	9	0.09	~	5.4	11.4	1.5	9	0.08	~
TROG	10.8	13.7	2.6	10	0.01	*	0.6	17.0	0.1	10	0.5	
Word repetition	13.6	19.2	2.4	10	0.02	*	18.2	36.3	1.6	10	0.07	~
Nonword repetition	14.8	12.3	4.3	12	0.000	*	2.8	24.6	0.4	12	0.3	
Maximal pair same/diff.	6.6	6.2	3.9	12	0.001	*	2.0	21.0	0.3	12	0.4	
Minimal pair discriminat.	7.5	8.2	3.3	12	0.003	*	0.6	12.1	0.2	12	0.4	
Same/diff: Nonwords	9.0	13.4	2.4	12	0.02	*	5.4	16.5	1.2	12	0.1	
Same/diff: Words	**3.9**	**8.8**	**1.6**	**12**	**0.07**	~	**8.0**	**15.8**	**1.8**	**12**	**0.04**	*
Same/diff: W (T)	**5.1**	**9.5**	**1.9**	**12**	**0.04**	*	**7.9**	**12.8**	**2.2**	**12**	**0.02**	*
Same/diff: W (NT)	0.2	8.7	0.1	12	0.5		7.9	33.0	0.9	12	0.2	

Table 3.8 *Linear (left hand column) and treatment (right hand column) effects of therapy for patients without frontal lobe involvement. Assessments are separated in colour bands according to the extent to which they were predicted to be targeted by the therapy; directly targeted by therapy (dark purple), involved in therapy but with no feedback (light purple) and not targeted by therapy (grey). Mean =*

*mean percentage improvement of the group, SD = standard deviation, dof= degrees of freedom used, P = p-value using a one sample t-test (one-tailed). * Significance level of P < 0.05, ~ approaching significance.*

3.3.4.3 Outcome of Therapy: Patients with a Lesion involving the Frontal Lobe (n=6).

3.3.4.3.1 Auditory Discrimination Skills

There were significant linear improvements in performance of minimal pair discrimination, same/different discrimination nonwords and words. However, when improvements due to therapy only were considered there were no significant improvements (*Table 3.9*).

All the tests were also combined to given a mean 'discrimination' score at each time point. Using this more general score, linear improvements were approaching significance (t (5) = 2, $P < 0.05$) but there were no treatment specific improvements (t (5) = 0.3, $P > 0.3$).

3.3.4.3.2 Repetition

There were significant linear improvements in performance on non-word repetition and word repetition was approaching significance. However, when improvements due to therapy were considered, only nonword repetition remained borderline significant (*Table 3.8).* All the tests were also combined to given a mean 'repetition' score at each time point. Using this more general score, there was a significant linear improvement (t (4) = 3.7, $P < 0.02$) but there were no treatment specific improvements (t (4) = 0.8, $P > 0.2$).

3.3.4.3.3 Untreated Language Skills

There were no significant linear improvements or improvements due to therapy in performance on spoken word comprehension, written word comprehension or picture description (*Table 3.9*). There were no significant linear or therapy improvements on the TROG; however, there was a significant negative performance on this test as a response to therapy. All the tests were also combined to given a mean 'comprehension' score at each time point. Using this more general score there were also, not surprisingly, no significant linear improvements (t (5) = 0.05, $P > 0.4$) or treatment specific improvements (t (5) = 0.9, $P > 0.2$).

	Linear improvements						Improvements due to therapy					
Assessment	*Mean*	*SD*	*t*	*dof*	*P*		*Mean*	*SD*	*t*	*dof*	*P*	
Picture Description	-0.4	4.6	-0.2	3	0.4		0.9	1.7	1.1	3	0.1	
Sp. word to pict. matching	7	11.3	1.4	5	0.1		-7.2	18.0	-1.0	5	0.2	
Written word comp.	3	24	0.2	3	0.4		11	28.3	0.8	3	0.3	
TROG	3	6.7	1	4	0.2		-9	8.9	-2.3	4	0.04	
Word repetition	25.3	24.0	2.3	3	0.06	~	16.3	24.0	-1.4	3	0.1	
Nonword repetition	7.1	7.4	2.2	4	0.05	*	8.7	9.3	2.1	4	0.05	~
Maximal pair same/diff	8.2	12.9	1.4	4	0.1		8.2	18.9	1.0	4	0.2	
Minimal pair discriminat.	0.5	4.2	2.9	4	0.5		-2.6	7.2	-0.3	4	0.4	
Same/diff: Nonwords	19.3	14.5	3.3	5	0.01	*	-0.3	21.9	-0.04	5	0.5	
Same/diff: Words	24.6	28.1	2.2	5	0.04	*	-7.6	22.8	-0.8	5	0.2	

Table 3.9 *Linear (left column) and treatment (right column) effects of therapy for patients whose lesion involves some frontal lobe. Assessments are separated in colour bands according to the extent to which they were predicted to be targeted by the therapy; directly targeted by therapy (dark purple), involved in therapy but with no feedback (light purple) and not directly targeted by therapy (grey). Mean= mean percentage improvement of the group, SD= standard deviation, dof= degrees of freedom used, P= p-value using a one sample t-test (one-tailed). *Significance level of P<0.05, ~ approaching significance.*

3.3.5 Patients: Self-monitoring Correlations

The accuracy of the repetition component of the fourth task was self-judged by the participant. To provide a measure for this self-monitoring ability we compared the number of errors recorded (*i.e.* the number of times the participant judged their repetition attempt as incorrect) to their actual performance of a test of word repetition. A percentage error score was derived ((number of errors recorded/ number of trials completed)*100). There was no correlation between this percentage error score and the patient's performance on a test of repetition (r = -.35, P > 0.1).

3.3.6 Healthy Volunteers: Tolerance and Compliance

Healthy participants were asked to spend a total of one hour per day, for two weeks on the computer training programme, so a total of 14 hours. One participant's data was not available due to technological issues. The PCs logged the actual time spent, and the mean was considerably less: 8.7 (SD ± 6.5) hours. As evident from the large standard deviation, the range of compliance was very variable (1.9- 24.6 hours). The total level reached and the number of trials completed at each level by each

participant is shown in *Figure 3.5*. No participants progressed to the final three levels, two progressed to the eighth, three to the fifth, sixth and seventh level, four to the fourth level, thirteen to the second and third level and only one subject did not move beyond the first level.

The first five healthy participants experienced intermittent technical difficulties with the programme, resulting in temporary cessation of progression from one task to the next. Task progression was easily resumed by all but one participant. I was required to carry out a home visit in order to teach this participant how to dismiss the error message; this visit was carried out less than 12 hours of the error being reported. The programme was subsequently amended and the remaining 14 participants did not experience this technical error. Using an independent samples *t*-test, there was no significant difference between the amount of time spent on therapy for those who used the initial programme ($M = 7.2$, $SD = 2.2$) and those using the final programme ($M = 9.4$, $SD = 7.8$); $t\ (14) =. 604$, $P = 0.56$ [95% *CI* -5.6 to 9.9].

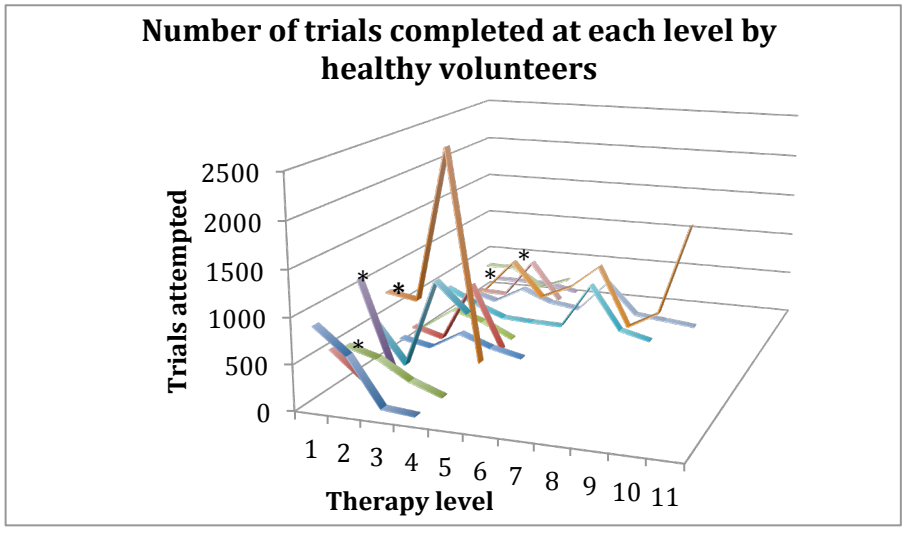


Figure 3.5 *3-D line graphs depicting the variability in the number of trials completed by each healthy participant at each training level (1-12). X-axis = training levels, Y-axis = number of trials. Lines marked with an * denote participants using the original training programme.*

3.3.7 Healthy Volunteers: Outcome of Behavioural Training

The on-line behavioural performance from the scanning sessions was used to investigate the healthy participants changes in ability to understand vocoded speech. Not surprisingly participants were better at repeating after listening to normal speech trials (ListNorm) than listening to vocoded speech trials (ListVoc) both before and after training; before training, using the combined semantic and articulation score as the measure: t (15) = 13; two-tailed; $P < 0.001$; [95% CI = 42.6 to 59.4], and after training: t (16) = 11.6, two-tailed; $P < 0.001$ [95% CI = 28.2 to 40.7].

The training programme, aimed at improving auditory perception and lexical recognition of three-channel noise-vocoded speech, demonstrated a difference between performance on pre- and post- training repeating vocoded speech trials (RepVoc) trials for all behavioural measures (articulation, semantic and the combined score). Thus, on the combined score, the mean improvement on noise-vocoded stimuli was 15.5%, an improvement that was significant: t (15) = 6.44, $P < 0.001$, two-tailed [95% CI = 10.4 - 20.6]. On the semantic score, the mean improvement on noise-vocoded stimuli was 17%, an improvement that was significant: t (15) = 7.81, $P <$ 0.001, two-tailed [95% CI = 12.5 – 22] and on the articulation score mean improvement on noise-vocoded stimuli was 10%, an improvement that was not significant: t (15) = 1.81, $P < 0.09$, two-tailed [95% CI = -1.9 – 22.5].

Predictably, there was no difference on repeating normal speech trials (RepNorm) trials (M = 1.1%) as the result of training. Performance was at ceiling at both time-points: t (16) = 1.5, $P > 0.1$, two-tailed [95% CI = -0.4 to 2.5] for the combined scores, t (16) = 1.5, $P > 0.1$, two-tailed [95% CI = -0.3 to 1.8] for the separate semantic scores and t (16) = 2.2, $P = 0.05$, two-tailed [95% CI = 0.02 to 1.8] for the separate articulation scores.

3.3.7.2 Correlations Between Amount of Therapy and Improvement.

In healthy volunteers the amount of time spent on training was correlated with the improvement (session two minus one) on in-scanner, on-line scores (r =.51, $P < 0.05$). However there was no correlation between time spent on therapy and improvement on in-scanner scores in patients, either using the same measure as the healthy volunteers (*i.e.* session three minus two) (r =-.035, $P > 0.8$), or the 'improvement due to therapy'

score based on the summary statistic described in section 3.3.3 (r =.95, P > 0.7). This lack of correlation was also evident when the frontal patients were excluded from the correlation between hours spent on therapy and both in-scanner change (r =.1, P > 0.7) and same/different discrimination (r =-.3, P > 0.2).

3.3.8 Outcome of Therapy: Between Group Comparisons

When comparing the combined online in–scanner scores (articulation and semantics) on RepNorm trials in the patients with the RepVoc in the healthy participants, an independent-samples *t*-test with equal variances not assumed, showed there was no difference between groups at sessions two and one respectively (t (22.7) = 1.7, P > 0.1) or sessions three and two respectively (t (20.3) = -.1, P > 0.8). However, there was a significant difference between RepNorm trials in the patients and the RepNorm trials in the healthy participants, an independent-samples *t*-test with equal variances not assumed, showed there was a difference between groups at session two and one respectively (t (15) = -4.7, P < 0.001) and session three and two respectively (t (16.1) = -4.6, P< 0.001). Therefore the aim of making the task approximately comparable in difficulty in patients and healthy participants was achieved (*Figure 3.6*).

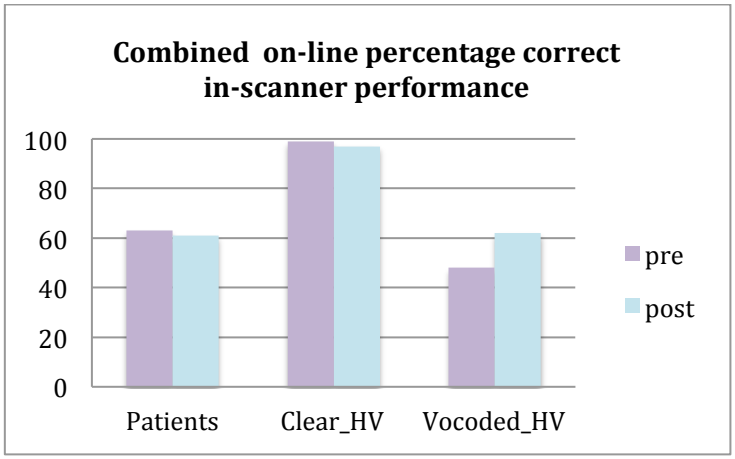


Figure 3.6 *Mean in-scanner performance of patients, healthy volunteers repeating clear speech and healthy volunteers repeating vocoded speech, before training (lilac) and after training (blue).*

3.3.9 Summary of Results

3.3.9.1 Patients

There was no improvement observed in on-line in-scanner performance or on the majority of behavioural assessments. When considering individual assessments using

the repeated measures analysis same/different nonwords and words (treated item only) discrimination improved specifically due to therapy. Also, using this method there were significant effects of lesion location on the performance of various tests including; same/different words and nonwords, maximal pair discrimination, word repetition, naming, written word comprehension and the TROG.

However, when the summary methods analysis was used only same/different discrimination of treated items demonstrated an improvement. When all assessments were combined to produce separate 'overall' scores for auditory discrimination, repetition, auditory comprehension and production, only auditory discrimination showed a significant improvement and this was in patients with a posterior lesion only.

Using this method, when the population of patients were divided into those with and without frontal lobe involvement, the response to treated same/different therapy items was quite different in the two groups. The 13 patients with infarction confined to the temporo-parietal region improved significantly in response to therapy when using a one-sample *t*-test (*M*=7.9, *SD*=12.84; *t* (12)=2.2, *P*=0.024, [95% *CI*= 1 to 16]. In contrast, those with infarction that included the left frontal lobe, showed no improvement (*M*=3, *SD*=34.9; *t* (5)=0.2, *P*=0.430 [95% *CI*= -34 to 39]. In addition there was no generalisation to untreated items. There was no correlation between the amount of therapy and either in-scanner behavioural change or same/different discrimination score. Therefore using either repeated measures analysis or the more stringent summary measure methods only very specific tests, targeted by the therapy improved due to therapy. No tests that were not targeted by the therapy improved.

3.3.9.2 Healthy Volunteers

Healthy volunteers results demonstrated that the use of vocoded stimuli was sufficiently challenging to induce a group level performance akin to the group level performance observed in patients listening to clear speech. In addition, there was a significant training effect observed in healthy participants ability to understand and repeat vocoded stimuli, where the amount of therapy completed correlated with the improvement observed. As expected there was no training effect for clear speech in the healthy volunteers.

3.4 Discussion

This study has demonstrated that self-administered computer-based SALT is effective within the aims of the therapy. The therapy programme was designed to treat one specific aspect of impaired language processing in aphasia, namely phonological discrimination. In addition the programme was used for a group of healthy volunteers as they trained on noise-vocoded speech, a simulation of the increased difficulty experienced by patients with aphasia during auditory comprehension tasks. The participants were advised on the daily 'dose' of therapy, which was thirty minutes three times per day for patients and two times per day for healthy volunteers. This form of therapy, without continuous supervision, resulted in a large variability in the amount of time spent on the rehabilitation/training programme. There is a lack of established evidence on the compliance of self-administered complex interventions that require a determined effort over time. This study therefore provides important data for the planning of future studies. Despite this variability of total time spent on the programme, the specific target of therapy, auditory discrimination, did significantly improve across the group of patients with temporal and /or parietal lesions, but not in those who had lesions extending into the frontal lobe. However, this *post-hoc* analysis is not conclusive due to the low numbers in the latter group, this is discussed further in Chapter Six. Interestingly, there was no correlation between the time spent on the therapy and the amount of improvement achieved in patients, although it has been asserted in a meta-analysis of multiple aphasia treatment studies that used very different designs, that many hours of therapy are required to achieve a consistent improvement (Bhogal *et al.,* 2003). The approach in this study was to investigate a small group of subjects, all with left temporal infarction and a greater or lesser degree of impairment in auditory discrimination.

This study demonstrates how to effectively manipulate performance of listening to and repeating speech in healthy volunteers so that it matches the performance level of a group of patients with post-stroke aphasia. Using a patient population that was identified based on lesion site, rather than residual cognitive deficits, probably contributed to the heterogeneity of behavioural performance. However, a variable performance was also observed in the healthy volunteers as they repeated the noise-vocoded stimuli. Repetition performance was initially more difficult for healthy

volunteers on noise-vocoded speech than it was for the patients to repeat normal speech with impairment in auditory discrimination. Nevertheless, the healthy participants made greater progress in online in-scanner performance than the patients. Whilst this could reflect the additional domain-general and –specific difficulties experienced by the patients, it more likely reflects the fact that the treatment process itself was different between groups, despite the identical programmes. The healthy participants were learning to map a distorted auditory verbal percept on to an intact auditory 'template', with the top-down support of an intact semantic and lexical system. Patients, however, were attempting to match the heard words on to more or less damaged perceptual 'templates'. This matching process in patients was confounded by additional deficits in top-down contributions from lexical and semantic systems. The presence of these additional deficits may explain why patients improved on the therapy-related assessment (which did not require lexical access) but not sentence comprehension and repetition inside the scanner. The therapy did not target sentence comprehension specifically, but as impaired phoneme discrimination is likely to exacerbate a comprehension deficit (Robson *et al.,* 2012*c*) it is anticipated that a sufficient dose may contribute to improved comprehension.

One obvious concern with these results is that maximal pair same/different discrimination and minimal pair word-picture matching did not improve, despite being targeted by the intervention. This lack of improvement could be due to the fact that these skills were practised less frequently in the therapy than same/different discrimination. It could also reflect that the patients typically found these two tests easier than same/different minimal pair discrimination. In the same/different minimal pair discrimination tasks the patients had no picture to assist with top-down semantic access, which probably assisted in the minimal pair word-picture matching task. Same/different minimal pair discrimination without pictures is purely an auditory task. Lexical information has been shown to be important in the perception of distorted speech (Davis *et al.,* 2005), and in same/different minimal pair discrimination residual lexical skills can only assist perception once access/retrieval has been achieved. However, in word to picture matching tasks some semantic top-down support is available simultaneously with the auditory presentation, so that even with a noisy phonological system intact picture recognition will support access to semantics in this task. Considering that these tests may have been 'too easy', the use

of a more subtle measure of discrimination might have been more useful, such as the one used by Robson and colleagues (2012*b*); although this was developed initially because the patients in their study found the discrimination tasks too difficult due to a more severe comprehension impairment.

As discussed at some length in the introduction, there is considerable debate as to the extent to which auditory discrimination skills and auditory comprehension skills are linked. Ultimately, the aim of any linguistic level therapy should be to contribute to better functional skills, such as sentence comprehension. Therefore, the lack of generalisation of improvement in phonological discrimination to sentence comprehension may seem disappointing. However, with a mean of just 20 hours of auditory discrimination therapy completed, it is perhaps not surprising, as Bhogal and colleagues (2003) have presented evidence that ~100 hours is required before functional gains can reliably be expected. In addition, only two types of sentence structures were used in this therapy (subject + verb + object and subject/object + verb + adjective), so there was limited exposure to a variety of syntactic structures which is likely to be an important aspect of any sentence level comprehension improvement. Somewhat surprisingly, the group of patients with frontal lobe involvement demonstrated a significant decline in performance on sentence comprehension assessments, which was attributed to the intervention specifically and not due to linear changes. It may be that the limited sentence structures used in the therapy impacted on this group's ability to understand a greater variety of sentence structures during assessments. This task inevitably requires additional domain-general skills, which may be affected in this group of patients, and so attending to lower level discrimination requirements of the task may have been at the cost of the additional domain-general mechanisms needed to complete it.

As discussed above, neither the patients, nor the healthy volunteers completed the prescribed amount of therapy. In the healthy volunteers this correlated with their improvement, but this was not the case in the patients. This is an important point for future studies. Subjective feedback from participants across groups suggested that the intervention was not engaging, and many described it as 'boring' after a number of sessions. By targeting such a specific deficit, as in this study, the evidence-based therapeutic techniques available have a limited number of possible variations. One

aim of the therapy design was to make the programme as engaging as possible by frequently varying the tasks. However, with superior software development support additional improvements could have been made, such as making the programme more interactive and game-like or providing a more motivating reward. Expanding the therapy aims to include higher levels of auditory comprehension such as lexical, semantic and even syntactic levels would have also provided more scope for a greater variety of tasks. Although this would have been less specific, with a sufficient dose, it would likely generalise to comprehension and therefore lead to an observed functional improvement.

A first impression is that there was no 'placebo' treatment arm to the study design. However, each patient had many speech and language deficits, not just a single syndrome of 'aphasia'. Many language functions improved linearly, and this can be attributed to practice effects on the test material, a placebo effect and other unknown factors that were not treatment-specific. They are unlikely to be due to spontaneous recovery as all patients participated at least six months post-stroke. In contrast, reliable treatment-related benefit was only observed on one test, and this was one that probed performance on the skill targeted by the therapy. This lack of generalisation to untargeted deficits, such as picture description and written word comprehension, argues strongly against a placebo effect.

Despite the inclusion of repetition in the therapy, repetition skills did not improve as assessed by standardised tests. The auditory and motor processing of language are intimately linked neural functions (Rauscheker & Scott, 2009), and it was a presumption when the study was designed that the requirement to repeat the stimuli during therapy might augment on-line accuracy of auditory phoneme discrimination. However, repetition *per se* was not expected to improve because the patients received no feedback as to their accuracy, unlike the immediate feedback they received for their accuracy on phonological discrimination. Although the participants were able to make self-judgements on their accuracy when repeating, aphasia often impairs post-articulatory self-monitoring (Marshall *et al.,* 1998; Nickels & Howard, 1995), and it was apparent in this study that actual performance on a test of repetition did not correlate with the participants' over-optimistic self-assessment of their accuracy. As participants might have expected their skill at repetition to improve, as it was included

in the therapy programme, repetition was a 'sham' treatment, and improvement did not occur at both a single word and non-word or at a sentence level.

An important point regarding generalisation concerns the mechanism by which therapy was changing the neural and linguistic system targeted by it. The patient group demonstrated a significant improvement on treated items of same/different discrimination tasks only, that is, the therapy did not generalise to novel, untreated items. This was disappointing as it suggests that therapy was not improving a 'mechanism' but rather individual items only, which is much less efficient for the patient. This lack of generalisation could again be partly explained by the insufficient dose. Davis and Johnsrude (2007) propose that learning to understand noise-vocoded speech is achieved by 'retuning' acoustic-phonetic feature representations that are shared among multiple lexical items, permitting generalisation to untreated stimuli. Whilst this may well have been the case in the healthy volunteers in this study, given their ability to generalise to the untreated in-scanner items, this cannot be the case for patients given their lack of generalisation. In patients it may be that the representations cannot be 'retuned' as they no longer exist due to the lesion, and so need re-establishing, or that the links between these shared representations are no longer intact. It may indicate that the therapy was either creating or strengthening existing whole word templates, or strengthening the access to these templates. It is beyond the data in this study to determine what mechanism was taking place but from a therapeutic perspective it suggests that future therapy may need to be item specific. This does not make intervention futile, but does dictate that the items selected for therapy should be ones that are likely to occur in the participant's everyday language and so be useful to them. Aside from the additional time and effort associated with this type of 'core vocabulary' approach (something that the use of computers may make less problematic), there are no therapeutic reasons not to implement this item specific approach. Many published studies of therapy emphasise the need to use stimuli that are salient to the patient (Meizner *et al.,* 2005) in order to maximise motivation and usefulness. In paediatrics, a 'core vocabulary' approach has been shown to be more beneficial to children with 'inconsistent' errors than 'consistent' ones (Crosbie *et al*., 2005), but this has not been explored specifically in adults.

There are two methodological issues with the study presented here. First, any age-related sensorineural hearing loss will have contributed to perceptual impairment, and a future study should include the results from pure tone audiometry as a regressor to ensure that partial deafness did not have a significant impact on the response to therapy. This is particularly important when the populations under investigation contain relatively small numbers of subjects. However, the subjects were able to adjust the level of loudness of the training stimuli, so it seems unlikely that partial deafness exerted a covert influence on the results. Second, there was no late follow-up assessment to investigate the persistence of improvement, or even carry-over to other domains once one skill was functioning more effectively. Similarly, the healthy volunteers did not have two pre-treatment assessments, and so in this group it was not possible to disambiguate linear improvements in performance from pre- and post-treatment improvements.

As the treatment effect did not generalise to more general measures of language skills, this study emphasises the need for intervention to target specific components of impaired language processing, and not attempt to treat post-stroke aphasia as a single disorder. Trials should perhaps be limited to patients who share both a common lesion site and a common impairment and, perhaps more importantly, are motivated to participate. In these regards, behavioural therapy cannot be judged by the standards of conventional drug trials. Taking a pill requires minimal effort, and if the drug is largely free of side effects and is used to treat a common condition, then even a small treatment effect is desirable. This justifies trials on large numbers of participants. In contrast, behavioural therapy will not be effective unless the participant puts in considerable effort over many hours, and a small effect size may not be perceived as being worthwhile and compliance will be poor. Therefore, a reasonably large effect size is required, and if this is not evident in small numbers of participants then further recruitment to produce a small, yet significant benefit is not justified (Friston, 2012).

3.4.1 Strengths and Weakness in Relation to other Studies

This is the first rehabilitation study to use computer-based rehabilitation of phonological discrimination deficits in patients with chronic post-stroke aphasia. Previous studies that have investigated the use of computer-based therapy for reading disorders (Katz & Wertz, 1997; Cherney, 2012), writing disorders (Seron *et al*., 1980;

Mortley *et al*., 2001), naming therapy and/word-finding (Mortley *et al*., 2004; Ramsberger & Marie, 2007; Pederson *et al*., 2001; Doesburgh *et al*., 2004; Lagarno *et al*., 2006; Palmer *et al*., 2012; Fink *et al*., 2010) and the production of speech sounds (Reeves *et al*., 2007; Lee *et al*., 2010) and spoken sentences (Linebarger *et al*., 2001). These previous studies have typically used a smaller numbers of subjects than in this study and have not targeted auditory comprehension at any level, including phonological discrimination. This is the first of such studies to consider lesion location as a determinant of success in therapy, illustrating that those patients with a lesion affecting the temporal +/- the parietal lobe, but excluding the frontal lobe are more likely to benefit.

This study also informs us about the need to ensure that the computer programme is engaging and appealing, in order to ensure that this self-administrating method of delivering therapy meets the aim of providing a sufficient dose. This technology provides the means to deliver such a dose, but it remains essential that in doing so the likelihood of compliance is maximised, through the use of better graphics, sound quality and interactivity, available to a more skilled software developer. In addition, the therapy presented here is perhaps more specific than some previous computer based therapies, and so may be considered less engaging as the tasks are more repetitive; this specificity does, however, allow conclusions to be drawn about specific areas of improvement.

This study cannot contribute to the debate about the extent to which discrimination and comprehension deficits are linked. There was no evidence that comprehension improved as a result of improving phonological discrimination in this study. However, this null result cannot be used to infer that the two are not linked, as this absence of evidence could be due to both an inadequate dose being administered and the use of assessments that did not accurately capture the extent of the deficit, unlike that used by Robson and colleagues (2012*b*). Morris and colleagues (1996) found a similar lack of generalisation to comprehension measures. The study by Maneta and colleagues (2001) reported no improvement after a similar therapy and suggested that this could be due to their patient having a more severe deficit. These authors also suggest that ‘more extensive therapy would achieve more extensive change’. However, they qualify this by stating that ‘simply arguing for more therapy fails to

take account of clinical reality'. Whilst this is indeed true, this study has demonstrated that providing an adequate dose is not an insurmountable problem, and needs to be provided before an intervention is deemed ineffective. The study presented here expanded on those by Morris and Maneta and their colleagues by both increasing the amount of therapy possible, through utilising computer-based delivery and it also, more importantly, demonstrated that this therapy is effective across a larger group of patients, defined by their lesion location.

3.4.2 Possible Implications from the Study

In the United Kingdom, one-to-one therapy is constrained by an increase in referrals to 'treat aphasia' and a decline in the amount of therapy time available (Code and Heron, 2003). The amount of therapy required to achieve benefit is likely to be many tens of hours, delivered intensively, and this is not practical given the current caseloads of a typical speech and language therapist. Self-evidently, access to therapy can never improve without considerable additional funding, or unless it is either delivered as group sessions or through utilising modern technology in order to considerably increase the time spent on therapy whilst maintaining the current levels of practitioner availability. This study has demonstrated that home-based computer-delivered therapy, with time-limited specialist support, can deliver a considerable amount of therapy, as long as the patient is motivated by the therapy. The use of this technology necessitates collaboration between a speech and language therapist and a software development professional, in order to ensure the software is sophisticated enough to remain engaging whilst also ensuring programmes use current best evidence available to plan the actual therapy component of the software.

This therapy targeted a phonological discrimination deficit, which is associated with lesions involving the posterior temporal region. The perception of phonetic differences depends primarily on auditory processing, but it also involves making a decision about whether a pair of words is matched, and so relies on domain-general systems encompassing attention, decision-making, conflict resolution and error monitoring. These processes involve frontal networks that include the frontal operculum and anterior insula, regions involved in the patients with additional frontal infarction. Patients with more extensive lesions that involved much of the middle

cerebral artery region including the frontal lobe had much lower skills in all domains, not just auditory discrimination. Clinical skill suggests that targeting therapy at this level of impairment would not be the priority for these patients. This suggests that when the treatment was more targeted in terms of lesion location, that is, excluding patients whose infarct may affect task-dependent domain-general cognitive functions, it resulted in a greater improvement on the behavioural measure. Future research studies should target therapy in terms of both lesion location and deficits. The functional impact of aphasia is important, but considering lesion location may help the therapist to direct patients to either linguistic or pragmatic therapy depending on the extent to which their domain-general cognitive systems are intact. This of course, requires that these domain-general skills be assessed in detail, which can be challenging in aphasic patients (Murray 2012; Fridriksson *et al.,* 2006).

The evidence from this study can be extended into further trials to explore the efficacy of rehabilitating different deficits with self-administered therapy, whilst also factoring in different lesion distributions and determining optimal 'doses' of treatment. With an increasing numbers of trials, power calculations will be progressively precise. Thus, it can be inferred from this study that to further investigate the effect of additional frontal lobe infarction on the rehabilitation of phonological discrimination in participants with temporo-parietal infarction, given the wide confidence intervals encountered in the behavioural data obtained in this study, that ~40 participants would be required in each group to give 95% confidence. Based on the recruitment experience of this study, to recruit 80 participants would require screening approximately 400-500 participants with chronic post-stroke aphasia.

The issues of cost (Thornton, 2012) and dose (Leff & Howard, 2012) are important, and computer-based self-delivered therapy with an automatic log of time spent on therapy addresses both these issues. The consultation and supervision by a speech and language therapist will remain essential, for initial assessment and monitoring of progress and to modify the 'prescription' as appropriate, but importantly the therapist will not need to be present during most of the therapy sessions. The aim would be to treat a number of specific impairments, in the expectation that relatively modest improvements on each programme may result in a greater overall improvement in everyday communication.

4 Investigating Mechanisms of Understanding Distorted Speech in the Healthy Brain

4.1 Aims and Hypotheses

The aims of the study were to investigate:

- The neural regions recruited during listening to both clear and distorted speech.
- The neural regions recruited during repeating previously heard sentences (using both clear and distorted speech).
- Neural changes within these systems as a response to two weeks intensive training

And to directly compare:

- The additional neural regions recruited by healthy volunteers listening to distorted speech versus clear speech, especially within higher-order, fronto-parietal, domain-general systems associated with cognitive control and attention.

It was expected that:

- Normal and noise-vocoded conditions would engage language-specific systems
- Listening to vocoded speech would also engage domain-general systems associated with the additional cognitive 'effort' required.
- A positive response to training would result in changes in the activity within these two broad systems when listening to or repeating noise-vocoded speech.

4.2 Material and Methods

4.2.1 Participants

The inclusion criteria were no history of neurological illness, no sinistrality, or history of dyslexia, no contraindications to MRI and English as the first language. In order to conform to ethics all subjects were aged between 18-85. A total of twenty-one healthy volunteers were recruited for the study. Two of these were excluded due to abnormal

findings on their anatomical scan and two withdrew from the study before completing the training programme. Seventeen subjects' data were acquired for both components of the study (11 females; mean age 60 years; range, 25–82 years). The relatively high mean age was because the subjects' data was used in another study to compare with aphasic stroke patients. The healthy participants had a mean of 15 years of formal education (range 10-20).

4.2.2 Experimental Design

Participants had two fMRI scans, two weeks apart. In between the two fMRI scans they participated in two weeks of home-based computerised behavioural training on discriminating phonological contrasts within noise-vocoded speech. The scanning protocol was identical for each session but used a different set of stimuli. Participants were asked to complete 30 minutes of training using the programme described in section 3.2.2 twice a day. The mean numbers of hours completed (Mean= 8.7 hours, SD ± 6.5, range 1.9- 24.6 hours) by the group was considerably less than requested (14 hours in total). This is discussed in greater detail in Chapter Three.

4.2.3 Scanning Paradigms

The scanning paradigm involved a 'listen-repeat-repeat' design across two runs (run A and B), separated by the acquisition of a structural scan. There were a total of 140 trials in each run (*Figure 4.1*). Participants were presented with Bamford-Kowal-Bench (BKB) sentences (Bench *et al.,* 1979), to which they were required to listen and then repeat in two subsequent trials. Each run consisted of twenty sentences presented using clear speech stimuli, and twenty using stimuli that had been noise-vocoded using three channels (Shannon *et al.*, 1995). Two repeat trials were used to observe the effects of masking auditory feedback with white noise on one of the two repetition trials. This was done as an approximation of the 'noisy' auditory feedback experienced by patients with aphasia. A low level auditory baseline (spaced irregularly between 'listen-repeat-repeat' patterns) of listening to segmented broadband noise bursts (white noise) matched in duration to sentence stimuli was also used. White noise was used as it is a complex sound but contains none of the spectrotemporal structure of speech.

A "sparse" fMRI design was used to minimise movement- and respiratory-related artifact associated with speech studies. Tasks were performed over 5.5 seconds while a visual task prompt was displayed. The disappearance of that prompt and the appearance of a fixation crosshair signalled to the subject to cease the task. Two seconds of data acquisition commenced 0.5 seconds later, during which the crosshair remained present. This was repeated for the duration of each run (*Figure 4.1*).

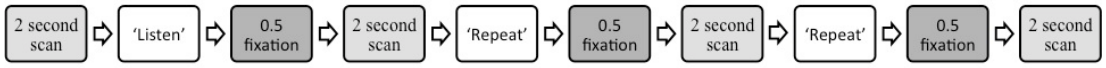


Figure 4.1 *fMRI 'sparse' scanning design used in this chapter.*

4.2.4 Stimuli

BKB sentences (Bench *et al.,* 1979) were used during the fMRI paradigms. These sentences do not contain complex syntax and have a low sentence-end predictability (*i.e.* 'he was buying some bread', where the last word cannot be readily predicted from the beginning of the sentence), which would limit the amount of top-down semantic processing being used to discriminate and understand the sentences. Chapter Three demonstrated that noise-vocoded speech reduces comprehension of simple sentences in healthy volunteers to a similar level to the aphasic speech comprehension deficits observed in the stroke patient population that I recruited. In this current chapter, three-channel noise-vocoded stimuli were used again to attempt to simulate the difficulties in comprehension seen in the patient group but in terms of neural activations, rather than behaviour. In Chapter One, I introduced the idea that even if tasks are manipulated to ensure that patients can perform them at a similar level to healthy volunteers, this matched level of performance might be at the expense of greater cognitive effort. So instead, in the study presented here, I attempted to match the difficulty experienced by the patients in tasks by making the task more difficult for the healthy volunteers by using three-channel noise-vocoded speech. In addition to these distorted stimuli, clear sentences (*i.e.* sentences without vocoding) were also presented to enable a comparison between the magnitude and distribution of activity elicited by the two stimulus types.

4.2.5 Measuring Behavioural Performance

Three scores for each participant's spoken responses during scanning were calculated, these included a semantic score, an articulation score and a combined semantic and articulation score. The combined score was used in order to provide a single score that would incorporate both the semantic and articulation accuracy, it was felt that this would be a fairer single score for all patients, given that they had different abilities in both semantics and articulation.

A semantic score of:

- Five points were scored if the whole sentence was repeated correctly;
- Four points if all the content words were produced but one or more function words were omitted;
- Three if greater than 50% of the content words were produced;
- Two if less than 50% of the content words were produced;
- One if a single appropriate word was attempted;
- Zero if there was no response or fillers only.

The same scoring system was used for the articulation score:

- Five points if the whole sentence was correctly articulated;
- Four points if all the content words were correctly articulated but some function words or inflections were incorrect or omitted;
- Three if greater than 50% of the sentence were correctly articulated;
- Two if less than 50% of the content words were produced;
- One if a single appropriate word was attempted;
- Zero if there was no response or fillers only.

The mean of the semantic and articulation score was calculated to produce the combined score. The scoring system was separated in this way in order to allow later comparisons with patients with post- stroke aphasia who may have had additional difficulties articulating the sentences (this is discussed further in Chapter Five).

4.2.6 Data Acquisition

See Methods section 2.3 for a detailed description of the imaging parameters.

4.2.7 Data Analysis

See Methods section 2.4.2 for a detailed description of the analysis methods.

4.3 Results

4.3.1 Behavioural Performance

Predictably, the participants were better at repeating after listening to normal speech trials (ListNorm) than listening to noise-vocoded speech trials (ListVoc) both before training (t (15) = 13; $P < 0.001$; [95% CI = 42.6 - 59.4]) and after training (t (16) = 11.6, $P < 0.001$; [95% CI = 28.2 - 40.7]). Subjects produced significantly fewer correct words (t (3) = 23.9, $P < 0.0001$) and more incorrect words (t (3) = 13.1, $P < 0.0001$) and omissions (t (3) = 14.9, $P < 0.0001$) when repeating noise-vocoded rather than normal speech. A paired two-sample t-test revealed no significant difference between correct responses in runs A and B (t (6) = 2.45, $P > 0.8$).

The training programme, aimed at improving auditory perception and lexical recognition of three-channel noise-vocoded speech, demonstrated a significant difference between pre- and post- training RepVoc trials for all behavioural measures (articulation, semantic and the combined score). Thus, on the combined score, the mean percentage improvement on noise-vocoded stimuli was 15.5%, an improvement that was significant: t (15) = 6.44, $P < 0.001$, two-tailed [95% CI = 10.4 - 20.6]. Predictably, there was no difference on RepNorm trials (M = 1.1%) as the result of training. Performance was at ceiling at both time-points: t (15) = 1.5, $P > 0.1$, two-tailed [95% CI = -0.4 to 2.5]. These behavioural results are discussed in greater detail in Chapter Three.

4.3.2 Functional MRI Results

4.3.2.1 2 x 2 x 2 ANOVA

The main interest in the fMRI results was the interactions evident in a Task (listening and repeating) x Intelligibility (clear and three-channel noise-vocoded speech) x Session (before and after training) ANOVA. There were no voxels that survived the statistical threshold for the Session x Task, Session x Intelligibility, and Session x

Task x Intelligibility interactions. A Task x Intelligibility interaction (*Figure 4.2*) was observed in the left inferior frontal gyrus (including both *pars opercularis* and *triangularis*) and the anterior insula (IFG/aI), extending up into the middle frontal gyrus (MFG), and in the dorsal anterior cingulate cortex and adjacent superior frontal gyrus (dACC/SFG). There were main effects of Task, Intelligibility but not Session.

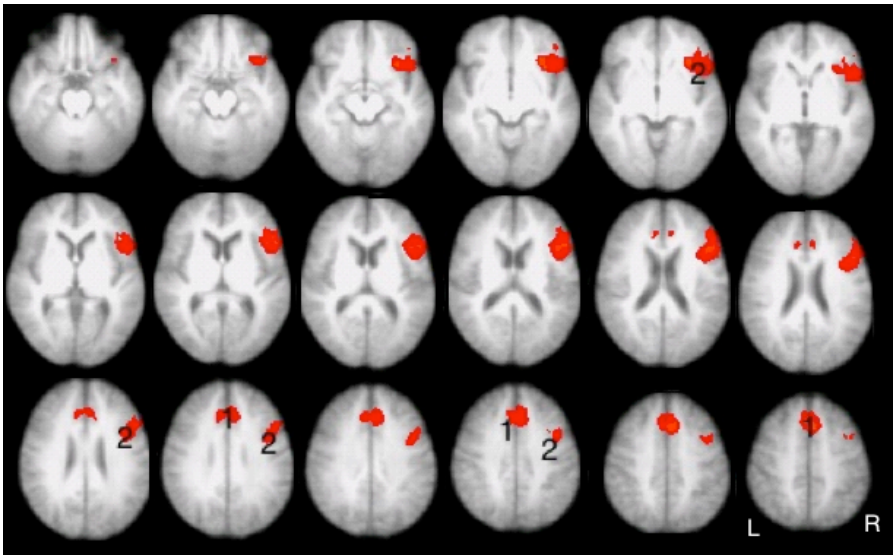


Figure 4.2 *Thresholded Z statistic images for the Task x Intelligibility interaction found in healthy volunteers. All images are thresholded using clusters determined by Z > 2.3 and a (corrected) cluster significance threshold of P = 0.05. Numbers identify activity within (1) the dACC/SFG and (2) IFG/aI*

4.3.2.2 Main Effects of Task and Post hoc Tests

4.3.2.2.1 Main Effect of Task

The main effect of Task demonstrated a network typically associated with the comprehension of heard speech (including primary and association auditory cortices in bilateral STG), and networks involved in speech production (including premotor cortex, primary sensorimotor cortex, bilateral thalami and bilateral paravermal cerebellum). In addition, there was activity in regions associated with both the cingulo-opercular or saliency network (SN), including dorsal anterior cingulate cortex (dACC) and bilateral inferior frontal gyrus/anterior insula (IFG/aI), and the fronto-parietal or central executive network (CEN), including bilateral dorsolateral prefrontal cortex (dlPFC) and dorsal inferior parietal cortex and adjacent intraparietal sulcus (PC). The scan volumes imaged in this study excluded all but the most superior part of the cerebellum. Activation was also observed in the posterior cingulate cortex (pCC) and precuneus and medial temporal structures (the hippocampi, rhinal cortices

and parahippocampal gyri). *Post hoc* contrasts were then carried out to investigate the extent to which each task contributed to the activations within the main effect of task.

4.3.2.2.2 Post hoc: Repetition versus Listening

The comparison of all repetition versus all listening trials (excluding white noise) did not demonstrate any activity. In contrast, bilateral sensorimotor activity was evident in the contrast of the repetition trials with the trials of listening to white noise (ListWhite). In addition, this contrast also revealed activations within the default mode network (DMN): bilateral angular gyri (AG), the precuneus, pCC, anterior medial frontal cortex and medial temporal cortex.

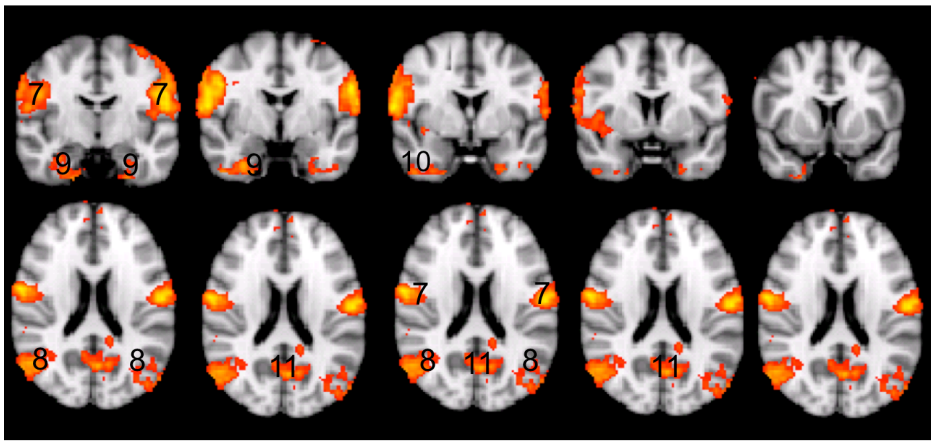


Figure 4.3 *Thresholded Z statistic images for the contrasts of all repeating trials versus listening to white noise. Numbers identify activity within (7) sensorimotor cortex, (8) angular gyrus, (9) parahippocampal gyrus, (10) fusiform gyrus and (11) precuneus/ posterior cingulate cortex.*

4.3.2.2.3 Post hoc: Listening versus Repetition

The activity observed in the contrast of all listening trials (excluding ListWhite) with all repeating trials was observed in bilateral medial premotor (supplementary motor area) and lateral premotor cortices, primary sensorimotor cortices, IFG/aI, the thalami and paravermal cerebellum. There was additional posterior activity within the pCC, bilateral lateral occipital cortices (but not primary visual cortex) and bilateral AG. In the temporal lobes there was activity in both the medial temporal lobes and along the inferior temporal gyri extending as far forward as the signal drop out associated with the susceptibility artefact due to local inhomogeneity of the magnetic field. In more

anterior regions, activity was observed along the length of the middle frontal gyri as far forward as the frontal poles.

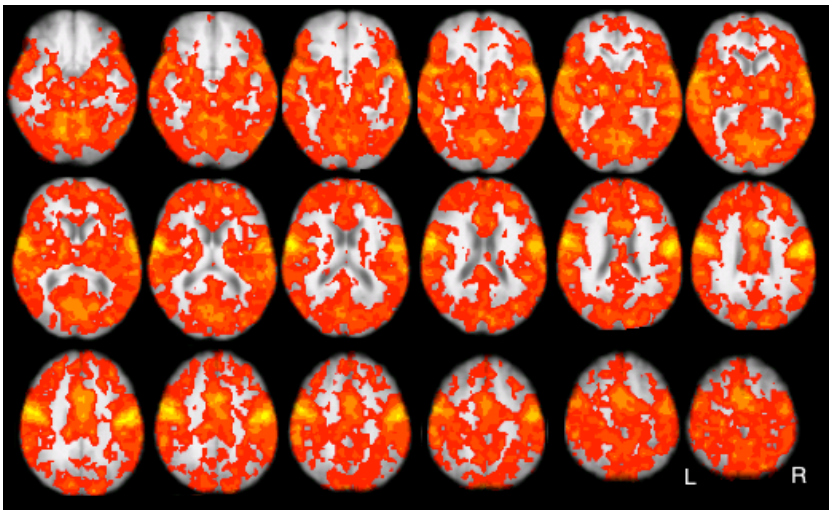


Figure 4.4 *Thresholded Z statistic images for the contrasts of listening (all Listen trials except white noise) versus all repeating trials.*

4.3.2.3 Main Effects of Intelligibility and Post hoc Tests

The main effect of intelligibility (*Figure 4.5*), revealed activity mainly within the SN and the CEN networks as described above. This main effect included both listening and repeating trials, so I conducted *post hoc* tests to contrast intelligibility within the Listen trials only, given that the contrast of the Repetition trials with the Listen trials contained little signal; that is, the Listen trials contained most of the signal of interest.

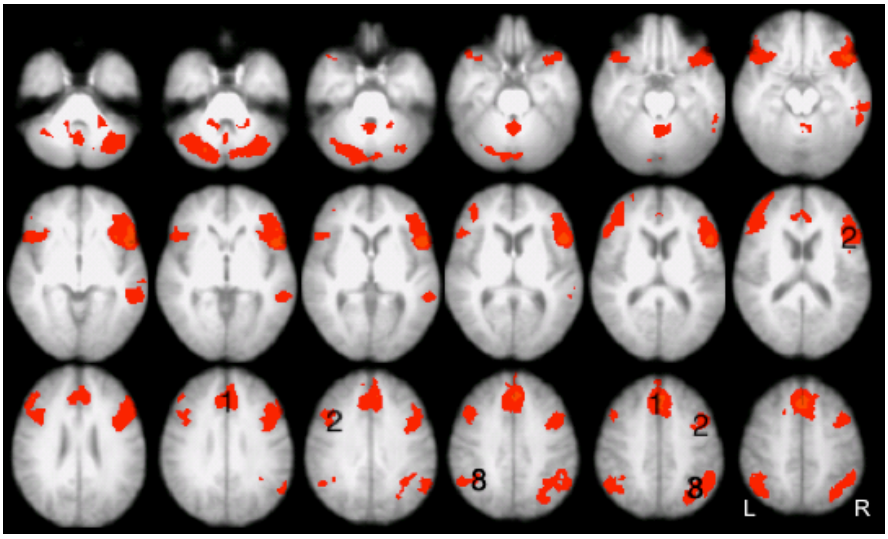


Figure 4.5 *Thresholded Z statistic images for the main effect of intelligibility in healthy volunteers. All Images are thresholded using clusters determined by Z > 2.3 and a (corrected) cluster significance threshold of P = 0.05. Numbers identify activity within (1) the dACC/SFG, (2) IFG/aI, (8) AG*

4.3.2.3.1 Post hoc tests: ListNorm versus ListVoc

The contrast of ListNorm versus ListVoc, averaging the data across both scanning sessions, demonstrated activity in systems usually observed during speech comprehension tasks (bilateral primary and association auditory cortices), speech production tasks and also components of the default mode network (medial ventral prefrontal cortex, pCC and adjacent precuneus).

4.3.2.3.2 Post hoc tests: ListVoc versus ListNorm

The reverse contrast of ListVoc with ListNorm demonstrated activity within the SN and CEN. There was additional activity in the left posterior middle and, to a lesser extent, the inferior temporal regions. Subcortically, there was bilateral activity in the basal ganglia (excluding the anterior striatum) and paravermal and lateral cerebellum.

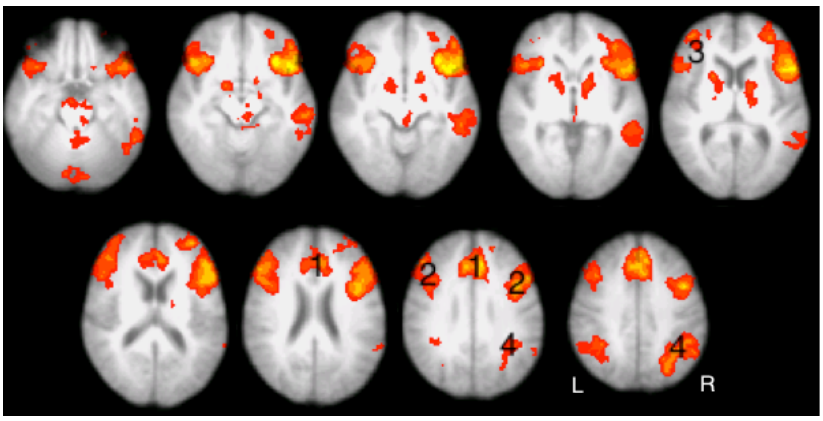


Figure 4.6 *Thresholded Z statistic images for the contrasts of listening to vocoded stimuli versus listening to normal stimuli in healthy volunteers (mean of both sessions). Numbers identify activity within (1) the dACC/SFG, (2) IFG/aI, (3) dlPFC, and (4) PC (dorsal inferior parietal cortex and adjacent lateral intraparietal sulcus).*

4.3.2.3.3 Post hoc: ListNorm versus ListWhite

The activity observed in the contrast of ListNorm versus ListWhite was consistent with that expected for the production of vocal output described above. There was also activity consistent with listening to speech; that is, in bilateral auditory cortex (including primary and association cortex, Heschl's gyrus, and the plana temporale and polare).

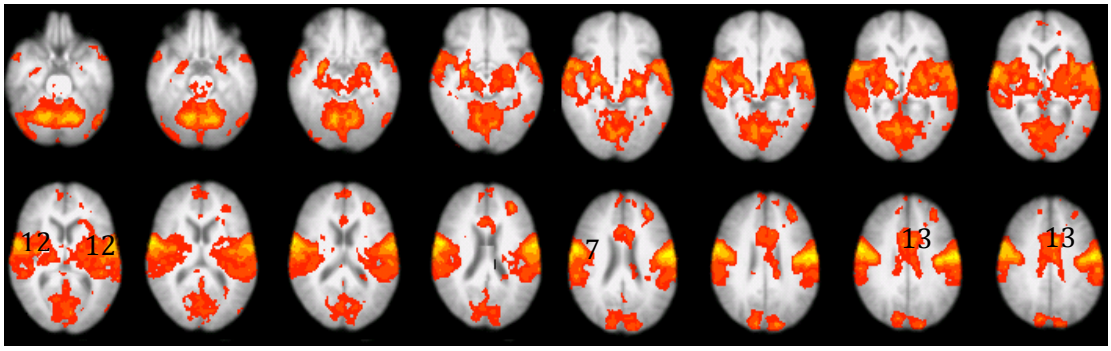


Figure 4.7 *Thresholded Z statistic images for the contrasts of listening to normal stimuli vs. listening to white noise stimuli in healthy volunteers. (7) Sensorimotor cortex, (12) auditory cortex (including primary and association cortex, Heschl's gyrus, and the plana temporale and polare), (13) vACC.*

4.3.2.3.4 Post hoc: ListVoc versus ListWhite

The contrast of listening to ListVoc versus ListWhite showed a very similar pattern of activation as the contrast of ListNorm versus ListWhite, shown above (*Figure 4.7*).

4.3.2.4 Main Effects of Session and Post hoc Tests

There was no main effect of Session, but as the main effect included both listening and repeating trials, *post hoc* tests were used to investigate the repetition and listening trials separately. There were no changes between sessions for all conditions, RepVoc, RepNorm, ListNorm and ListVoc, each versus ListWhite trials.

4.3.2.5 Summary of Results

The behavioural training, as discussed in Chapter Three, was effective at improving noise-vocoded speech comprehension in healthy volunteers. However, there was no fMRI BOLD signal correlate of this improved behavioural performance. A 2 x 2 x 2 ANOVA revealed only a Task x Intelligibility interaction, with no two- or three-way interaction with Session evident in the whole-brain univariate analyses. The main effect of Task demonstrated networks associated with auditory speech comprehension and speech production, with additional activity in the SN and the CEN that was most associated with ListVoc trials. A *post hoc* comparison of all repetition versus all listening trials (excluding white noise trials) did not demonstrate the motor-related activity that might be expected during overt speech production, indicating that listening-and-preparing-to-repeat activated the output as well as the input systems.

Sensorimotor activity was evident in the contrast of the repeating trials with ListWhite. Additional activity associated with the listening trials was present in both temporal lobes, in the ventromedial regions, except where there was signal drop out associated with the susceptibility artefact due to local inhomogeneity of the magnetic field. Therefore, these contrasts demonstrated the extent of cognitive processing associated with listening to sentences in preparation to repeat, including high-order prefrontal, parietal and midline regions, and memory-related (semantic and episodic) regions in the temporal lobes. The main effect of intelligibility, revealed activity mainly within the SN and the CEN networks, included both listening and repeating trials. The *post hoc* contrast of ListNorm versus ListVoc, demonstrated activity in bilateral primary and association auditory cortices, networks involved in speech production and also components of the DMN (medial ventral prefrontal cortex, pCC and adjacent prcuneus). The reverse contrast of ListVoc with ListNorm demonstrated activity within the SN and CEN. The activity observed in the contrast of ListNorm versus ListWhite was consistent with that expected for the production of vocal output described above. There were no changes between sessions for all conditions; RepVoc, RepNorm, ListNorm and ListVoc, each contrasted with ListWhite.

4.4 Discussion

This chapter has demonstrated the role of the domain-general cognitive control systems in functional imaging studies of language, especially when comprehension is made more difficult. The recruitment of these networks has important implications for the interpretation of functional imaging data in patient populations, especially when compared to data from healthy participants.

The imaging analyses on the listening trials performed by the participants listening to vocoded speech stimuli separated three different networks. First, there was the expected speech perception network associated with activity in the STG (Jacquemot *et al.,* 2003; Scott and Wise, 2004; Spitsyna *et al*., 2006; Warren *et al.,* 2009). However, when participants knew that during the following trial they would be required to repeat back what they had just heard, there was additional activity within areas associated with a second network, that concerned with speech production (Braun *et al.*, 1997; Blank *et al.,* 2003). This indicated that the motor preparation for

the following repetition trial occurred during the listening trial, despite close monitoring for overt vocalisations during the scan. This was further supported by the contrast of the repetition trials with listening to white noise, which revealed that the expected sensorimotor activations were present during the repetition trials. The additional activity observed in the medial temporal lobes can be attributed to episodic memory encoding of the verbal message. Third, there was also activation in the cingulo-opercular and dorsolateral prefrontal-parietal networks (SN and CEN, respectively). Increased activity in these networks was revealed in the participants when they listened to three-channel noise-vocoded speech in both whole-brain and region of interest analyses.

This study has highlighted the contribution of domain-general regions to effortful language comprehension in healthy participants. It has been proposed that the dACC region, activated during the more difficult task of listening to noise-vocoded stimuli, plays a role in exerting top-down control over sensory and limbic regions during both task preparation and maintenance (Dosenbach *et al.,* 2007). It has also been shown to be engaged when willed control of behaviour is important, and when learned responses are not available to guide behaviour (Raichle *et al.,* 1994; see also Paus, 2001). This domain-general region was activated only when the participants were required to attend to more challenging and novel stimuli rather than the normal speech, which could be processed automatically. The ventral component of the SN is located in the bilateral IFG/aI (Menon and Uddin, 2010) and is frequently implicated in domain-specific language networks, such as Broca's area and its homologue in the right cerebral hemisphere. However, the studies implicating this region in language invariably use tasks that require 'effortful' manipulation of a stimulus, and therefore increased top-down control (*i.e.* Friederici *et al*., 2003; Ben-Shachar *et al.,* 2004). Most language studies attribute IFG activation, especially on the left, as being specific to linguistic domains such as syntax (*i.e.* Friederici *et al*., 2003; Ben-Shachar *et al.,* 2004; Tettamanti *et al.,* 2009) and semantic predictability (Obleser *et al.,* 2007). Some authors (Sharp *et al.,* 2004*a*; Fridriksson and Morrow, 2005) have suggested that the IFG/aI activation in their studies in healthy volunteers and patients with aphasia, respectively, was not the result of a language process *per se* but rather reflected task difficultly, due to additional working memory processing associated with the more difficult task used. Eisner and colleagues (2010) also found that activity in this region

correlated both with phonological working memory scores and with left inferior parietal activity. They suggested that the response in this frontal-parietal network was part of a more general learning mechanism, activated when a task is more effortful, such as tasks requiring increased working memory. However, Barch and colleagues (1997) used both memory tasks (long and short-term) and visual stimuli (clear and degraded) specifically to separate the neural contributions of the frontal lobe to both task difficultly and increased working memory. They demonstrated that activity within the anterior cingulate component of the SN increased due to task difficulty rather than working memory load. They also found that activity in the dLPFC increased in response to greater working memory regardless of difficulty. In the results presented here, working memory is unlikely to account for the increased dACC/SFG or IFG/aI activation observed. There was no additional working memory load associated with the noise-vocoded speech stimuli rather than the clear speech stimuli, as the main experimental manipulation was the task difficulty. This result is in accord with the double dissociation described by Barch and colleagues (1997).

There was little suppression of the DMN when the healthy participants listened to clear speech, but it was evident on the trials when they listened to noise-vocoded sentences. Suppression of the DMN occurs during goal-directed cognitive processes (Raichle *et al.,* 2001). The 'passive' perception of stimuli or tasks that are habitual or easy to perform on the presented stimuli is thought to suppress the DMN less than tasks that require increased control from executive and attentional networks (Anticevic, 2012). The task of listening to noise-vocoded stimuli was more effortful and less habitual than the more automatic comprehension of normal speech.

The only lateralised cortical component during listening to noise-vocoded speech was confined to the posterior left middle and adjacent inferior temporal gyri. Sharp and colleagues (2004*b*) compared the activation of healthy volunteers listening to noise-vocoded speech and clear speech with the activation in nine patients with aphasia. They found that the only difference in activation using clear speech trials across both groups was in the left fusiform gyrus. A ROI analysis in this region demonstrated that activity in this region was similar for patients and healthy volunteers using noise-vocoded speech but increased when healthy volunteers listened to clear speech. The peak for their ROI was more anterior than the posterior ITG/MTG peak in the present

study. In addition they used semantic decision tasks rather than sentence comprehension, whilst these both implicate semantics the former is more transient and relies more on comparing semantic representations. However, in the study presented in this chapter, parts of the stimulus sentence can be understood as the sentence progresses. High-order anaphoric processing is probably recruited to a greater extent in distorted conditions rather than passive listening of clear speech in order to aid the semantic identification of previous items in the sentence. This region, based both on lesion and functional imaging studies, has become strongly associated with language-specific processes (Devlin *et al.,* 2000; Hickok and Poppel, 2007; Price, 2010). However, the sentences presented during the ListNorm and ListVoc trials in this study were semantically and grammatically equivalent. This suggests that the increased activity in the left inferior temporal region during listening to perceptually difficult noise-vocoded speech was the consequence of increased top-down effort, originating from the activity within the SN and CEN. This would support a role for this region in the controlled access to meaning when perceiving speech (Whitney e*t al.,* 2011), with activity increasing as mapping from construct to concept becomes less automatic with degraded speech stimuli.

Another important component of the study was the neural responses to behavioural training. The healthy participants responded to two weeks of training on the noise-vocoded sentences and showed a significant improvement in their ability to perceive and repeat these sentences. Despite these specific responses to training, there was no functional imaging correlate evident in the contrasts between pre- and post- training imaging data. Whilst no change would be expected for the repetition or ListNorm trials, as the participants had no motor deficit or comprehension deficit, a change in relation to the ListVoc was expected, given the large training effect. In the study by Eisner and colleagues (2010) activity within the left IFG correlated with short intensive behavioural training of understanding noise-vocoded speech, as did the strength of a functional correlation between STG and IFG. Their data was collected from a greater number of subjects (n = 25), and they were younger (19-31 years) than those in this study. However, the activation of these regions at the group level was only evident in their study by the use of a statistical threshold uncorrected for multiple comparisons. The functional imaging community are now coming under severe criticism for using uncorrected statistics. The results presented in this Chapter report

conventional univariate statistical analyses that have all been corrected for multiple comparisons. Therefore, the result reported here is more reliable than that of Eisner and colleagues. Using more sensitive multivariate techniques may reveal session effects in future analyses, which will be part of my future work (see Chapter Seven).

Finally, most studies investigating neural mechanisms of recovery in aphasia have compared the results from patients and healthy participants performing the same simple task, which inevitably results in a different amount of additional 'cognitive' effort being required by the patients. The results from this study, in which the strategy was to manipulate task difficulty for the healthy participants and therefore reduce their in-scanner task performance to the level of that observed in the patients (as shown in Chapter Three), suggest that the additional domain-general systems recruited during adverse listening conditions may be better investigated by manipulating task difficulty in healthy volunteers, rather than patients.

The SN and CEN are considered to be functionally separable (Dosenbach *et al*., 2007; 2008), but are usually co-activated as in this study. It has been suggested that the CEN is responsible for on-line monitoring and 'adaptive control' during the performance of a task on a trial-by-trial basis, whereas the SN maintains performance over the time course of repeated trials on that task (Dosenbach *et al.,* 2007). However, there is no consensus about the precise function of these two networks. For example, an alternative hypothesis about the function of the SN is that it manipulates rapid changes of activity in other networks in response to changes in task demands and contexts after perception of salient stimuli (Menon *et al.,* 2010; Bonnelle *et al.,* 2012). The in-scanner task of recognising distorted forms of intact representations in order to attempt to repeat them requires the identification of salient features within a stimulus that allows mapping to occur. This will be assisted by domain-specific top-down support based on established semantic and syntactic knowledge. This task requires the maintenance of attention across the entire trial in order to extract as much meaning as possible, whilst on-line monitoring assists in ensuring that the interpretation that is most likely to be correct has been achieved. As discussed above, it also seems that effective task performance depends on 'deactivating' the DMN, and some authors consider that the SN, and in particular the right IFG/aI acts as a 'switch', allowing interoceptive processing under the control of the DMN to be interrupted so that

attention to external stimuli is engaged. The deactivation of the DMN was evident in the contrast of ListNorm versus ListVoc. More detailed analysis of the anticorrelation between the SN/CEN and DMN networks during language-related tasks in healthy participants will require further studies in the future. However, the relationship between these networks is explored further in Chapter Five, in relation to aphasic stroke.

5 Investigating mechanisms of understanding speech in patients with post-stroke aphasia.

5.1 Aims and Hypotheses

The aims of this chapter were to investigate:

- The neural systems that patients with aphasia recruited during listening to and preparing to repeat normal sentences in the presence of a comprehension deficit;
- The similarities and differences between activation of these different systems in both healthy volunteers, described in the previous chapter, and the patient group presented in this chapter;
- Changes in activations in perisylvian and domain-general regions associated with a behavioural response to the therapy described in Chapter Three;
- The extent to which activation in these regions could predict residual language skills in post-stroke aphasia.

The hypotheses were that:

- Patients would recruit similar, domain-specific and domain-general, regions to those used by healthy volunteers under the distorted speech conditions in Chapter Four;
- The between subject variability of this activation would reflect the heterogeneity of residual functional language skills;
- The behavioural changes observed as a response to the therapy, presented in Chapter Three, would be reflected in changes of activation within domain-general and domain- specific neural networks.

5.2 Material and methods

5.2.1 Participants

Of the 88 right-handed patients with persistent post-stroke aphasia that were screened in Chapter Three, only 16 patients (five females, mean age 60 years; range 37-84 years) completed this imaging study (these patients are highlighted in section 3.2.1 in table 3.1 with an asterix). The mean duration of formal education for this group of patients was 15 years (range 10-18). All patients were at least six months post-stroke

(mean = four years, range: six months to 11 years), at a time when further spontaneous recovery is likely to be negligible (Lendrem and Lincoln, 1985). All patients had a lesion involving the left temporal plus/minus inferior parietal lobe involvement, and four patients had a lesion extending into the frontal lobe but not involving anterior cerebral artery territory (*Figure 3.1*). The patients' comprehension was sufficient for them to give informed consent and to understand what was required of them. Most patients' production skills were sufficient to allow them to attempt to repeat short sentences, although in two patients only single words were produced when attempting to repeat the sentences. Other inclusion criteria were no history of other neurological illness, no sinistrality, and at the time of participation none were receiving SALT.

5.2.2 Experimental Design

Patients had three functional magnetic resonance imaging (fMRI) scans; each four weeks apart. In between the first and second scanning sessions the participants did not receive any therapy. Between the second and third scanning session they participated in four weeks of home-based computerised behavioural therapy that targeted phonological discrimination. At each scanning session patients also participated in extensive behavioural testing reported in Chapter Three (*Figure 5.1*). The scanning protocol was identical for each session but used a different set of stimuli.

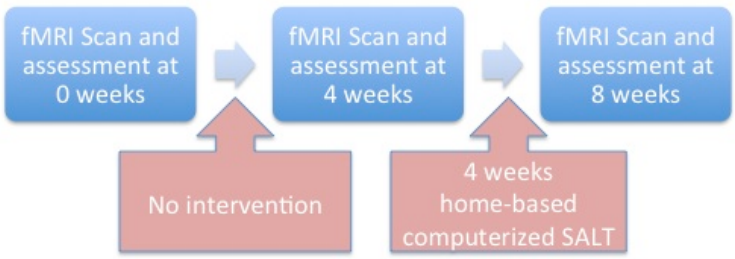


Figure 5.1 *Flow chart representing the different components of the entire longitudinal experiment.*

Participants were asked to complete thirty minutes of therapy three times a day. The mean amount completed by this group was considerably less (Mean = 20.8 hours, SD = 14.5, range = 2.8 to 53.8 hours) than they were requested to complete (42 hours in

total). The details of this therapy and the compliance are discussed in greater detail in Chapter Three.

5.2.3 Scanning Paradigms

A similar, yet simpler and shorter, paradigm to that presented in Chapter Four was given to patients with aphasia in the experiment presented in this chapter. I felt that shortening the duration of scanning would be essential in order to make the procedure more acceptable to patients with both cognitive and physical impairment.

As with the healthy volunteers in Chapter Four, patients were presented with a BKB sentence using only clear speech (*i.e.* not noise-vocoded) inside the scanner. They were required to listen to each sentence and then repeat it in the subsequent trial (*Figure 5.2*). A total of 84 trials were used in each of two runs per scanning session. A low-level auditory baseline of listening to segmented broadband noise bursts was also included. Each run within a scanning session consisted of 28 sentences presented using clear speech stimuli (ListNorm). Each ListNorm trial was followed by one of 28 'repeat' trials (RepNorm), where the patient was required to repeat the ListNorm sentence that they had heard in the previous trial. There were also 28 trials of a low level auditory baseline (spaced irregularly between 'listen-repeat' patterns) of listening to white noise (ListWhite). These ListWhite stimuli were matched in duration to sentence stimuli.

A "sparse" fMRI design was again used to minimise both movement and respiratory-related artifact associated with speech studies. Tasks were performed over 5.5 seconds while a visual task prompt was displayed. The disappearance of that prompt and the appearance of a fixation crosshair signalled to the subject to cease the task. Two seconds of data acquisition commenced 0.5 seconds later, during which the fixation crosshair remained present (*Figure 5.2*).

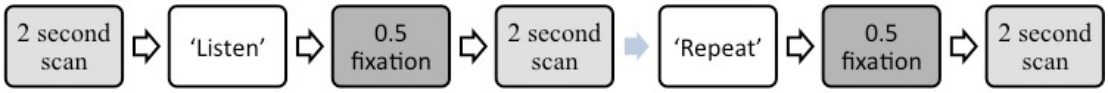


Figure 5.2 *fMRI 'sparse' scanning design used for the patients in this chapter.*

Before each scanning session, patients were practised in how to complete the paradigm. Particular emphasis was placed on ensuring they ceased speech production when the fixation crosshair appeared in order to minimise movement during the two second scanning acquisition. The amount of trials required until I was confident that patients understood the task varied between patients, and so training continued until each patient was completing the 'listen-repeat' pattern correctly and without prompting. Stimuli used during the practise trials were not presented during the scanning session. When the scan commenced, in-scanner responses were monitored in order to ensure that the patient was completing trials correctly. On four occasions scanning was stopped within the first two trials in order to remind the patient of the task procedure.

5.2.4 Stimuli

As described in Chapter Four, Bamford-Kowal-Bench (BKB) sentences (Bench *et al.,* 1979) were used during the fMRI paradigms. These sentences do not contain complex syntax and most importantly these have a low sentence-end predictability which would limit the amount of top-down semantic processing being used to discriminate and understand the sentences. The visual prompt used throughout the trials consisted of the image of a black and white line drawing of a face, with either the word 'listen' (in red) or 'repeat' (in green) below the face and an arrow pointing towards the ears for 'listen' trials, and from the mouth for 'repeat' trials.

5.2.5 Measuring Behavioural Performance

Again, the method of scoring in-scanner behavioural performance is described in detail in Chapter Four. To emphasise, the rationale for this scoring system was to account for any speech errors, both articulatory and phonological, produced by the patients whilst speaking. Had it not been for these potential errors, then a simple measure of key words produced might have sufficed. However, during scoring I did not want to penalise patients who may have attempted to produce the correct word but were unable to produce the correct form of that word. Three scores for each participant's spoken responses during scanning were calculated. These included a semantic score, an articulation score and a combined semantic and articulation score. These scores were out of five, as described in Chapter Four. The mean of the semantic and articulation scores was calculated to produce a combined score, which presents a

fairer representation of the patients' ability to reproduce a sentence whilst acknowledging the impact of any misarticulations.

5.2.6 Data Acquisition and Analysis

See also Methods section (2.3) and Chapter Four (section 4.2.6).

5.2.6.1 Lesion Masking

Individual three-dimensional lesions were hand drawn on T1-weighted templates for each slice using FMRIB Software Library image viewer (FSLView). A lesion mask was then created by binarising the image and then inverting it. The patients' fMRI scans were registered to their structural T1 using FLIRT with 6 degrees of freedom. Next, the patient's structural image was registered to the standard MNI anatomical template using FLIRT with 12 degrees of freedom, with the binary inverted lesion image as an input-weighting mask to minimise the influence of the damaged area on the registration solution, and so avoid the distortion associated with normalisation of brains with sizeable infarcts. The two resulting transformation matrices (functional to structural and structural to standard) were then concatenated and applied to the functional data to achieve functional to standard registration.

5.2.6.2 Univariate Analysis

See Methods section 2.4 and/or Chapter Four 'Univariate analysis'

5.2.6.3 Comparison Between Groups

The two imaging studies presented in Chapter Four and this present Chapter, were designed to be as similar as possible in order to allow comparison between the group of healthy volunteers (in Chapter Four) and patients with post-stroke aphasia (this Chapter) to be made. The results from the second level, fixed-effects analyses from subjects within each group were taken to a third level analysis. At this third level a group mixed-effects analysis modelled an independent samples *t*-test comparing patient and control groups.

5.2.6.4 Region of Interest Analysis

To provide an unbiased way of extracting data, the region of interest was defined by multiplying the functional activation observed in healthy volunteers in a contrast of

interest by the probabilistic anatomical masks for that region from the FSL Harvard-Oxford Cortical Structural Atlas. The ROI masks were then re-registered to the same space as individual pre-processed functional data from the univariate analysis. Using FSL FEATQuery (an FSL tool to interrogate univariate data within a defined region), effect sizes for the different conditions and different runs were calculated for each patient. The mean effect size across the two runs was then calculated to provide an average effect size for each scanning session. Bivariate correlations and *t*-tests were used to analyse the ROI data using SPSS (IBM Corp).

5.3 Results

5.3.1 In-scanner Behavioural Performance

Despite wide inter-individual variability, patients' performance was consistent across sessions. Thus, the patients' performance on repeating the ListNorm trials (RepNorm) correlated significantly (using the combined score for articulation and semantics) between scanning sessions one and two (r = .88, $P < 0.001$); between sessions two and three (r = .84, $P < 0.001$); and between sessions one and three (r = .94, $P < 0.001$). Similarly, paired *t*-tests demonstrated no significant differences between any sessions using any of the three measures ($P > 0.1$).

When comparing these combined scores (articulation and semantics) on RepNorm trials in the patients with the RepVoc in the healthy participants (discussed in Chapters Three and Four), an independent-samples *t*-test with equal variances not assumed, showed there was no difference between groups (t (22.7) = 1.7, P = 0.1). Therefore, the aim of making the task of approximately comparable difficulty in patients and healthy participants was achieved (*Figure 3.6*).

5.3.2 Functional MRI Analysis

The patients had three scans compared to the healthy participants' two scans. This was to enable the patient population, who were expected to find the scanning experience more stressful than the healthy population, to acclimatise to the experience before obtaining pre- and post-training scan data. This additional initial scan also acted as a baseline scan in order to evaluate any non-specific neural changes

occurring due to effects of anxiety or familiarity with the scanning environment changing with experience, rather than changes associated specifically with a response to therapy. A repeated measures analysis was carried out to investigate functional differences between scanning sessions using contrasts of ListNorm with ListWhite for each session. Assuming that activity in response to ListWhite was stable across sessions, there was no greater activity in cortical or subcortical grey matter regions in response to ListNorm during session one relative to either sessions two or three, or in session two relative to session three.

As there was no difference between sessions, session one was excluded from the analysis in order to make equivalent later comparisons with the data from the healthy participants. Once this initial scan was excluded a Task (listen and repeat) x Session (pre- and post- training) ANOVA was performed and no Task x Session interaction was evident.

5.3.2.1 Main Effect of Task and Post-hoc Tests

The main effect of Task revealed extensive activation in bilateral premotor (lateral and medial) and primary somatosensory-motor cortices, along the length of both superior temporal gyrus from the plana temporale to the temporal poles, the dACC/SFG and bilateral IFG/aI (the SN), bilateral dlPFC and right PC (the CEN), posterior midline cortex and posterior right inferior parietal cortex (the DMN). Small areas of the left posterior middle temporal gyrus and left parietal operculum were also activated in those patients in whom those regions remained intact. Subcortical regions included bilateral basal ganglia (but not the anterior striatum), the thalami and bilateral paravermal cerebellum.

Post hoc comparisons revealed that all the regions active in the main effect of task were more active in the ListNorm relative to the RepNorm trials (*Figure 5.3*), except the posterior midline cortex (PCC and adjacent precuneus) and right inferior parietal cortex, components of the DMN (minus the infarcted left inferior parietal cortex). These regions of the DMN were evident in the contrast of RepNorm versus ListNorm.

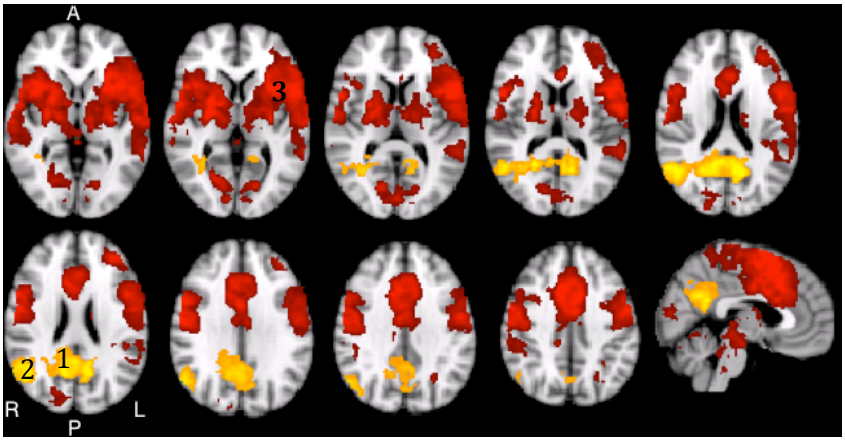


Figure 5.3 *Thresholded Z statistic images for the contrast of ListNorm versus RepNorm (red) and RepNorm versus ListNorm (yellow). (1) pCC/preCu, (2) PC (3) IFG/aI All images are thresholded using clusters determined by Z > 2.3 and a (corrected) cluster significance threshold of P = 0.05.*

The additional contrast of ListWhite versus ListNorm also revealed areas associated with the DMN that overlapped with the regions evident in the contrast of RepNorm with ListNorm.

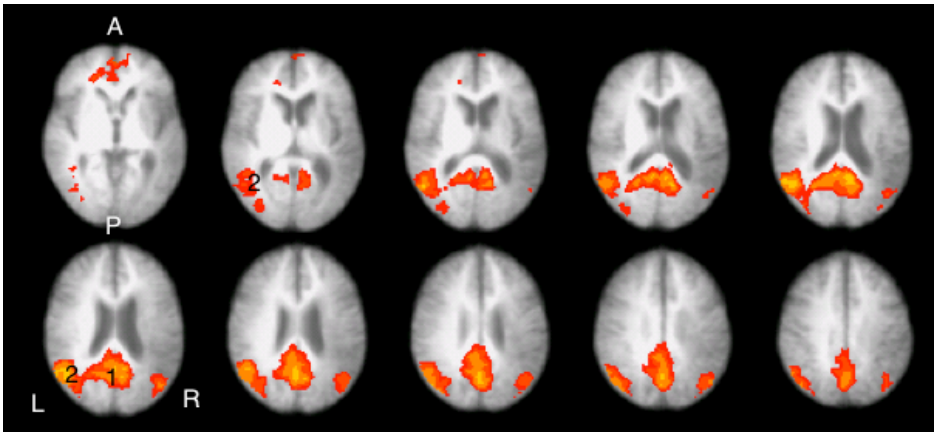


Figure 5.4 *Thresholded Z statistic images for the contrast of ListWhite versus ListNorm. Numbers identify activity within (1) pCC/preCu, (2) PC. (A=anterior, P=posterior, L=left, R=right).*

5.3.2.2 *Main Effect of Session and Post-hoc Tests*

A main effect of session revealed a small area of activation in the precuneus. Paired *post hoc t*-tests were used to investigate between Session effects for each of the tasks separately (ListNorm and RepNorm) compared to the baseline (ListWhite). These separate *t*-tests demonstrated no differences between the two sessions, as indicated in the initial repeated measures analysis.

5.3.2.3 Summary of Patient Whole-Brain Analyses

Post hoc comparisons revealed that, as in the study with healthy volunteers described in Chapter Four, regions associated with speech comprehension and production were more active in the ListNorm relative to the RepNorm trials, including expected sensorimotor areas. Components of the DMN (PCC and adjacent precuneus, and right inferior parietal cortex) were evident in the RepNorm and ListWhite trials both versus the ListNorm trials. There were no effects of session (*i.e.* training effects) evident using univariate analysis.

5.3.3 Between Group Comparisons

A direct comparison between the patients and the healthy participants (presented in Chapter Four) was carried out to investigate both the neural differences in activations due to the presence of a lesion during the ListNorm trials, and also similarities due to simulating the functional effects of the lesion by using noise-vocoded speech in the healthy participants presented in Chapter Four.

A mixed-effects, independent samples *t*-test (ListNorm contrasted with ListWhite for both patients and healthy participants) was carried out to investigate differences in processing clear speech between patients and healthy participants. The contrast of healthy participants versus patients demonstrated greater activity within the DMN, including the precuneus, pCC and medial pre-frontal cortex. The reverse contrast of patients versus healthy participants demonstrated greater activity in the SN (cingulo-opercular) network for both sessions (*Figure 5.5*).

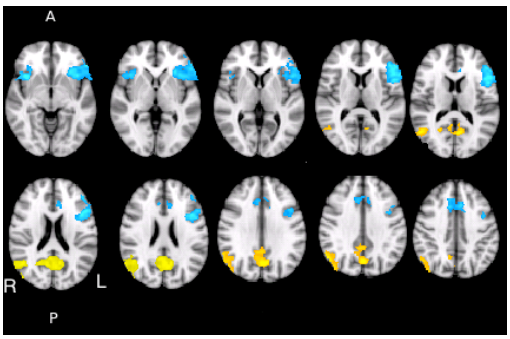


Figure 5.5 *Thresholded Z statistic images for the contrast of healthy volunteers versus patients (both listening to ListNorm) in yellow, and the reverse patients versus healthy volunteers (blue).*

A mixed-effects, independent samples *t*-test, (using ListNorm contrasted with ListWhite for patients and ListVoc contrasted with ListWhite for the healthy participants) was then carried out to investigate differences associated with increased difficulty during processing of clear and vocoded speech in the patient and healthy groups respectively. These comparisons revealed no differences in either the pre- or post- training sessions and so highlight the similarities between the neural systems recruited by the two groups during these two different conditions (*Figure 5.6*).

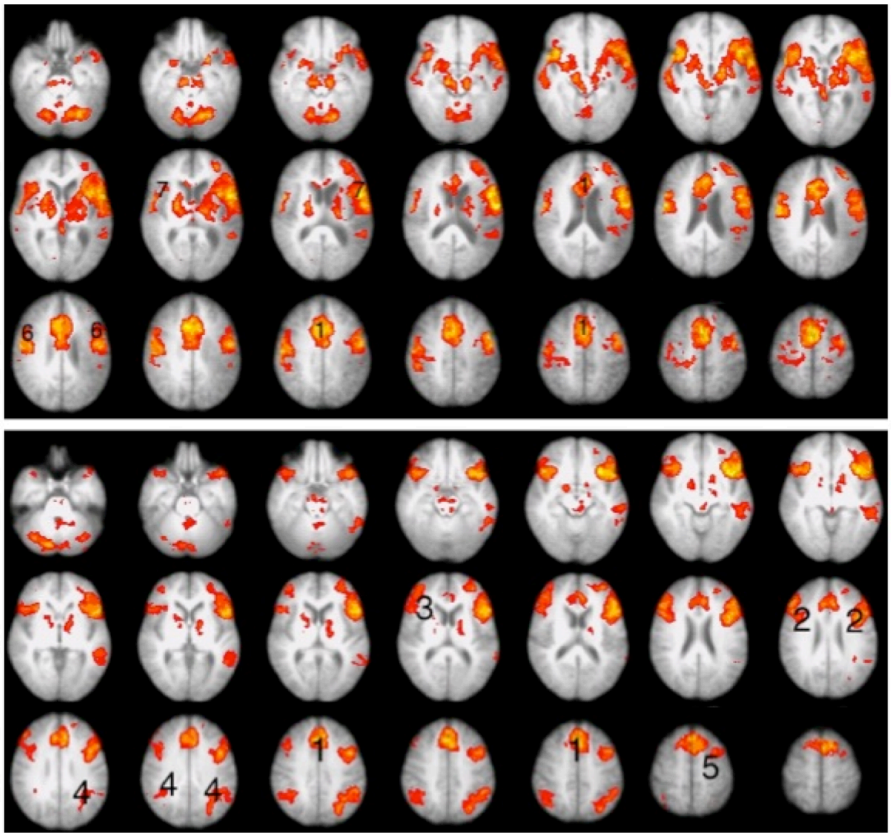


Figure 5.6 *Thresholded Z statistic images for the contrasts of Upper panel: listening to normal stimuli versus repeating normal stimuli in participants with aphasia (mean of both scanning sessions). Lower panel: listening to vocoded stimuli versus listening to normal stimuli in healthy volunteers (mean of both sessions). Numbers identify activity within (1) the dACC/SFG, (2) IFG/aI, (3) dlPFC, (4) PC (dorsal inferior parietal cortex and adjacent lateral intraparietal sulcus) and (5) MFG.*

A direct multiplication of the two contrast images derived from these listening conditions (ListNorm versus ListWhite in patients and ListVoc versus ListNorm in healthy volunteers) revealed areas specifically related to task difficulty across groups. These activations common to both groups lay in dACC/SFG and IFG/aI, and PC

(dorsal inferior parietal cortex and adjacent lateral intraparietal sulcus), the component parts of the SN and CEN (*Figure 5.7*).

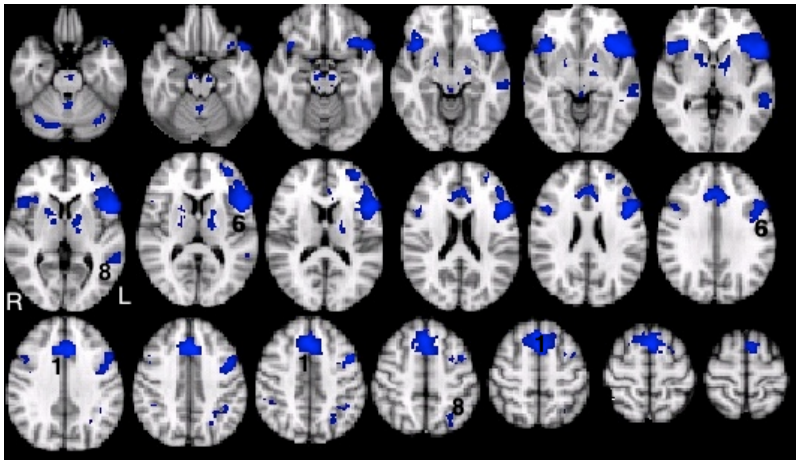


Figure 5.7 *Thresholded Z statistic images for the contrasts of listening to vocoded stimuli versus listening to normal stimuli in healthy volunteers (mean of both sessions) multiplied by the contrast of listening to normal stimuli versus listening to white noise in patients (mean of sessions 2 and 3). Numbers identify activity within (1) the dACC/SFG and (6) IFG/aI, (8) PC (dorsal inferior parietal cortex and adjacent lateral intraparietal sulcus).*

5.3.4 Region of Interest Analysis

Based on the results from the whole-brain analyses, with activity in high-order cognitive cortices demonstrable with increased difficulty (as the result of stroke in the patients and manipulated perceptual difficulty in the healthy participants), a ROI analysis was performed in order to correlate neural activity with off-line residual language function in the patients with aphasia. The dACC/SFG was chosen as it is located in anterior cerebral artery territory, and therefore outside the vascular territory of infarction in the patients. A standard anatomical template for the cingulate cortex and adjacent SFG from FSLs anatomical atlas was multiplied by the activated voxels in this region from the contrast of 'ListVoc versus ListNorm' in the healthy participants. There was no significant difference in the group of healthy volunteers between activation in this region before or after training in either the ListVoc trials versus ListWhite trials (t (16)=.99, $P > 0.3$) or ListNorm trials versus ListWhite trials (t (16)=.67, $P > 0.5$). There was, as expected from the whole-brain analyses, a significant difference in activation of the dACC/SFG between the ListVoc trials and the ListNorm trials, both before training (t (18)=3.5, $P < 0.005$) and after training (t (16)=6.4, $P > 0.001$). In patients there was no significant difference between sessions

2 and 3 (t (15)=0.03, P > 0.9). There was no significant difference between sessions in either RepNorm trials in patients, or RepNorm or RepVoc in healthy participants. There was also no significant difference between the mean (of both pre and post training sessions) percentage BOLD signal change either using an paired sample t-test with data from healthy volunteers performing RepNorm versus RepVoc trials (t (16)=-.3, P>.7) or using an independent samples t-test, with equal variances not assumed, using data from healthy volunteers performing RepVoc versus patients performing RepNorm trials (t (18, 31)=-1.2, P>.2).

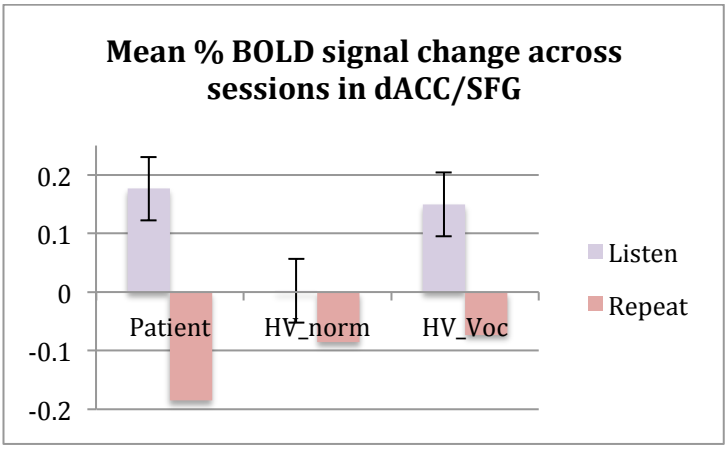


Figure 5.8 *Bar chart, with standard error bars, showing the mean dACC/SFG activation during Listening trials (lilac) in healthy volunteers listening to Normal or vocoded stimuli, and patients listening to Normal stimuli, and activation during repetition trials (red) as described above.*

Whilst there was no difference between the two sessions in either group, an important finding was that the variability within the patient group during ListNorm trials was greater, both before (Mean=0.177, SD=0.29) and after (Mean=0.18, SD= 0.27) therapy, than the variability in the healthy volunteers during ListVoc trials again both before (Mean = 0.145, SD= 0.11) and after (Mean= .156, SD 0.16) training (*Figure 5.9*).

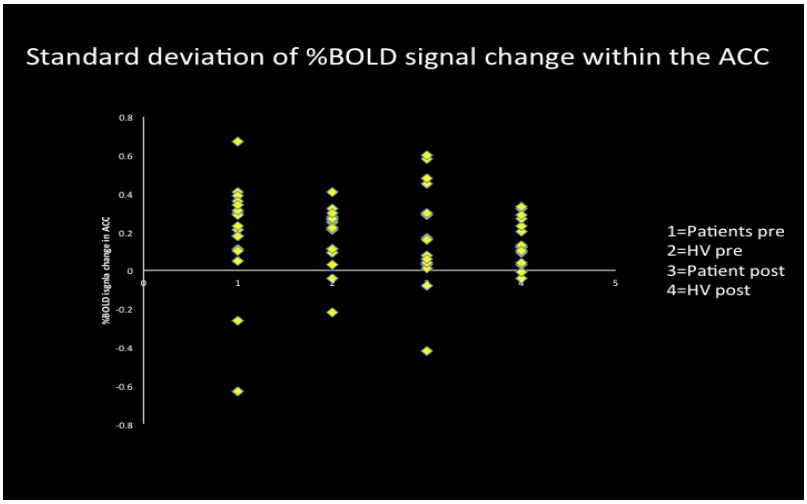


Figure 5.9 *The variability in percentage BOLD signal change within the aCC/SFG before (1,2) and after (3,4) treatment for both patients listening to normal sentences versus white noise (1,3) and HVs listening to vocoded sentences versus ListNorm (2,4).*

Having defined this functional-anatomical region in the group of healthy participants and multiplied it with the standard template, this ROI was then applied to the patient data. Activity from within the dACC/SFG in the patients was then correlated with their off-line performance on the picture description task. There is abundant evidence in the literature that demonstrates the internal generation of narrative speech activates the dACC/SFG, and the ability of the patients to activate this region during the 'surrogate' task of listening-and preparing-to-repeat was used as an index of their ability to activate this region during picture description. A one-way repeated measures ANOVA was used to investigate the effect of different sessions on performance when completing the picture description test. Mauchley's test indicated that the assumption of sphericity had been violated (X^2 (2) = 7.3, $P < 0.05$), and therefore the degrees of freedom were corrected using Huynh-Feldt estimates of sphericity ($\varepsilon = 0.76$). The results showed that the picture description score was not significantly different between any of the three sessions [F (1.5, 23) = 1.73, $P > 0.05$]. A one-way repeated measures ANOVA was also conducted to compare the effect of session on the percentage BOLD signal change within the dACC/SFG activation. This demonstrated that there was no difference between sessions [F (2, 45) = 0.6, $P > 0.5$] with sphericity assumed. The mean performance on the picture description test across the three sessions was then correlated with the mean dACC/SFG activation across three sessions. There was a significant positive correlation ($r = .63$, $P < 0.01$), with better

picture description scores associated with greater dACC/SFG activation (*Figure 5.10*).

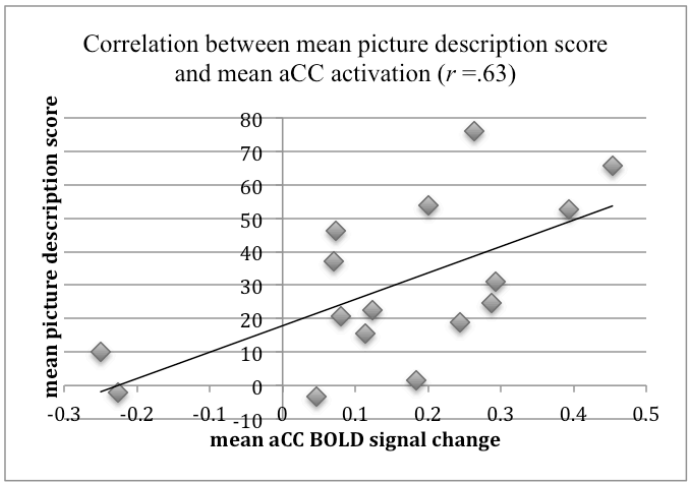


Figure 5.10 *Correlation between patients' mean picture description scores and mean dACC/SFG percentage signal change across all three sessions.*

A multiple regression analysis was used to investigate which of the following best accounted for participants' picture description score: dACC/SFG activation; age at the start of the study or lesion volume. The results of this regression indicated that the model was statistically significant and accounted for 50% of the variance [R^2= .501, F (3,12) = 4.02, P < 0.03]. It was found that dACC/SFG activation predicted picture description score (β = .56, P < 0.03), but age (β = .16, P < 0.46) and lesion volume did not (β = -.28, P = 0.22) (*Table 5.1*).

	B	SE B	β
Constant	9.3	25.80	
mean aCC activation	69.98	27.29	.56*
Age	0.29	0.38	.16
Lesion volume	0.00	0.00	-.28

Note: *P < 0.03, R^2 = . 501

Table 5.1 *Results for the multiple regression analysis of the dependent variables mean dACC/SFG activation, age and lesion volume and the dependent variable picture description score.*

The activation in the right IFG/aI was interrogated using ROI analysis in the same way as the dACC. Due to the presence of a lesion in the left IFG/aI in four patients, an ROI analysis was not performed on this side. Within the anatomical toolkit in FSL, *pars opercularis* and *pars triangularis* are separate masks, so data was extracted from the two regions separately. The aI does not have a separate designation within the anatomical toolkit, so this sub-region was not included in the analysis. Like the correlations with the dACC/SFG, the mean performance on the picture description test across the three sessions was then correlated with the mean *pars opercularis* and *pars triangularis* activation on the right. There was a significant positive correlation with better picture description scores associated with greater right *pars opercularis* activation ($r = .7$, $P < 0.007$) and to a lesser extent in the right *pars triangularis* ($r = .5$, $P < 0.05$).

As these regions form part of the SN, the activation from them was correlated with the activation in the dACC/SFG, all during the ListNorm versus ListWhite trials and there were significant corelations between dACC/SFG activation before therapy and both right *pars opercularis* ($r = .64$, $P < 0.01$) and *pars triangularis* ($r = .88$, $P < 0.001$), and after therapy in both right *pars opercularis* ($r = 0.8$, $P < 0.001$) and *pars triangularis* ($r = .5$, $P < 0.05$).

5.3.5 Summary of Results

The networks previously observed when healthy volunteers attempted to understand degraded speech stimuli, shown in Chapter Four, namely the SN and CEN, were also active when patients attempted to understand and repeat normal spoken sentences in the presence of a comprehension impairment. There were no activations evident when these two 'difficult' conditions (*i.e.* ListVoc in Healthy participants and ListNorm in the presence of an aphasic comprehension impairment) were contrasted directly, suggesting that the increased difficulty associated with the presence of aphasia was well-matched by using noise-vocoded speech in the healthy volunteers. Like the univariate analyses in Chapter Four, the majority of activity was observed in ListNorm trials rather than RepNorm trials. This included the sensorimotor regions normally associated with the production of speech rather than perception.

Whole-brain analyses revealed that there were no effects of session (*i.e.* training effects) evident using univariate analysis. Region of interest analyses in areas of common activation, namely the dACC/SFG, further demonstrated no difference between sessions, and, as predicted by the univariate analyses, a significant difference between the ListNorm and ListVoc trials was observed in the healthy volunteers. The variability between activation was, not unexpectedly, greater in the patient group than the healthy volunteers. There was a significant correlation across sessions between activation in the dACC/SFG and performance on an off-line picture description performance score. A multiple regression analysis revealed that this correlation could not be explained by lesion volume or age, but rather dACC/SFG activation only. The activation in both the dACC/SFG and right IFG regions correlated significantly and performance on the picture description test also correlated with right IFG.

5.4 Discussion

The study presented in this Chapter demonstrates that the domain-general cognitive control systems, highlighted in Chapter Four, were again important when patients with post-stroke aphasia attempted to 'listen to and prepared to repeat' simple sentences, and that activation in these regions can be used to help predict residual language function in patients with aphasia.

The imaging analyses of the listening trials performed by the patients, as in Chapter Four, again separated three broad networks: the expected activity in the superior temporal gyri in response to the perception of speech stimuli; areas associated with speech production (Braun *et al.,*1997; Blank *et al.,* 2002); and the same cingulo-opercular and dorsolateral prefrontal-parietal networks (SN and CEN, respectively) observed when healthy volunteers listened to vocoded speech. Therefore, by making listening-and-preparing-to-repeat approximately equal in difficulty for both populations, with similar rates of subsequent repetition success, the increased activity in domain-general attentional and cognitive control was similar across both groups. This study therefore highlighted the implication of regions, namely the dACC/SFG and IFG/aI, within these networks in general task difficulty, rather than linguistic complexity. This suggests an important alternative interpretation of the role of these regions in studies of both language comprehension and production that rely on manipulation of linguistic skills at the expense of increased cognitive effort.

The analysis of the results in this Chapter then turned to whether the function of a central component of the combined domain-general SN and CEN networks reflected language recovery. The dACC/SFG was chosen as it lies in anterior cerebral artery territory, and therefore outside middle cerebral artery territory in which the aphasic strokes had occurred. This region was macroscopically intact in all patients. Activating the dACC/SFG with one task ('listen-and-prepare-to-repeat'), in the knowledge that self-generated speech also activates this region, motivated the analysis correlating its function with the patients' out-of-scanner performance on a widely-used and ecologically-valid assessment of language production in aphasia - namely picture description. The result demonstrated that in chronic aphasic patients the activation of the dACC/SFG predicted performance on this test. This correlation did not change when a multiple regression analysis was performed that included the volume of infarction and the ages of the patients. Whilst the in-scanner task and the picture description task required different input and output systems, the activation in the dACC/SFG reflected increased task difficulty regardless of whether the specific language task emphasises speech comprehension or production. Therefore, the role of the dACC/SFG is not specific to one of the two broad divisions applied to language - namely 'receptive' or 'expressive' - but to the cognitive control of language processing in general. In addition, activation within the right IFG/aI regions (both *opercularis* and *triangularis*) also correlated with picture description scores, and with the activation in the dACC/SFG. These common correlations further support the notion that these two distinct cortical regions are operating within the same network, namely the SN, when a task is more difficult to complete. As the left IFG/aI was lesioned in four patients, correlations with activity in this area were not possible. In summary, these correlations of SN activation with behaviour provides direct evidence in support of the clinical intuition, familiar to most people experienced with working with people with post-stroke aphasia, that domain-general cognitive control is an essential factor contributing to the potential for recovery from aphasic stroke.

Evidence for this clinical intuition is much needed. Continued constraints on the amount of time available for aphasia therapy necessitate the requirement to prioritise limited resources based on clinical need and clinical benefit. The results from this chapter provide direct evidence that patients with intact domain-general cognitive

control are able to recover better language function after a stroke. This was only achieved through comparing the results in patients with those in healthy volunteers completing the same task under similar levels of difficulty.

The use of 'Sparse' scanning removed the confound of completing the task in the presence of background scanner noise. This was especially important in this study as the scanner noise may have resulted in under-recognised cognitive effort in patients with damaged sensory and/or cognitive systems compared to healthy volunteers. To make between-group comparisons it is not sufficient to argue that the task itself is well-matched if the task-specific demands are not. One important advantage to this study was that the comparisons to healthy volunteers were made when task difficulty was increased in the healthy participants in order to equate to the level of difficultly that observed in the patients.

This study recruited a reasonably large group of patients selected primarily on lesion location. A consequence of this method of selection resulted in very variable behavioural performance across the group of patients. Studies are typically controlled for behavioural performance, without controlling for lesion localisation or lesion extent. It was the variability of performance but the relative homogeneity in lesion location that allowed the relationship between domain-general activity and the residual ability to communicate in speech to become apparent. This study did not have a sufficient number of patients with a lesion extending to the frontal lobe to separate the analyses into the two groups. Future studies would be better placed to investigate domain-general activations by directly comparing two groups of patients with and without lesions involving specified domain-general networks.

The patients' response to therapy, as demonstrated in Chapter Three, was not evident in any of the whole-brain analyses completed in this chapter. The group-level changes were small -yet significant - and were not evident in terms of behaviour until participants with involvement of the frontal lobes were excluded. As suggested above the low number of patients with a frontal lobe lesion did not permit a statistically valid separation of the groups for further analysis. Thus, it may be that whole-brain changes as a response to therapy were not revealed due to the statistical influence of the absence of improvement from this sub-group of patients. Nevertheless, future

developments in multivariate analyses comparing patient and healthy populations and within-group comparisons before and after therapy may prove sensitive at detecting neural changes within domain-specific language networks.

Previous functional imaging studies of post-stroke aphasia have largely depended on patients responding to or generating verbal information, varying from naming paradigms to other tasks outside the usual common experience, such as verbal fluency (*e.g*. generating verbs appropriate to an object noun) or word stem completion (*e.g.* viewing three letters and generating one or more words that incorporate these three initial letters). Although these tasks present healthy participants with a cognitive challenge, there may be a rapid reduction in task-associated activity as the task becomes more familiar or stimuli are repeated (Raichle *et al.,* 1994). In many participants with aphasia the task will prove more challenging and task habituation will occur more slowly in the face of increased difficulty due to the presence of the lesion. It can be predicted from the present study that these tasks will also involve activation of domain-general SN and CEN, in addition to language-specific systems. Most studies have related the results in patients to healthy participants responding to exactly the same stimuli and tasks as those given to the patients. One temptation has been to suggest that the right cerebral hemisphere activity in the patient group relative to the healthy group, particularly when it is in or close to what might be regarded as the right hemisphere homologue of Broca's area, is a shift in the lateralisation of language-specific processes (see Price and Crinion (2005)). The results from this study, in which the strategy has been to increase task difficulty for the healthy participants and reduce their in-scanner task performance to the level of the patients, suggest that the previous studies were observing up-regulation of normal domain-general cognitive control systems in the patients as they attempted a task that was unusually difficult for them as the consequence of their stroke (Rosen *et al*., 2000; Wise *et al*., 2003).

Alternative interpretations of the role of the IFG in recovery have been suggested. One suggestion is that activation in the right IFG is a response to a maladaptive strategy as evidenced by improvement in language function when patients have activity in the right IFG suppressed using inhibitory rTMS (Naeser *et al.,* 2006). However, if this region is part of the same SN identified in the healthy volunteers,

then the presence of activations in both groups suggests that activation in this region does not necessarily indicate a maladaptive mechanism, but rather a normal response to increased task difficultly. Furthermore, the extent to which additional cognitive effort impacts on domain-general skills, especially in aphasia, is not well understood and it could be that the extra recruitment of domain-general systems may be at the expense of domain-specific systems.

A study with very similar results to the present study but with a very different interpretation is that proposed by Saur and colleagues (2006). They demonstrated a positive correlation between language score and activity in the SMA, and left and right IFG. These authors used a task that required identifying semantic violations within auditory sentences. Although the authors interpreted the activity in these regions in terms of recovery of language networks, the co-ordinates of the regions they termed SMA, insula and IFG are identical with those identified in the present study as the dACC/SFG and IFG/aI, respectively. As in many studies investigating language recovery, the tasks used not only necessitated the recruitment of residual language skills, but also increased cognitive control and attention. Therefore, the data of Saur and colleagues is entirely in accord with the present study, and the disagreement is one of interpretation. Similarly, a single-case (uncorrected) study by Meizner and colleagues (2006) demonstrated a correlation between improvements due to naming therapy on activity during naming tasks that correlated with increased activity in the right IFG and dACC. The authors attribute these changes to a 'language domain-specific plasticity process', due to the absence of these activations in the group of healthy volunteers. This, as in many such studies, took no account of the differences in cognitive effort between the patient and healthy volunteers when performing a naming task.

Even when considering the classic language area of Broca, the division between domain-specific and domain–general activity is far from straightforward. Fedorenko and colleagues (2012) performed an fMRI study on healthy participants, and demonstrated that voxels within both left Brodmann's areas 44 (*pars opercularis)* and 45 (*pars triangularis*) responded to multiple tasks, both verbal and non-verbal. Only voxels within *pars opercularis* voxels found to be selective for language processing. The authors' concluded that although Broca's area contains domain-specific language

sub-regions, as has been the dogma for centuries, these neural components responded to tasks but were not specific to a domain.

Menon and colleagues (2010) propose that the IFG/aI is sensitive to transient salient environmental events, and its function is to mark salient events for additional processing. Marking salient events is essential to performing a picture description task. As described in the introduction, the subject is required to visually 'wander around' the picture and identify components that they think are distinct and important enough to describe verbally. However, they can be easily distracted by another component in the picture, or even semantic associations of a component, or extraneous thoughts triggered by the picture. This division of attention can increase word retrieval deficits even in mildly aphasic patients, and so can provide a useful insight into functional communication. This 'wandering' is similarly required when generating and contributing to spontaneous conversation, an area that most patients with aphasia report as being both disrupted and socially isolating to some degree. Perhaps correlating activity in the SN with a more general measure of residual language skill, such as a formal conversational analysis, would have more meaningful implications for predicting outcome. However, such an analysis is both extremely time-consuming and difficult to control across patients, so it is not routinely carried out in either neurology or SALT clinics, therefore restricting the clinical validity of such a potential correlation. Had I completed this type of assessment then one would expect that it would also correlate with activity in the SN. Therefore, the test chosen to ascertain 'residual language' ability, which did demonstrate this correlation, is arguably not the best, but is more clinically useful due to the ease with which it can be completed and scored.

A disappointing null result in this Chapter was that despite the patient group completing a mean of 20 hours therapy, and the healthy volunteers only 9 hours, both groups showed a significant behavioural improvement but this was not reflected in the whole-brain analyses. There are very few studies that have specifically investigated the neural underpinnings of a specific response to therapy. Fridriksson (2010) found that in 16 patients, it was in those that improved naming skills in response to 30 hours naming therapy that showed an increase in activity across the left hemisphere cortex, especially the parietal and premotor regions. In a subsequent reanalysis, and including

an additional 14 patients, Fridriksson and colleagues (2011) demonstrated a correlation between improved language performance in response to naming therapy and activity in left perilesional tissue. Similarly, following 30 hours of naming therapy in a group of ten patients, Pulvermuller and colleagues (2005) found that those patients that improved behaviourally also demonstrated a stronger early evoked-potential in three disparate regions across the brain. It may be that the greater number of treatment hours completed in these studies allowed visualisation of neural changes that were not revealed in the present study. Alternatively, it may be that targeting such a 'low-level' skill as same/different discrimination affords less sensitivity for a functional imaging investigation of rehabilitation.

5.4.1 Possible Implications for Future Studies

The same domain-general systems, namely the SN and CEN, were activated in patients with aphasia and healthy volunteers listening to noise- vocoded speech. The activation of these networks was only evident by using a novel method of manipulating stimuli for healthy volunteers in order to simulate the extent of impairment observed in patients with aphasic comprehension deficits. Most previous studies have not demonstrated these systems associated with task difficulty, because they have used identical stimuli and tasks for both healthy volunteers and patients. Price and Friston (1999) recommended "scanning patients with tasks they can perform", but this is a goal that is difficult to achieve for most patients (accuracy may not equate with cognitive effort when comparing patients and healthy subjects), and would limit studies to patients who have had a complete, or near complete, recovery. Therefore, this method of manipulating task difficulty in healthy participants has important implications for the planning of future imaging studies of patient groups.

Assessing the efficiency of this top-down control in aphasia is not routinely carried out, not least because linguistic impairments may impact on the accuracy of completing and interpreting formal assessments of cognitive control and *vice versa* (Fridriksson *et al.,* 2006). Of course, formal assessment is one method of investigating this. However clinical intuition is also an important aspect of identification of such impairment. The obvious outcome of this would be that patients are essentially 'triaged' for suitability of linguistic level therapy very soon after their

stroke. Triaging patients according to lesion localisation and residual domain-general cognitive skills does not equate with withholding therapy from those less suitable, but instead provides an evidence based mechanism for the current distribution of therapy approaches within many SALT clinics. Frequently 'frontal' patients are often given pragmatic approaches to therapy aimed at improving communicative participation through utilising intact skills, or educating family, whereas 'non frontal' patients are given cognitive neuropsychological based language intervention - even if under-dosed.

Although the importance of lesion location, irrespective of total lesion volume and impairment of particular language processes, will undoubtedly account for some of the variance observed in language recovery, this study has demonstrated that the function of domain-general cognitive control systems also has a significant impact on recovery. This study was not designed to determine why the dACC/SFG and the IFG/aI had such variable function across the group. In addition to a remote effect of long fibre tract infarction the microscopic effects of disease predisposing to stroke (such as hypertension and diabetes) and biological (which is not necessarily the same as chronological) ageing are probable factors influencing the SN function. Future studies could incorporate metabolic and neuroligand positron emission tomographic studies of this region, coupled with diffusion tensor MR imaging of white matter tracts, to investigate these possibilities.

In summary, this study has demonstrated the role of domain-general cognitive control systems in language tasks and the potential influence of their activation on the interpretation of functional imaging data in patient populations. More importantly, this study has indicated that impaired function of these systems has an impact on final outcome and so provides direct evidence for the frequent clinical intuition that impaired function of these domain-general systems leads to a poorer prognosis in post-stroke aphasia.

6 Discussion

6.1 Summary of Aims

In this thesis I have presented the results from three studies investigating the auditory perception of speech in healthy participants during both normal and degraded speech conditions and in patients with post-stroke aphasia. The broad aims of these three studies were:

- First, in Chapter Three, to develop and investigate the effectiveness of a computer-based therapy programme designed to improve phonological discrimination in patients with post-stroke aphasia. A subsidiary aim was to investigate how effective a noise-vocoded version of this training programme was at improving healthy volunteers ability to decode noise-vocoded speech.
- Second, in Chapter Four, to investigate the different neural mechanisms used to understand and repeat both normal and distorted sentences in healthy volunteers.
- And in Chapter Five, to investigate the systems that patients with aphasia recruited during 'listening-to-and-preparing-to-repeat' normal sentences in the presence of a comprehension deficit and compare these systems directly with those observed in healthy volunteers listening to distorted speech.

6.2 Summary of key results

This body of research set out to develop and investigate the effectiveness of a computer-based therapy programme designed to improve phonological discrimination in patients with post-stroke aphasia. Functional imaging was used to investigate the domain-specific neural systems supporting improvement in this linguistic area, but ultimately this line of investigation produced a null result. However, the analyses demonstrated the role of domain-general systems in supporting residual language function in chronic aphasic stroke. This was achieved by investigating both behavioural and functional imaging responses in patients and comparing their cerebral activity with that observed in healthy volunteers. One important consideration when comparing a patient group with a healthy population is that up-regulation of task-dependent domain-general activity will be observed in patients if they find the task more difficult than the healthy volunteers. This activity will most probably originate from cognitive control and attentional networks, rather than arising from reorganised

domain-specific language systems. To overcome this confound, it has been argued that patients should be given tasks that limit the additional effort required (Price and Friston, 1999; Sharp *et al.,* 2004*b*). However, in reality this is difficult to achieve because even if the patients behavioural performance closely matches that observed in the healthy participants, this is likely to be at the expense of greater cognitive 'effort'. An alternative is to match the difficulty experienced by the patients by making the task more difficult for healthy volunteers. Therefore, in my studies healthy volunteers were given three-channel noise-vocoded versions of the same BKB sentence stimuli given to the patients. This enabled the investigation of both domain-specific and domain-general systems associated with both normal and impaired speech perception and repetition.

In Chapter Three, I developed and investigated the effectiveness of a computer-based therapy programme designed to improve phonological discrimination in patients with post-stroke aphasia and a noise-vocoded version of this training programme in healthy volunteers. A group of 19 patients with post-stoke auditory comprehension and repetition deficits participated in home-based computerised therapy that resulted in an improvement in their ability to complete a same/different auditory discrimination task only, an area specifically targeted by the therapy programme. This was only apparent when patients without frontal lobe involvement in their lesion were excluded from the statistical analysis. A weakness of this *post hoc* analysis was that the study was not originally designed to compare treatment of phonological discrimination in two groups of patients with temporo-parietal lesions, namely those with and without additional frontal lobe infarction. However, this plausible *post hoc* observation generates the hypothesis for a further larger study.

As in many studies of behavioural aphasia therapy, the improvement was for treated items only. Furthermore, their ability to repeat did not improve. This may reflect parallel damage to posterior-anterior speech production pathways, which were not the target of the behavioural therapy. In contrast, the healthy participants responded to two weeks of training on the noise-vocoded sentences and showed a significant improvement in their ability to perceive and repeat these sentences. Importantly, the behavioural performance on these stimuli in healthy volunteers was well matched to

that in the patients. This permitted a more meaningful comparison of the functional imaging data between the two groups.

In Chapter Four, I presented the findings from the fMRI scanning sessions that took place before and after the training presented in Chapter Three. In this fourth Chapter, I aimed to investigate the different neural mechanisms used to understand and repeat both normal and distorted sentences in healthy volunteers. The results demonstrated that participants activated the expected domain-specific regions during listening-to-and-preparing-to-repeat both normal speech and noise-vocoded speech. In addition sensorimotor activations expected in the 'Repeat' trials were actually evident in these Listen trials when compared to the Repeat trials, indicating the extent to which pre-articulatory and sub-vocal rehearsal was taking place. There was no effect of session; that is, training did not change the pattern of activation based on a univariate statistical analysis. The most important finding from this Chapter was the additional activity within domain-general networks evident in the contrast of ListVoc versus ListNorm trials. As further confirmation of this result, a very recent and similar study on healthy participants has shown an identical result (Erb *et al.,* 2013). These networks, the SN and CEN, were engaged in the present study when the task of listening was more demanding and the participant needed to focus greater attention and cognitive control for each trial, and sustain this across all trials. Predictably, increased activity in the SN/CEN was also associated with greater deactivation of the DMN (see also, Erb *et al.,* 2013).

Finally, in Chapter Five, the systems that patients with aphasia recruited during 'listening-to-and-preparing-to-repeat' normal sentences in the presence of a comprehension deficit were explored and compared directly with those observed in healthy volunteers listening to distorted speech. It was demonstrated that the patients recruited the same domain-specific and domain-general regions as were observed in the healthy volunteers under the distorted speech conditions in Chapter Four, except in those regions that had been infarcted. This result highlighted the importance of domain-general cognitive control systems in functional imaging studies of language, especially when comprehension is made more difficult. This was only possible by manipulating task difficulty for the healthy participants, thereby reducing their in-scanner task performance to the level of the patients. Importantly, the recruitment of

these domain-general networks correlated with behavioural performance on an off-line assessment of residual language function.

Three broad contributions to the field have been made from these three results chapters of my thesis:

The first is that computer-based training on an identified component of abnormal speech processing, namely phonological discrimination, can be achieved in chronic aphasic patients. However, importantly, generalisation of this improved performance to untrained items may be more challenging, and there was preliminary evidence that lesion distribution also influences the response to this training. This highlights both the feasibility and the need to develop and refine additional home-based computerised therapy programmes. Specifically, for the first time a therapy aimed at alleviating an auditory discrimination deficit has been shown to be effective using a case-series design. This is a more robust methodology than the previous single case studies demonstrating effectiveness of therapy targeting this deficit. The importance of lesion location and extent when considering appropriateness of therapy has been proposed, which may prove to be important factors when practising speech and language therapists are required to make difficult clinical decisions about the allocation of appropriate therapy resources.

The second is that my thesis demonstrates that the ability to activate domain-general cognitive control influences outcome after aphasic stroke. Whilst, further research is required to be able to make informed clinical decisions based on this knowledge, this finding may allow clinicians, both medical doctors and allied health professionals, to make more accurate forecasts about the ability of patients to respond to behavioural therapy. Investigating the function of the SN/CEN with fMRI may not be practical in a clinical setting, but directed neuropsychological investigations may prove both sensitive and specific to this end. In the context of unimpaired language systems, cognitive control is required at every level of language comprehension and production. A person must first determine what incoming information is relevant, or salient, and then access higher-order cognitive systems such as semantics and pragmatics, in order to make processing more rapid. Simultaneously to this they will be eliminating and re-directing attention from unwanted stimuli in the background,

auditory or visual, and perhaps accessing short-term and semantic memory systems, in addition to continuing to attend to pragmatic and nonverbal cues. In an injured brain, not only is the language system impaired, affecting their ability to decode and access linguistic components of language, but their lesion is also likely to impact on some of the higher-order, domain-general systems that are utilised during language comprehension and production. Therefore damage to the feedforward and feedback mechanisms between these domain-general and domain-specific systems are also likely to compound the reduced performance of these systems.

Third, the same domain- general systems, namely the SN and CEN, were activated in patients with aphasia and healthy participants attempting to understand and repeat degraded stimuli, but not when healthy volunteers listened to clear speech. This clear versus degraded comparison facilitated interpretation of the data when subsequently comparing the function of healthy and diseased brains. The results from this study, in which the strategy was to manipulate task difficulty for the healthy participants and therefore reduce their in-scanner task performance to the level of the patients (as shown in Chapter Three), was the opposite to that recommended by Price and Friston (1999). It is a readily achievable goal, and avoids the difficulty inherent in 'giving patients tasks they can do', which is that this strategy limits clinical studies to patients with only minor impairments. This important methodological finding is probably not restricted to patient studies concerned with post-stroke aphasia but likely relevant to a range of cognitive and motor deficits.

7 Implications for Future Research

Factors that influence recovery from aphasic stroke remain largely unknown. The size of the lesion and the age of the patient only account for some of the variance (Lendrem *et al.,* 1985; Kertesz *et al*., 1979) but have been shown to contribute little to our understanding as to why some patients with chronic post-stroke aphasia make considerable progress following aphasia therapy whilst for others it is limited. The extent and type of aphasic deficits to be rehabilitated are usually assessed and interpreted in terms of domain-specific linguistic processes. However, domain-general processes (*i.e*. attention and executive control) inevitably play a crucial role in any domain-specific deficit but are not routinely considered empirically. The strong implication from this study about the importance of activating these domain-general networks in terms of residual language function and the suitability of this therapy for patients without frontal lobe involvement, suggests that testing executive function in patients in aphasia is important in determining the likelihood of therapy outcome. Although this has previously been suggested and some research groups do carry out more extensive cognitive testing on patients with aphasia (Purdy, 2002; Murray, 2012; Fridriksson *et al.,* 2006; Jefferies *et al*., 2006; Corbett *et al.,* 2009), this is still largely, both in research and clinically, only carried out in the form of a screening assessment (*i.e*. the short version of Raven's matrices or forward digit span) to ensure that a patient is not severely impaired on these more general cognitive tasks. However, I would like to investigate the extent to which a more detailed assessment of these non-linguistic abilities, applicable to a variety of therapies, can be used to predict outcome, both in terms of spontaneous recovery and in response to therapy. This could be achieved, for example, through using a refined version of the therapy programme presented here in a larger group of patients and incorporating more robust domain-general assessments. In addition, it may be that targeting therapeutic strategies, pharmacological or behavioural, at domain-general brain systems, rather than, or in addition to language-specific systems, may benefit aphasic stroke rehabilitation.

The outcome of carrying out such detailed assessments may allow SALTs to objectively direct patients towards the most appropriate type of therapy; impairment based or pragmatic. Patients with limited executive functioning skills will still benefit

from rehabilitation from a SALT but this is likely to involve approaches targeting general communicative abilities such as maximising participation in conversation, improving use of gesture, facilitating the use of writing to aid communication or even a picture exchange system. Alternatively, it may be that targeting the executive functioning skills themselves may be required initially in order to improve the patients potential for improvement. Whereas patients with more intact executive functioning skills may be directed to impairment based therapy with/without additional pragmatic therapy.

Given the wide confidence intervals encountered in the behavioural data obtained in this study, ~40 participants would be required in each group, those with and without frontal lobe involvement. From my data this population size will give 95% confidence in a positive result from a specific investigation of the effect of additional frontal lobe infarction on the rehabilitation of phonological discrimination in participants with temporo-parietal infarction. Based on the recruitment experience of this study, to recruit 80 participants would require screening approximately 400-500 participants with chronic post-stroke aphasia. Few other studies report the extent to which recruitment is problematic in studies such as these. Saur and colleagues (2006) did report their recruitment rate, which involved recruiting just fourteen patients from a total of 198. Regular publication of recruitment rate in studies of patients with aphasia would highlight the effort required to conduct such studies, which is important information for those both awarding and, applying for, financial support, but also contributes to the discussion pertaining to the practicalities of conducting large RCTs in this population.

Whilst the science of constructing such RCTs in this field continues to prove challenging at many levels (Leff and Howard, 2012), the need for a more robust evidence base is ecumenically accepted. The best research methodology to undertake this remains contentious, despite decades of discussion. A large part of this contention arises from poor multi-disciplinary communication concerning the complexities of treating aphasia, not as a unitary phenomenon, but instead as a complex disease with multiple levels of deficit. General outcome measures, typically used in RCTs, which assess broad untreated, yet functional, outcome measures, will not contribute to this evidence base. Instead studies need to assess the outcome of specifically what

component of language was targeted, perhaps in addition to functional carry-over. Once this evidence base is established the field can then begin to investigate how multiple therapies can affect more functional communication measures.

The proposal would be to be able to 'prescribe' from a number of previously designed software programmes, on the basis of the initial clinical assessment of aphasic impairments, lesion localisation and clinical priority. The patient would likely be prescribed with two or three programmes to engage with on a daily basis. The aim would be to treat a number of specific impairments, in the expectation that relatively modest improvements on each programme would result in a greater overall improvement in everyday communication. Although aphasia is a syndrome and not a disease, different approaches to improve specific components comprising the whole spectrum of aphasia might be expected to result in a greater sum of overall benefit. In order to achieve this, the results presented in this thesis highlight the need to ensure that future software programmes are of suitably high quality and interest to ensure that participants engage sufficiently with the programme to benefit from the increased dose available using this service-delivery. The use of more sophisticated 'gaming' type approaches are likely to improve response to therapy participation. Equally, incorporating a more diverse therapy programme into such 'games' is likely to impact both on participation, generalisation and functional outcome. The art will be in ensuring that the therapy is specific enough to reliably measure effectiveness of the programme, whilst maximising these additional contributing factors to ensure compliance over extended time periods.

In terms of auditory discrimination deficits specifically, the neural mechanisms by which the therapy improves performance remain undefined. Investigating this may shape the way in which therapy is conducted in terms of both which items should be used (*i.e.* assuming generalisation of items or building a 'core vocabulary') and for whom the therapy is useful. There has been some discussion in the noise-vocoding behavioural training literature as to whether high-variability training (multiple speakers stimuli) rather than low (single speaker stimuli) is required in order to generalise auditory items as has been shown to be the case when learning novel foreign stimuli (Bradlow *et al.,* 1997; Fu *et al.,* 2005, Stacey and Summerfield, 2007).

This dimension may be an important factor that has not been considered in this present study but should be relatively straightforward to investigate.

Importantly, the initial motivation behind the development of computerised therapy is that by allowing the patient to complete this without the constant 1:1 supervision of a speech and language therapist enables them to maximise dose whilst minimising additional costs. The cost effectiveness of such interventions obviously needs to be established. Palmer and colleagues (2012) investigated the cost effectiveness of the 'Step-by-step' computerised therapy for anomia in 15 patients. They used the 'quality-adjusted life year' (QALY) measures (NICE, 2008), which calculates the 'burden' of a disease, including both the quality and quantity of life in their calculations and determine the cost effectiveness of a medical intervention. These authors found that a 20% improvement on naming ability gained one QALY. One QALY is considered to be cost effective if it costs less than £20,000. Palmer and colleagues (2012) calculated that their 'step-by-step' programme cost the service provider approximately £3000 per year and so was considered to be highly cost effective. However, this improvement was not maintained over time, suggesting that participation in therapy may need to be reinforced. The cost-effectiveness of this study, and many other computer-based studies, could be established using similar measures in order to demonstrate the potential capacity for ensuring dose requirements are met even under current financial constraints. Establishing such cost-effectiveness in terms of quality of life improvements may add credibility to an essential component of post-stroke rehabilitation that is becoming increasingly undervalued.

In terms of the functional imaging component of this thesis it may be helpful to include a number of physiological measures in future studies on stroke patients. These could include measuring, rather than assuming, the shape of the haemodynamic response function (HRF), or measuring the reactivity of the cerebral vasculature (Murphy *et al.,* 2011). The HRF used in the imaging Chapters of this thesis were assumed to be canonical. However, as mentioned in the introduction, there is some debate in the literature as to whether assuming a canonical HRF is methodologically valid in some stroke patients due to the presence of cardiovascular disease that has

been shown to delay the onset and the peak of the HRF. This delay could lead to an underestimation of the extent of activation in some regions, making comparisons between patients and healthy volunteers challenging. Future studies would benefit from utilising this approach in order to ensure that any activations, such as those related specifically to improvement in therapy, are detected. This methodological factor may have contributed to the null result in left perisylvian cortex in my population of patients with aphasia.

Finally, multivariate statistical analyses, which generate different but often overlapping independent spatial maps, might afford new insights from my data. As well as activation patterns, components will isolate some artifacts such as head movement that has not been removed by standard image preprocessing. By accounting for various sources of noise, the sensitivity for detecting biological signal is increased. Therefore by reducing the noise in the data and accounting for overlapping networks, such multivariate analyses can extract additional functional information from the data that may not be apparent from a subtractive univariate analysis (*e.g.* Geranmayeh *et al.,* 2012). I have begun to carryout such multivariate analyses using independent-component analyses (ICA) within FSL. However, the presence of a large lesion has proved problematic is terms of comparing distributed networks in this way. I am currently endeavouring to compare systems between healthy volunteers and patients in the intact hemisphere only. However, this analysis is further confounded in my dataset as the images were acquired using 'sparse scanning', for reasons outlined in the methods chapter, which reduces the number of functional imaging volumes within the dataset.

By implementing these improvements on the research presented in this thesis and extending it in the ways presented above, I have considerable scope to contribute to the fields of neuroscience, clinical practice and aphasiology. I look forward to forging my career around these developments and seeing the real contributions these can make to patient outcome.

8 References

Abo M, Senoo A, Watanabe S, Miyano S, Doseki K, Sasaki N, Kobayashi K, Kikuchi Y, Yonemoto K. (2004) Language-related brain function during word repetition in post-stroke aphasics. Neuroreport 15:1891-1894.

Acosta-Cabronero J, Patterson K, Fryer T, Hodges J, Pengas G, Williams G, Nestor PJ. (2011) Atrophy, hypometabolism and white matter abnormalities in semantic dementia tell a coherent story. Brain 134:2025-2035.

Anticevic A, Cole MW, Murray JD, Corlett PR, Wang XJ, Krystal JH. (2012) The role of default network deactivation in cognition and disease. Trends in Cognitive Sciences 16:584-592.

Archibald L, Orange J, Jamieson DJ. (2009) Implementation of computer-based language therapy in aphasia. Therapeutic Advances in Neurol. Dis. 2:299-311.

Awad M, Warren J, Scott SK, Turkheimer FE, Wise RJ. (2007) A common system for the comprehension and production of narrative speech. J. Neurosci.27:11455-11464.

Baker E, Blumstein S, Goodglass H. (1981) Interaction between phonological and semantic factors in auditory comprehension. Neuropsychologia 19:1-165.

Bakheit AM, Shaw S, Carrington S, Griffiths S. (2007) The rate and extent of improvement with therapy from the different types of aphasia in the first year after stroke. Clin. Rehabil. 21:941-949.

Barch D, Braver TS, Nystrom LE, Forman SD, Noll DC, Cohen JD. (1997) Dissociating working memory from task difficulty in human prefrontal cortex. Neuropsychologia 35:1373-1380.

Barlow J, Geirut, J. (2002) Minimal Pair Approaches to phonological remediation. Seminars in Speech and Language 23:57-67.

Bartha L, Benke T. (2003) Acute conduction aphasia: an analysis of 20 cases. Brain and Language 85:93-108.

Basso A, Casati G, Vignolo LA. (1977) Phonemic identification defect in aphasia. Cortex 13:85-95.

Baumgaertner A, Hartwigsen G, Roman S. (2013) Right-hemispheric processing of non-linguistic word features: implications for mapping language recovery after stroke. Human Brain Mapping 34:1293-1305.

Beckmann C, Jenkinson M, Smith SM. (2003) General multilevel linear modeling for group analysis in FMRI. Neuroimage 20:1052-1063.

Behrmann M, Lieberthal T. (1989) Category-specific treatment of a lexical-semantic deficit: a single case study of global aphasia. Br. J. Disord. Commun. 24:281-299.

Belin P, Van Eeckhout P, Zilbovicius M, Remy P, Francois C, Guillaume S, Chain F, Rancurel G, Samson Y (1996) Recovery from nonfluent aphasia after melodic intonation therapy: a PET study. Neurology 47:1504-1511.

Belin P, Zatorre R (2000) 'What', 'where' and 'how' in auditory cortex. Nature Neuroscience 3:965-966.

Bench J, Kowal A, Bamford J (1979) The BKB (Bamford-Kowal-Bench) sentence lists for partially-hearing children. British Journal of Audiology 13:108-112.

Ben-Shachar M, Palti D, Grodzinsky Y. (2004) Neural correlates of syntactic movement: converging evidence from two fMRI experiments. Neuroimage 21:1320-36.

Berthier M, Garcia-Casares N, Walsh S, Nabrozidis A, Ruiz de Mier R, Green C, Davila G, Gutierrez A, Pulvermuller F. (2011) Recovery from post-stroke aphasia: lessons from brain imaging and implications for rehabilitation and biological treatments. Discovery Medicine 12:275-289.

Bhogal SK, Teasell, R, Speechley, M. (2003) Intensity of Aphasia Therapy, Impact on Recovery. Stroke 34:987-993.

Binder J, Frost J, Hammeke T, Bellgowan P, Rao S, Cox R (1999) Conceptual processing during the conscious resting state: a functional MRI study. J Cogn Neurosci 11:80 –93.

Binder JR, Desai RH. (2011) The neurobiology of semantic memory. Trends in Cognitive Sciences 15:527-536.

Bishop D, Brown B, Robson J. (1990) The relationship between phoneme discrimination, speech production, and language comprehension in cerebral-palsied individuals. Journal of Speech, Language and Hearing Disorders 33:210-219.

Blank C, Bird, H, Turkheimer, F, Wise, RJ. (2003) Speech production after stroke: the role of the right pars opercularis. Annals of Neurology 54:310-320.

Blink E. (2010) Basic MRI Physics. http://mri-physicsnet.

Blumstein S, Baker E, Goodglass H. (1977) Phonological factors in auditory comprehension in aphasia. Neuropsychologia 15:19-30.

Boatmann D, Gordon B, Hart J, Selnes O, Miglioretti D, Lenz F. (2000) Transcortical sensory aphasia: revisited and revised. Brain 123:1634-1642.

Bogen J, Bogen GM. (1976) Wernicke's region-Where is it? Annals of the New York Academy of Sciences 280:834-843.

Boller F, Kim Y, Mack JL. (1977) Auditory comprehension in aphasia. New York: Academic Press.

Bonakdarpour B, Parrish TB, Thompson CK. (2007) Hemodynamic response function in patients with stroke-induced aphasia: implications for fMRI data analysis. Neuroimage 36:322-331.

Bonnelle V, Ham T, Leech R, Kinnunen K, Mehta M, Greenwood R, Sharp D. (2012) Salience network integrity predicts default mode network function after traumatic brain injury. Proceedings of the National Academy of Sciences 109:4690-4695.

Bowen A, Hesketh A, Patchick E, Young A, Davies L, Vail A, Long AF, Watkins C, Wilkinson M, Pearl G, Ralph MA, Tyrrell P. (2012) Effectiveness of enhanced communication therapy in the first four months after stroke for aphasia and dysarthria: a randomised controlled trial. BMJ 345:e4407.

Brady M, Kelly H, Godwin J, Enderby P. (2012) Speech and language therapy for aphasia following stroke. In: The Cochrane Collaboration.

Braun A, Varga M, Stager S, Schulz G, Selbie S, Maisog JM, Carson RE, Ludlow CL. (1997) Altered patterns of cerebral activity during speech and language production in developmental stuttering. An $H^2(15)O$ positron emission tomography study. Brain 120:761-784.

Brett M, Leff AP, Rorden C, Ashburner J. (2001) Spatial normalization of brain images with focal lesions using cost function masking. NeuroImage 14:484-500.

Brownsett SLE, Wise RJS. (2009) The Contribution of the Parietal Lobes to Speaking and Writing. Cerebral Cortex 20:517-523.

Butterworth, B., *et al.* (1984). The semantic deficit in aphasia: the relationship between semantic errors in auditory comprehension and picture naming. Neuropsychologia 22: 409-426.

Butti C, Santos M, Uppal N, Hof PR. (2013) Von Economo neurons: clinical and evolutionary perspectives. Cortex 49:312-326.

Byng S, Coltheart M. (1986) Aphasia therapy research: methodological requirements and illustrative results. Amsterdam: North-Holland Publishing.

Byng S, Nickels LA, Black M. (1994) Replicating therapy for mapping deficits in agrammatism: remapping the deficit. Aphasiology 8:315-341.

Callan DE, Jones JA, Callan AM, Akahane-Yamada R. (2004) Phonetic perceptual identification by native- and second-language speakers differentially activates brain regions involved with acoustic phonetic processing and those involved with articulatory-auditory/orosensory internal models. NeuroImage 22:1182-1194.

Callan DE, Tajima K, Callan AM, Kubo R, Masaki S, Akahane-Yamada R. (2003) Learning-induced neural plasticity associated with improved identification performance after training of a difficult second-language phonetic contrast. NeuroImage 19:113-124.

Caplan D, Gow D, Makris N. (1995) Analysis of lesions by MRI in stroke patients with acoustic-phonetic processing deficits. Neurology 45:293-298.

Caplan D, Hildebrandt N, Makris N. (1996) Location of lesions in stroke patients with deficits in syntactic processing in sentence comprehension. Brain 119:933-949.

Cappa S, Perani D, Grassi F, Bressi S, Alberoni M, Franceschi M, Bettinardi V, Todde S, Fazio F. (1997) A PET follow-up study of recovery after stroke in acute aphasics. Brain and Language 56:55-67.

Caramazza A, Berndt R, Basili AG. (1983) The selective impairment of phonological processing: a case study. Brain and Language 18:128-174.

Catani M, Jones DK, ffytche DH. (2005) Perisylvian language networks of the human brain. Annals of Neurology 57:8-16.

Cherney L, Small SL. (2006) Task-dependent changes in brain activation following therapy for nonfluent aphasia: discussion of two individual cases. Journal of the International Neuropsychological Society 12:828-842.

Cherney LR. (2010) Oral reading for language in aphasia (ORLA): evaluating the efficacy of computer-delivered therapy in chronic nonfluent aphasia. Topics in Stroke Rehabilitation 17:423-431.

Cherney L, Halper A, Holland A, Cole R. (2008) Computerized script training for aphasia: preliminary results. American Journal of Speech-Language Pathol. 17:19-34.

Chrysikou E, Hamilton RH. (2011) Noninvasive brain stimulation in the treatment of aphasia: exploring interhemispheric relationships and their implications for neurorehabilitation. Restor. Neurol. Neurosci. 29:375-394.

Cochrane A. (1972) Effectiveness and Efficiency. Random Reflections on Health Services. London: Nuffield Provincial Hospitals Trust.

Code C, Heron C. (2003) Services for aphasia, other acquired adult neurogenic communication and swallowing disorders in the United Kingdom, 2000. Disability and Rehabilitation 25:1231–1237.

Coelho CA. (2002) Story narratives of adults with closed head injury and non-brain-injured adults: influence of socioeconomic status, elicitation task, and executive functioning. Journal of Speech Lang. Hear. Res. 45:1232-1248.

Coelho CA, Liles BZ, Duffy RJ. (1995) Impairments of discourse abilities and executive functions in traumatically brain-injured adults. Brain Inj. 9:471-477.

Concato J. (2013) Study design and "evidence" in patient-oriented research. Am J Respir. Crit. Care Med. 187:1167-1172.

Corbett F, Jefferies E, Ehsan S, Lambon Ralph M. (2009) Different impairments of semantic cognition in semantic dementia and semantic aphasia: evidence from the non-verbal domain. Brain 132:2593-2608.

Crerar M, Ellis AW, Dean EC. (1996) Remediation of sentence processing deficits in aphasia using a computer-based microworld. Brain and Language 52:229-275.

Crosbie S, Holm A, Dodd B. (2005) Intervention for children with severe speech disorder: a comparison of two approaches. International Journal of Language and Communication disorders 40:467-491.

Davis AG, Wilcox MJ. (1981) Incorporating parameters of natural conversation in aphasia treatment. Baltimore, MD: Williams & Wilkins.

Davis M, Johnsrude IS. (2003) Hierarchical processing in spoken language comprehension. Journal of Neuroscience 23:3423-3431.

Davis M, Johnsrude IS. (2007) Hearing speech sounds: Top-down influences on the interface between audition and speech perception. Hear. Res. 229:132-147.

Davis MH, Hervais-Adelman A, Taylor K, McGettigan C, Jonsrude IS. (2005) Lexical information drives per- ceptual learning of distorted speech: Evidence from the comprehension of noise-vocoded sentences. Journal of Experimental Psychology: General 134: 222–241.

Demeurisse G, Verhas M, Capon A. (1991) Remote cortical dysfunction in aphasic stroke patients. Stroke 22:1015-1020.

Devlin J, Russell RP, Davis MH, Price CJ, Wilson J, Moss H, Matthews P, Tyler L. (2000) Susceptibility-Induced Loss of Signal: Comparing PET and fMRI on a Semantic Task. NeuroImage 11:589-600.

Dhanjal N, Handunnetthi L, Patel M, Wise RJ. (2008) Perceptual systems controlling speech production. Journal of Neuroscience 28:9969-9975.

Doesborgh S, van de Sandt-Koenderman M, Dippel D, van Harskamp F, Koudstaal P, Visch-Brink E. (2004) Effects of semantic treatment on verbal communication and linguistic processing in aphasia after stroke: a randomized controlled trial. Stroke 35:141-146.

Dosenbach N, Fair D, Cohen A, Schlaggar B, Petersen S. (2008) A dual-networks architecture of top-down control. Trends in Cognitive Sciences 12:99-105.

Dosenbach N, Fair D, Miezin F, Cohen A, Wenger K, Dosenbach R, Fox M, Snyder A, Vincent J, Raichle M, Schlaggar B, Petersen S. (2007) Distinct brain networks for adaptive and stable task control in humans. Proceedings of the National Academy of Sciences 104:11073-11078.

Dronkers N, Wilkins D, Van Valin R, Redfern B, Jaeger J. (2004) Lesion analysis of the brain areas involved in language comprehension. Cognition 92:145-177.

Engelter ST, Gostynski M, Papa S, Frei M, Born C, Ajdacic-Gross V, Gutzwiller F, Lyrer PA. (2006) Epidemiology of aphasia attributable to first ischemic stroke: incidence, severity, fluency, etiology, and thrombolysis. Stroke 37:1379-84.

Eisner F, McGettigan C, Faulkner A, Rosen S, Scott SK. (2010) Inferior frontal gyrus activation predicts individual differences in perceptual learning of cochlear-implant simulations. Journal of Neuroscience 30: 7179-7186.

Eliades S, Wang X. (2008) Neural substrates of vocalization feedback monitoring in primate auditory cortex. Nature 453: 1102-1106.

Erb J, Henry M, Eisner F, Obleser J. (2013). The brain dynamics of rapid perceptual adaptation to adverse listening conditions. J Neurosci 33: 10688-10697.

Fedorenko E, Duncan JS, Kanwisher N. (2012) Language-selective and domain-general regions lie side by side within Broca's area. Current Biology 22: 2059-2062.

Fernandez B, Cardebat D, Demonet J, Joseph P, Mazaux J, Barat M, Allard M. (2004) Functional MRI follow-up study of language processes in healthy subjects and during recovery in a case of aphasia. Stroke 35: 2171-2176.

Field, A. (2005). Discovering statistics using SPSS (2nd ed) pp348-60. London: Sage.

Fillingham J, Sage K, Lambon Ralph MA. (2006) The treatment of anomia using errorless learning. Neuropsychological Rehabilitation 16:129-154.

Fink RB, Brecher A, Sobel P, Schwartz MF. (2005) Computer-assisted treatment of word retrieval deficits in aphasia. Aphasiology 19: 943-954

Francis D, Riddoch J, Humphreys G. (2001) Cognitive Rehabilitation of Word meaning Deafness. Aphasiology 15: 749-766.

Franklin S. (1989) Dissociations in auditory word comprehension: evidence from nine fluent aphasic patients. Aphasiology 3: 189-207.

Franklin S, Buerk F, Howard D. (2002) Generalised improvement in speech production for a subject with reproduction conduction aphasia. Aphasiology 16:1087-1114.

French J, Williamson PD, Thadani VM, Darcey TM, Mattson RH, Spencer SS, Spencer DD. (1993) Characteristics of medial temporal lobe epilepsy: I. Results of history and physical examination. Annals of Neurology 34: 774-780.

Fridriksson J. (2010) Preservation and modulation of specific left hemisphere regions is vital for treated recovery from anomia in stroke. Journal of Neuroscience 30: 11558-11564.

Fridriksson J, Nettles C, Davis M, Morrow L, Montgomery A. (2006) Functional communication and executive function in aphasia. Clinical Linguistics & Phonetics 20: 401-410.

Fridriksson J, Richardson J, Fillmore P, Cai B. (2012) Left hemisphere plasticity and aphasia recovery. NeuroImage 60: 854-863.

Friederici AD, Rüschemeyer SA, Hahne A, Fiebach CJ. (2003) The role of left inferior frontal and superior temporal cortex in sentence comprehension: localizing syntactic and semantic processes. Cereb Cortex. 13:170-7.

Friston KJ. (2003) Introduction: Experimental design and statistical parametric mapping. In: Human Brain Function (Frackowiak, R. *et al*., eds): Academic Press.

Friston K.(2012) Ten ironic rules for non-statistical reviewers. Neuroimage 61: 1300-10.

Fu C, Vythelingum G, Brammer M, Williams S, Amaro E, Andrew C, Yaguez L, van Haren N, Matsumoto K, McGuire P. (2006) An fMRI study of verbal self-monitoring: neural correlates of auditory verbal feedback. Cerebral Cortex 16: 969-977.

Gainotti G, Miceli G, Silveri MC, Villa G. (1982) Some anatomo-clinical aspects of phonemic and semantic comprehension disorders in aphasia. Acta Neurologica Scandinavica 66: 652–665.

Geranmayeh F, Brownsett SL, Leech R, Beckmann CF, Woodhead Z, Wise RJ. (2012) The contribution of the inferior parietal cortex to spoken language production. Brain and Language 121: 47-57.

Geschwind N. (1965*a*) Disconnexion syndromes in animals and man. I. Brain 88: 237-294.

Geschwind N. (1965*b*) Disconnexion syndromes in animals and man. II. Brain 88: 585-644.

Gielewski EJ (1989) Acoustic analysis and auditory retraining in the remediation of sensory aphasia. In: Aphasia therapy (Code, C. and Muller, D., eds) London: Whurr.

Goodglass H, Kaplan E, Barresi B. (2001) The Assessment of Aphasia and related disorders. Baltimore: Lippincott Williams &Wilkins.

Grawemeyer B, Cox R, *et al*. (2000) AUDIX: a knowledge-based system for speech-therapeutic auditory discrimination exercises. Stud Health Technol Inform 77:568-72.

Greenberg S, Carvey H, Hitchcock L, Chang S. (2003) Temporal properties of spontaneous speech-a syllable-centric perspective. Journal of Phonetics 31: 465-485.

Greener J, Enderby P, Whurr R. (2002) Speech and language therapy for aphasia following stroke. In: Cochrane Database Systematic Reviews, vol. 2, p CD000425.

Greicius M, Menon V. (2004) Default-mode activity during a passive sensory task: uncoupled from deactivation but impacting activation. Journal of Cognitive Neuroscience 16: 1484–1492.

Greicius MD. (2002) Functional connectivity in the resting brain: A network analysis of the default mode hypothesis. Proceedings of the National Academy of Sciences 100: 253-258.

Griffiths TD, Warren JD. (2002) The planum temporale as a computational hub. Trends in Neurosciences 25: 348-353.

Guenther FH. (2006) Cortical interactions underlying the production of speech sounds. Journal of Communication Disorders 39: 350–365.

Hall D, Haggard MP, Akeroyd MA, Palmer AR, Summerfield AQ, Elliott MR, Gurney EM, Bowtell RW. (1999) "Sparse" temporal sampling in auditory fMRI. Human Brain Mapping 7: 213–223.

Hall D, Johnsrude I, Haggard M, Palmer A, Akeroyd M, Summerfield A. (2002) Spectral and temporal processing in human auditory cortex. Cereb. Cortex 12: 140-9.

Hart J, Gordon B. (1990) Delineation of single-word semantic comprehension deficits in aphasia, with anatomical correlation. Annals of Neurology 27: 226-231.

Heiss W, Kessler J, Karbe H, Fink GR, Pawlik G. (1993) Cerebral glucose metabolism as a predictor of recovery from aphasia in ischemic stroke. Arch Neurol 50: 958-964.

Heiss W, Thiel A. (2006) A proposed regional hierarchy in recovery of post-stroke aphasia. Brain and Language 98: 118-123.

Helm-Estabrooks N. (2002) Cognition and aphasia: A discussion and a study. Journal of Communication Disorders 35: 171–186.

Hickok G. (2009) The functional neuroanatomy of language. Phys Life Rev 6: 121–143.

Hickok G, Buchsbaum B, Humphries C, Muftuler T. (2003) Auditory-motor interaction revealed by fMRI: speech, music, and working memory in area Spt. Journal of Cognitive Neuroscience 15:673–682.

Hickok G, Okada K, Barr W, Pa J, Rogalsky C, Donnelly K, Barde L, Grant A. (2008) Bilateral capacity for speech sound processing in auditory comprehension: evidence from Wada procedures. Brain & Language 107: 179–184.

Hickok G, Poeppel D. (2000) Towards a functional neuroanatomy of speech perception. Trends in Cognitive Sciences 4: 1463-1467.

Hickok G, Poeppel D. (2007) The cortical organization of speech processing. Nature Reviews Neuroscience 8: 393-402.

Hillis AE. (1993) The role of models of language processing in rehabilitation of language impairments. Aphasiology 7: 5-26.

Hillis AE. (2006) The right place at the right time? Brain 129: 1351-1356.

Hinckley J. (2002) Models of language rehabilitation. New York: Guilford Press.

Holland A. (1970) Case studies in aphasia rehabilitation using programmed instruction. Journal of Speech and Hearing Disorders 35: 377-390.

Howard D. (1986) Beyond randomised controlled trials: the case for effective case studies of the effects of treatment in aphasia. Br, J Disord Commun 21: 89-102.

Howard D, Hatfield FM. (1987) Aphasia Therapy: Historical and Contemporary Issues. London: Erlbaum.

Inoue Y, Takemoto K, Miyamoto T, Yoshikawa N, Taniguchi S, Saiwai S, Nishimura Y, Komatsu T. (1980) Sequential computed tomography scans in acute cerebral infarction. Radiology 135: 655-662.

Jacquemot C, Scott S. (2006) What is the relationship between phonological short-term memory and speech processing? Trends in Cognitive Sciences 10: 480-486.

Jefferies E, Lambon Ralph M. (2006) Semantic impairment in stroke aphasia versus semantic dementia: A case-series comparison. Brain 129: 2132-2147.

Jenkinson M, Smith S. (2001) A global optimization method for robust affine registration of brain images. Med Image Anal 5: 143–156.

Jenkisnon, M (2001). Registration, brain atlases and cortical flattening. In Jezzard P, Clare S. Principles of nuclear magnetic resonance and MRI. . In: Functional MRI (Jezzard, P. et al., eds) Oxford: Oxford Univ. Press.

Jezzard P, Clare S. (2001) Principles of nuclear magnetic resonance and MRI. . In: Functional MRI (Jezzard, P. et al., eds) Oxford: Oxford Univ. Press.

Katz R, Wertz RT. (1997) The efficacy of computer-provided reading treatment for chronic aphasic adults. J Speech Lang Hear Res 40: 493– 507.

Katz RC. (2010) Computers in the treatment of chronic aphasia. Seminars in Speech and Language 31: 34-41.

Kay J, Coltheart M, Lesser R. (1992) Psycholinguistic Assessments of Language Processing in Aphasia (PALPA). Hove, UK: Laurence Erlbaum Associates.

Kayser C, Logothetis NK. (2007) Do early sensory cortices integrate cross-modal information? Brain Structure and Function 212: 121-132.

Kelly H, Brady MC, Enderby P. (2010) Speech and language therapy for aphasia following stroke. The Cochrane Collaboration.

Kennerley S, Walton M, Behrens T, Buckley M, Rushworth M. (2006) Optimal decision making and the anterior cingulate cortex. Nature Neuroscience 9: 940–947.

Kertesz A. (1983) Aphasia in Clinical Practice. Canadian Fam. Phys. 29: 128-132.

Kertesz A, Lau WK, Polk M. (1993) The structural determinants of recovery in Wernicke's aphasia. Brain and Language 44: 153-164.

Kinsella G. (1998) Assessment of attention following traumatic brain injury: A review. Neuropsychological Rehabilitation 8: 351–375.

Kiran S, Ansaldo A, Bastiaanse R, Cherney L, Howard D, Faroqi-Shah Y, Meinzer M, Thompson CK. (2013) Neuroimaging in aphasia treatment research: standards for establishing the effects of treatment. NeuroImage 76: 428-435.

Kreisler A, Godefroy O, Delmaire C, Debachy B, Leclercq M, Pruvo JP, Leys D. (2000) The anatomy of aphasia revisited. Neurology 54: 1117-1123.

Kremer C, Perren F, Kappelin J, Selariu E, Abul-Kasim K. (2013) Prognosis of aphasia in stroke patients early after iv thrombolysis. Clinical Neurology and Neurosurgery 115: 289-292.

Laganaro M, Di Pietro M, Schnider A. (2006) Computerised treatment of anomia in acute aphasia: Issue of treatment intensity and training size. Neuropsychological Rehabilitation 44: 534–545.

Lambon Ralph M, Cipolotti L, Manes F and Patterson K. (2010*a*) Taking both sides: do unilateral anterior temporal lobe lesions disrupt semantic memory? Brain: 133: 3243–3255.

Lambon Ralph M, Snell C, Fillingham J, Conroy P, Sage, K. (2010*b*) Predicting the outcome of anomia therapy for people with aphasia post CVA: Both language and cognitive status are key predictors. Neuropsychological Rehabilitation 20: 289–305.

Lambon Ralph M, Patterson K. (2008) Generalization and differentiation in semantic memory: insights from semantic dementia. Ann N Y Acad Sci 1124: 61-76.

Laplane D, Degos JD, Bauloc M, Gray F. (1981) Bilateral infarction of the anterior cingulate gyri and of the fornices. J Neurol Sci 51: 289–300.

Laska A, Hellblom A, Murray V, Kahan T, Von Arbin M. (2001) Journal of Internal Medicine. 249: 413-422

Lee JM, Fowler R, Rodney D, Cherney LR, Small SL. (2010) IMITATE: An intensive computer-based treatment for aphasia based on action observation and imitation. Aphasiology 24: 449-465.

Leeper H, Shewan CM, Booth JC. (1986) Altered acoustic cue discrimination in Broca's and conduction aphasics. Journal of Communication Disorders 19: 83-103.

Leff A, Crinion J, Scott S, Turkheimer F, Howard D, Wise R. (2002) A physiological change in the homotopic cortex following left posterior temporal lobe infarction. Annals of Neurology 51: 553-558.

Leff A, Iverson P, Schofield T, Kilner, J, Crinion J, Friston K, Price C, (2009). Vowel-specific mismatch responses in the anterior superior temporal gyrus: an fMRI study. Cortex 45: 517-526.

Leff AP, Howard D. (2012) Stroke: Has speech and language therapy been shown not to work? Nat Rev Neurol 8: 600-601.

Lendrem W, Lincoln N. (1985) Spontaneous recovery of language in patients with aphasia between 4 and 34 weeks after stroke. J Neurol Neurosurg Psych 48: 743–748.

Liberman AM, Cooper FS, Shankweiler DP, Studdert-Kennedy M. (1967) Perception of the speech code. Psychol Review 74: 431-461.

Lincoln NB, McGuirk E, Mulley GP, Lendrem W, Jones AC, Mitchell JRA. (1984) The effectiveness of speech therapy for aphasic stroke patients: a randomised control trial. Lancet 1: 1197-1200.

Lovstad M, Funderud I, Meling T, Kramer U, Voytek B, *et al*. (2012) Anterior cingulate cortex and cognitive control: neuropsychological and electrophysiological findings in two patients with lesions to dorsomedial prefrontal cortex. Brain Cognition 80: 237-249.

Luria AR. (1970) Traumatic Aphasia: Its Syndromes, Psychology, and Treatment. Mouton de Gruyter.

Linebarger, M, Schwartz, M, Kohn, S. (2001) Computer-based training of language production: An exploratory study. Neuropsychological Rehabilitation 11: 57–96.

Maneta A, Marshall JC, Lindsay J. (2001) Direct and indirect therapy for word sound deafness. International journal of language and communication disorders 36: 91-106.

Marshall J, Robson J, Pring T, Chiat S. (1998) Why does monitoring fail in jargon aphasia? Comprehension, judgment, and therapy evidence. Brain and Language 63: 79–107.

Marshall JC, Newcombe F. (1966) Syntactic and semantic errors in paralexia. Neuropsychologia 4: 169–176.

Marshall JC, Newcombe F. (1973) Patterns of paralexia: a psycholinguistic approach. Journal of Psycholinguist Researcg 2: 175–199.

Marshall RC, Wertz RT, Weiss DG, Aten J, Brookshire RH, Garcia-Bunuel L, *et al.* (1989) Home treatment for aphasic patients by trained nonprofessionals. Journal of Speech and Hearing Disorders 54: 462–470.

Marslen-Wilson WD, Tyler LK. (1980) The temporal structure of spoken language understanding. Cognition 10: 1-71.

Matthews JN, Altman DG, Campbell MJ, Royston P. (1990) Analysis of serial measurements in medical research. BMJ 300: 230-235.

Mattingly IG, Liberman A. (1990) Speech and other auditory modules. In: Signal and Sense: Local and Global Order in Perceptual Maps (G.M. Edelman, W. E. G., and W.M. Cowan, ed) New York: Wiley.

McGuire P, Silbersweig D, Frith CD. (1996) Functional neuroanatomy of verbal self-monitoring. Brain 119: 907-917.

Meinzer M, Djundja D, Barthel G, Elbert T, Rockstroh B. (2005) Long term stability of improved language functions in chronic aphasia after constraint-induced aphasia therapy. Stroke 36: 1462-1466.

Meinzer M, Flaisch T, Breitenstein C, Wienbruch C, Elbert T, Rockstroh B. (2008) Functional re-recruitment of dysfunctional brain areas predicts language recovery in chronic aphasia. NeuroImage 39: 2038-2046.

Meinzer M, Flaisch T, Obleser J, Assadollahi R, Djundja D, Barthel G, Rockstroh B. (2006) Brain regions essential for improved lexical access in an aged aphasic patient: a case report. BMC Neurology 17:6-28.

Meinzer M, Streiftau S, Rockstroh B. (2007) Intensive language training in the rehabilitation of chronic aphasia: efficient training by laypersons. Journal of the International Neuropsychological Society 13: 846-853.

Menon V, Uddin LQ. (2010) Saliency, switching, attention and control: a network model of insula function. Brain Struct Funct 214: 655-667.

Mesulam M. (2009) Defining neurocognitive networks in the BOLD new world of computed connectivity. Neuron 62: 1-3.

Miller GA, Nicely P. (1954) An analysis of the confusion among English consonants heard in the presence of random noise. Journal of the Acoustical Society of America 26: 953–953.

Mitchell J, Lang E. (2011) Evidence-based emergency medicine. Update: effect of thrombolysis in acute ischemic stroke. Ann Emerg Med 57: 16-17.

Mitchum C, Haendiges AN, Berndt RS (1995) Treatment of thematic mapping in sentence comprehension: Implications for normal processing. Cognitive Neuropsychology 12: 503-547.

Morris J, Franklin S, Ellis A, Turner J, Bailey P. (1996) Remediating a speech perception deficit in an aphasic patient. Aphasiology 10: 137-158.

Mortley J, Enderby P, Petheram P. (2001) Using a computer to improve functional writing in a patient with severe dysgraphia. Aphasiology 15: 443-461.

Mortley J, Wade J, Enderby P. (2004) Superhighway to Promoting a Client-Therapist Partnership? Using the Internet to Deliver Word-Retrieval Computer Therapy, Monitored Remotely with Minimal Speech and Language Therapy Input. Aphasiology 18: 193-211.

Morton J. (1969) Interaction of information in word recognition. Psychological Review 165-178.

Morton J, Patterson K. (1980) A new attempt at an interpretation, or, an attempt at a new interpretation. In: Deep dyslexia (Coltheart, M., Patterson, K., & Marshall, J. C., ed) London: Routledge & Kegan Paul.

Mummery C, Patterson K, Price CJ, Ashburner J, Frackowiak RS, Hodges JR. (2000) A voxel-based morphometry study of semantic dementia: relationship between temporal lobe atrophy and semantic memory. Annals of Neurology 47: 36-45.

Murphy K, Harris A, Wise RG. (2011) Robustly measuring vascular reactivity differences with breath-hold: normalising stimulus-evoked and resting state BOLD fMRI data. Neuroimage 54: 369-379.

Murray L, Holland A, Beeson P. (1998) Spoken language of individuals with mild fluent aphasia under focused and divided-attention conditions. Journal of Speech, Language, and Hearing Research 41: 213–227.

Murray LL. (2012) Attention and other cognitive deficits in aphasia: presence and relation to language and communication measures. American Journal of Speech-Language Pathology 21: 51-64.

Musso M, Weiller C, Kiebel S, Muller SP, Bulau P, Rijntjes M. (1999) Training-induced brain plasticity in aphasia. Brain 122:1781-1790.

Naeser M, Haas G, Mazurski P, Laughlin S. (1986) Sentence level auditory comprehension treatment program for aphasic adults. Arch Phys Med Rehabil 67: 393-399.

Naeser M, Martin P, Baker E, Hodge S, Sczerzenie S, Nicholas M, Palumbo C, *et al*. (2004) Overt propositional speech in chronic nonfluent aphasia studied with the dynamic susceptibility contrast fMRI method. NeuroImage 22: 29-41.

Naeser M, Martin P, Nicholas M, Baker E, Seekins H, Helm-Estabrooks N, *et al*. (2005) Improved naming after TMS treatments in a chronic, global aphasia patient--case report. Neurocase 11: 182-193.

Naeser MA, Martin PI, Nicholas M, Baker EH, Seekins H, Kobayashi M, *et al*. (2005) Improved picture naming in chronic aphasia after TMS to part of right Broca's area: An open- protocol study. Brain and Language 93: 95-105.

Narain C, Scott SK, Wise RJS, Rosen S, Leff AP, Iversen SD, *et al*. (2003) Defining a left-lateralized response specific to intelligible speech using fMRI. Cerebral Cortex 13: 1362–1368.

National Institute for Health and Clinical Excellence. Guide to the methods of Technology Appraisal. 2008. p.1-76. NICE, London

Nemeth G, Hegedus K, Molnar L. (1988) Akinetic mutism associated with bicingular lesions: clinicopathological and functional anatomical correlates. Eur Arch Psychiatr Neurol Sci 237: 218-222.

Nickels L, Howard D. (1995) Phonological errors in aphasic naming: comprehension, monitoring and lexicality. Cortex 31: 209-237.

Nickels LA. (2002) Theoretical and methodological issues in the cognitive neuropsychology of spoken word production. Aphasiology 16: 3-19.

Noppeney, U., *et al.* (2007). Temporal lobe lesions and semantic impairment: a comparison of herpes simplex virus encephalitis and semantic dementia. Brain 130: 1138-1147.

Nudo RJ, Milliken GW, Jenkins WM, Merzenich MM. (1996) Neural substrates for the effects of rehabilitate training on motor recovery after ischemic infarct. Science 171:1791–1794.

Obleser J, Zimmermann J, Van Meter J, Rauschecker J. (2007) Multiple stages of auditory speech perception reflected in event-related fMRI. Cereb. Cortex 17: 2251-7.

Okada K, Hickok G. (2006) Left posterior auditory-related cortices participate both in speech perception and speech production: Neural overlap revealed by fMRI. Brain and Language 98: 112-117.

Okada K, Hickok G. (2009) Two cortical mechanisms support the integration of visual and auditory speech: A hypothesis and preliminary data. Neuroscience Letters 452: 219-223.

Ong Y, Brown M, Robinson P, Plant G, Husain M, Leff AP. (2012) Read-Right: a "web app" that improves reading speeds in patients with hemianopia. J Neurol 259: 2611-2615.

Palmer R, Enderby P, Cooper C, Latimer N, Julious S, *et al*. (2012) Computer therapy compared with usual care for people with long-standing aphasia post-stroke: a pilot randomized controlled trial. Stroke 43:1904-1911.

Patterson K, Nestor P, Rogers TT. (2007) Where do you know what you know? The representation of semantic knowledge in the human brain. Nature Reviews Neuroscience 8:976-988.

Patterson KE, Shewell C. (1987) Speak and Spell: Dissociations and word-class effects. In: The Cognitive Neuropsychology of Language (Coltheart, M. *et al*., eds) London: Erlbaum.

Paus T. (2001) Primate anterior cingulate cortex: where motor control, drive and cognition interface. Nature Reviews Neuroscience 2: 417-424.

Pedersen PM, Vinter K, Olsen TS. (2001) Improvement of oral naming by unsupervised computerised rehabilitation. Aphasiology, 15, 151-169.

Pobric G, Jefferies E, Ralph MA. (2007) Anterior temporal lobes mediate semantic representation: mimicking semantic dementia by using rTMS in normal participants. 104. Proc Natl Acad Sci USA 104: 20137–20141.

Pobric G, Lambon Ralph M, Jefferies E. (2009) The role of the anterior temporal lobes in the comprehension of concrete and abstract words: rTMS evidence. Cortex 45: 1104-10.

Poldrack RA. (2000) Imaging brain plasticity: conceptual and methodological issues--a theoretical review. NeuroImage 12:1-13.

Price C, Friston KJ. (1999) Scanning patients with tasks they can perform. Human Brain Mapping 8: 102–108.

Price CJ. (2010) The anatomy of language: a review of 100 fMRI studies published in 2009. Ann NY Acad Sci 1191: 62-88.

Price CJ, Crinion J. (2005) The latest on functional imaging studies of aphasic stroke. Current Opinion in Neurobiology 18: 429-434.

Pulvermuller F, Neininger B, Elbert T, Mohr B, Rockstroh B, *et al*. (2001) Constraint-induced therapy of chronic aphasia after stroke. Stroke 32: 1621-1626.

Pulvermuller F, Hauk O, Zohsel K, Neininger B, Mohr B. (2005) Therapy-related reorganization of language in both hemispheres of patients with chronic aphasia. NeuroImage 28: 481–489.

Purdy MH. (2002) Executive function ability in persons with aphasia. Aphasiology 16: 549-557.

Raboyeau G, De Boissezon X, Marie N, Balduyck S, Puel M, Bezy C, Demonet JF, Cardebat D. (2008) Right hemisphere activation in recovery from aphasia: lesion effect or function recruitment? Neurology 70: 290-298.

Raichle M, Fiez J, Videen T, MacLeod A, Pardo J, Fox P, Petersen S. (1994) Practice-related changes in human brain functional anatomy during nonmotor learning. Cerebral Cortex 4: 8-26.

Raichle M, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL. (2001) A default mode of brain function. PNAS 98: 676-682.

Ramsberger G, Marie B. (2007) Self-administered cued naming therapy: a single-participant investigation of a computer-based therapy program replicated in four cases. American Journal of Speech-Language Pathology 16: 343-358.

Rauschecker J, Scott SK. (2009) Maps and streams in the auditory cortex: nonhuman primates illuminate human speech processing. Nature Neuroscience 12: 718-724.

Rauschecker J, Tian B. (2000) Mechanisms and streams for processing of "what" and "where" in auditory cortex. PNAS 97: 11800–11806.

Rauschecker JP. (1998) Cortical processing of complex sounds. Current Opinion in Neurobiology 8: 516-521.

Rauschecker JP. (2011) An expanded role for the dorsal auditory pathway in sensorimotor control and integration. Hear Res 271:16-25.

RCSLT. (2006) Communicating Quality 3 [CQ3]: RCSLT's Guidance on Best Practice in Service Organization and Provision. London: RCSLT.

Recanzone GH. (2000) Spatial processing in the auditory cortex of the macaque monkey. PNAS 97: 11829-11835.

Reeves N, Jefferies L, Cunningham S, Harris C. (2007) A multimedia PDA/PC speech and language therapy tool for patients with aphasia. Int J Electon Healthc 3:135-149.

Remez R, Rubin PE, Pisoni DB, Carrell TD. (1981) Speech perception without traditional speech cues. Science 212: 947-949.

Rhodes R, Pflanzer R. (1996). Sensory systems and their processes. In, Human Physiology. 3rd Edition. Florida, Saunders College Publishing.

Robertson I, Murre JM. (1999) Rehabilitation of brain damage: brain plasticity and principles of guided recovery. Psychological Bulletin 125: 544-575.

Robey RR. (1998) A meta-analysis of clinical outcomes in the treatment of aphasia. Journal of Speech, Language and Hearing Disorders 41:172-187.

Robson H, Grube M, Lambon Ralph M, Griffiths T, Sage K. (2012*a*) Fundamental deficits of auditory perception in Wernicke's aphasia. Cortex 49: 1808-22.

Robson H, Keidel J, Ralph Lambon M, Sage K. (2012*b*) Revealing and quantifying the impaired phonological analysis underpinning impaired comprehension in Wernicke's aphasia. Neuropsychologia 50: 276-288.

Robson H, Sage K, Lambon Ralph M. (2012*c*) Wernicke's aphasia reflects a combination of acoustic-phonological and semantic control deficits: a case-series comparison of Wernicke's aphasia, semantic dementia and semantic aphasia. Neuropsychologia 50: 266-275.

Rogalsky C, Pitz E, Hillis A, Hickok G. (2008) Auditory word comprehension impairment in acute stroke: relative contribution of phonemic versus semantic factors. Brain and Language 107: 167-169.

Rosen HJ, Petersen SE, Linenweber MR, Snyder AZ, White DA, Chapman L, Dromerick AW, Fiez JA, Corbetta M. (2000) Neural correlates of recovery from aphasia after damage to left inferior frontal cortex. Neurology 55: 1883-1894.

Royal College of Physicians (RCP) Intercollegiate Stroke working Party. (2012). National clinical guidelines for stroke- 4th Edition. Royal College of Physicians.

Rudd A, A. CD, Wolfe CD. (2012) Is early speech and language therapy after stroke a waste? BMJ 345:4870.

Rushworth M, Hadland KA, Gaffan D, Passingham RE. (2003) The effect of cingulate cortex lesions on task switching and working memory. Journal of Cognitive Neuroscience 15: 338–353.

Rvachew S. (1994) Speech perception training can facilitate sound production learning. Journal of Speech and Hearing Research 37: 347-357.

Saur D, Lange R, Baumgaertner A, Schraknepper V, Willmes K, Rijntjes M, Weiller C. (2006) Dynamics of language reorganization after stroke. Brain 129: 1371-1384.

Savoy, R.L. (2001). Functional MRI. In V.S. Ramachandran (Ed.). Encyclopedia of the Brain. San Deigo, CA: Academic Press.

Scott S, Johnsrude I. (2003) The neuroanatomical and functional organization of speech perception. Trends in Neurosciences 26: 100–107.

Scott SK, Blank CC, Rosen S, Wise RJS. (2000) Identification of a pathway for intelligible speech in the left temporal lobe. Brain 123: 2400–2406.

Seeley WW, Menon V, Schatzberg AF, Keller J, Glover GH, Kenna H, Reiss AL, Greicius MD. (2007) Dissociable intrinsic connectivity networks for salience processing and executive control. Journal of Neuroscience 27: 2349-2356.

Selnes O, Knopman D, Niccum N, Rubens AB. (1985) The critical role of Wernicke's area in sentence repetition. Annals of Neurology 17: 549-557.

Seron X, Deloche G, Moulard G, Rousselle M. (1980) A computer-based therapy for the treatment of aphasic subjects with writing disorders. Journal of Speech Hear Disorders 45: 45-58.

Shannon R, Zeng F, Kamath V, *et al*. (1995) Speech recognition with primarily temporal cues. Science 270: 303–304.

Sharp DJ, Scott S, Wise, R. (2004*a*) Monitoring and the Controlled Processing of Meaning: Distinct Prefrontal Systems. Cerebral Cortex 14: 1-10.

Sharp DJ, Scott, S, Wise, R. (2004*b*) Retrieving Meaning after Temporal Lobe Infarction: The Role of the Basal Language Area. Ann Neurol. 56: 836-46.

Sharp D, Turkheimer F, Bose S, Scott S, Wise RJ. (2010) Increased frontoparietal integration after stroke and cognitive recovery. Annals of Neurology 68: 753-756.

Skinner BF. (1957) Verbal Behavior. Cambridge, MA: Copley Publishing Group.

Smiley JF, Hackett TA, Ulbert I, Karmas G, Lakatos P, Javitt DC, Schroeder CE. (2007) Multisensory convergence in auditory cortex, I. Cortical connections of the caudal superior temporal plane in macaque monkeys. J Comp Neurol 502: 894-923.

Smith SM. (2002) Fast robust automated brain extraction. Human Brain Mapping 17:143-155.

Spitsyna G, Warren J, Scott S, Turkheimer, F, Wise, R. (2006) Converging Language Streams in the Human Temporal Lobe. Journal of Neuroscience 26: 7328-7336.

Sridharan D, Levitin D, Menon V. (2008) A critical role for the right fronto-insular cortex in switching between central-executive and default-mode networks. Proc Natl Acad Sci USA 105: 12569-12574.

Stacey PC, Summerfield AQ. (2007) Effectiveness of computer-based auditory training in improving the perception of noise-vocoded speech. The Journal of the Acoustical Society of America 121: 2923–2935.

Swinburn K, Porter G, Howard D. (2004) Comprehensive aphasia test. Routledge. Psychology Press.

Tallal P, Newcombe F. (1978) Impairment of auditory-perception and language comprehension in dysphasia. Brain and Language 5:13-24.

Teisser C, Weill-Chounlamountry A, Michelot N, Pradat-Diehl P. (2007) Rehabilitation of word deafness due to auditory analysis disorder. Brain Injury 21:1165-1174.

Teki S, Barnes GR, Penny W, Iverson P, Woodhead Z, Griffiths TD, Leff AP. (2013) The right hemisphere supports but does not replace left hemisphere auditory function in patients with persisting aphasia. Brain 136:1901-1912.

Tettamanti M, Rotondi I, Perani D, Scotti G, Fazio F, Cappa S, Moro A. (2009) Syntax without language: neurobiological evidence for cross-domain syntactic computations. Cortex 45: 825-838.

Thiel A, Schumacher B, Wienhard K, Gairing S, Kracht L, Wagner R, Haupt W, Heiss WD. (2006) Direct demonstration of transcallosal disinhibition in language networks. J Cereb Blood Flow Metab 26: 1122-1127.

Thompson C. (2000) Neuroplasticity: Evidence from Aphasia. Journal of Communication Disorders 33: 357-366.

Thompson C, den Ouden D, Bonakdarpour B, Garibaldi K, Parrish TB. (2010) Neural plasticity and treatment-induced recovery of sentence processing in agrammatism. Neuropsychologia 48: 3211-3227.

Thompson C, Shapiro L. (2005) Treating agrammatic aphasia within a linguistic framework: Treatment of Underlying Forms. Aphasiology 19: 1021-1036.

Thornton JG. (2012) Money well spent? In: Bmj author reply e6023. doi: 10.1136/bmj.e6020.

Thulborn K, Carpenter PA, Just MA. (1999) Plasticity of language-related brain function during recovery from stroke. Stroke 30: 749-754.

Tian B, Reser D, Durham A, Kustov A, Rauschecker JP. (2001) Functional specialization in rhesus monkey auditory cortex. . Science 292: 290-293.

Toothaker L, Banz M, Noble C, Camp J, Davis D. (1983) N = 1 Designs: The Failure of ANOVA-Based Tests. Journal of Educational and Behavioural statistics 21: 289-309.

Tourville JA, Reilly KJ, Guenther FH. (2008) Neural mechanisms underlying auditory feedback control of speech. Neuroimage 39: 1429-1443.

Turkeltaub P, Coslett H, Thomas A, Faseyitan O, Benson J, Norise C, Hamilton RH. (2012) The right hemisphere is not unitary in its role in aphasia recovery. Cortes 48: 1179-1186.

Turkeltaub P, Messing S, Norise C, Hamilton R. (2011) Are networks for residual language function and recovery consistent across aphasic patients? Neurology 76: 1726-34.

Ueno T, Saito S, Rogers T, Lambon Ralph MA. (2011) Lichtheim 2: synthesizing aphasia and the neural basis of language in a neurocomputational model of the dual dorsal-ventral language pathways. Neuron 72: 385-396.

Ungerleider L, Mishkin M. (1982) Two Cortical Visual Systems. In: Analysis of Visual Behavior (Ingle, D. M., A. *et al*., eds). Massachusetts: The MIT Press.

van Oers C, Vink M, van Zandvoort M, van der Worp H, de Haan E, *et al.* (2010) Contribution of the left and right inferior frontal gyrus in recovery from aphasia. A functional MRI study in stroke patients with preserved hemodynamic responsiveness. NeuroImage 49: 885-893.

Varley R. (2011) Rethinking aphasia therapy: a neuroscience perspective. International journal of Speech and Language Pathology 13: 11-20.

Varney N. (1984) Phonemic imperception in aphasia. Brain and Language 21: 85–94.

Visser, M. and M. A. Lambon Ralph (2011) Differential contributions of bilateral ventral anterior temporal lobe and left anterior superior temporal gyrus to semantic processes. J Cogn Neurosci 23: 3121-3131.

Vitali P, Abutalebi J, Tettamanti M, Danna M, Asaldo A, Perani D, Joanette Y, Cappa SF. (2007) Training-induced brain remapping in chronic aphasia: a pilot study. Neurorehabil Neural Repair 21: 152-160.

Wade J, Mortley J, Enderby P. (2003) Talk about IT: Views of people with aphasia and their partners on receiving remotely monitored computer-based word finding therapy. Aphasiology 11: 1031-1056.

Warburton E, Price, C, Swinburn K, Wise, R. (1999) Mechanisms of recovery from aphasia: evidence from positron emission tomography studies. J Neurol Neurosurg Psychiatry 66: 155-161.

Warren JD, Zielinski BA, Green G, Rauschecker JP, Griffiths TD. (2002) Analysis of sound source motion by the human brain. Neuron 34: 1-20.

Warren J, Crinion J, Lambon Ralph M, Wise R. (2009) Anterior temporal lobe connectivity correlates with functional outcome after aphasic stroke. Brain 132: 3428-42.

Warren J, Wise R, Warren J. (2005) Sounds do-able: auditory–motor transformations and the posterior temporal plane. Trends in Neurosciences 28: 636-643.

Warren R. (1970) Perceptual Restoration of Missing Speech Sounds. Science 167: 392-393.

Wee J, Menard M. (1999) "Pure Word Deafness": Implications for Assessment and Management in Communication Disorder: A Report of Two Cases. Arch Phys Med Rehabil 80: 1106-1109.

Weiner F (1981) Treatment of phonological disability using the method of meaningful minimal contrast: two case studies. J Speech Hear Disorders 46:97–103.

Welbourne S and Ralph M (2005). Exploring the impact of plasticity-related recovery after brain damage in a connectionist model of single-word reading." Cogn Affect Behav Neurosci 5: 77-92.

Whitney C, Kirk M, O'Sullivan J, Lambon Ralph M, Jefferies E. (2011) The Neural Organization of Semantic Control: TMS Evidence for a Distributed Network in Left Inferior Frontal and Posterior Middle Temporal Gyrus. Cerebral Cortex 21: 1066-75.

Whitworth A, Webster J, Howard D. (2005) A cognitive neuropsychological approach to assessment and intervention in aphasia. A clinician's guide. Psychology Press.

Winhuisen L, Thiel A, Schumacher B, Kessler J, Rudolf J, Haupt W, *et al*. (2005) Role of the contralateral inferior frontal gyrus in recovery of language function in poststroke aphasia: A combined repetitive transcranial magnetic stimulation and positron emission tomography study. Stroke 36:1759-1763.

Winhuisen L, Thiel A, Schumacher B, Kessler J, Rudolf J, Haupt W, *et al*. (2007) The right inferior frontal gyrus and post-stroke aphasia: A follow-up investigation. Stroke 38: 1286-1292.

Wise R. (2003) Language systems in normal and aphasic human subjects: functional imaging studies and inferences from animal studies. Brit Medical Bulletin 65: 95-119.

Wise R, Scott S, Blank S, Mummery C, Murphy K, Warburton E. (2001) Separate neural subsystems within 'Wernicke's area'. Brain 124: 83-95.

Worsley K. (2001) Statistical analysis of activation images. In: Functional MRI: an introduction to methods (Jezzard, P. *et al*., eds), pp 251–270 Oxford: Oxford UP.

Xu J, Kemeny S, Park G, Frattali C, Braun A. (2005) Language in context: emergent features of word, sentence, and narrative comprehension. NeuroImage 25: 1002-1015.

Zheng ZZ, Munhall KG, Johnsrude IS. (2010) Functional Overlap between Regions Involved in Speech Perception and in Monitoring One's Own Voice during Speech Production. Journal of Cognitive Neuroscience 22: 1770-1781.

9 Appendices

9.1 Appendix 1: Email permission for the reproduction of *Figure 2*.

From: jn permissions <jnpermissions@sfn.org>
Date: Fri, 26 Jul 2013 16:16:08 +0000
To: "Brownsett, Sonia L E" <s.brownsett@csc.mrc.ac.uk>, jn permissions <jnpermissions@sfn.org>
Subject: RE: permission to reproduce for non-profit academic writing.

Dear Ms. Brownsett,

Thank you for your email. Since you will be publishing the material for non-commercial reuse, then permission is granted to republish Figure 1 from the article listed below in print and online. If the Figure is to be changed in anyway, then you will need to notify the original authors before the Figure can be republished. Proper citation of the original source must be added. For any subsequent editions, ancillaries and other derivative works, in any form or medium, in all languages, you will need to contact SFN for additional approval.

Please do not hesitate to contact us if you have any questions.

Regards,
Chanelle Grannum
SfN Central Office
Journal of Neuroscience

SfN Article:
Sandra Da Costa, Wietske van der Zwaag, Jose P. Marques, Richard S. J. Frackowiak, Stephanie Clarke, and Melissa Saenz
Human Primary Auditory Cortex Follows the Shape of Heschl's Gyrus
The Journal of Neuroscience, 5 October 2011, 31(40):14067-14075; doi:10.1523/JNEUROSCI.2000-11.2011

From: Brownsett, Sonia L E [mailto:s.brownsett@csc.mrc.ac.uk] **Sent:** Friday, July 26, 2013 10:00 AM **To:** jn permissions **Subject:** permission to reproduce for non-profit academic writing.

Dear Journal of Neuroscience permissions,

I would like to request permission to reproduce parts of Figure 1 in the article below for incorporation not my PhD thesis and subsequent teaching presentations in order to explain tonotopy within the auditory cortex. I shall, of course, reference the article in full. This will be entirely not for profit.

Da Costa S, van der Zwaag W, Marques JP, Frackowiak RS, Clarke S, Saenz M. Human primary auditory cortex follows the shape of Heschl's gyrus.

J Neurosci. 2011 Oct 5;31(40):14067-75. doi: 10.1523/JNEUROSCI.2000-11.2011.
Many thanks

Sonia Brownsett

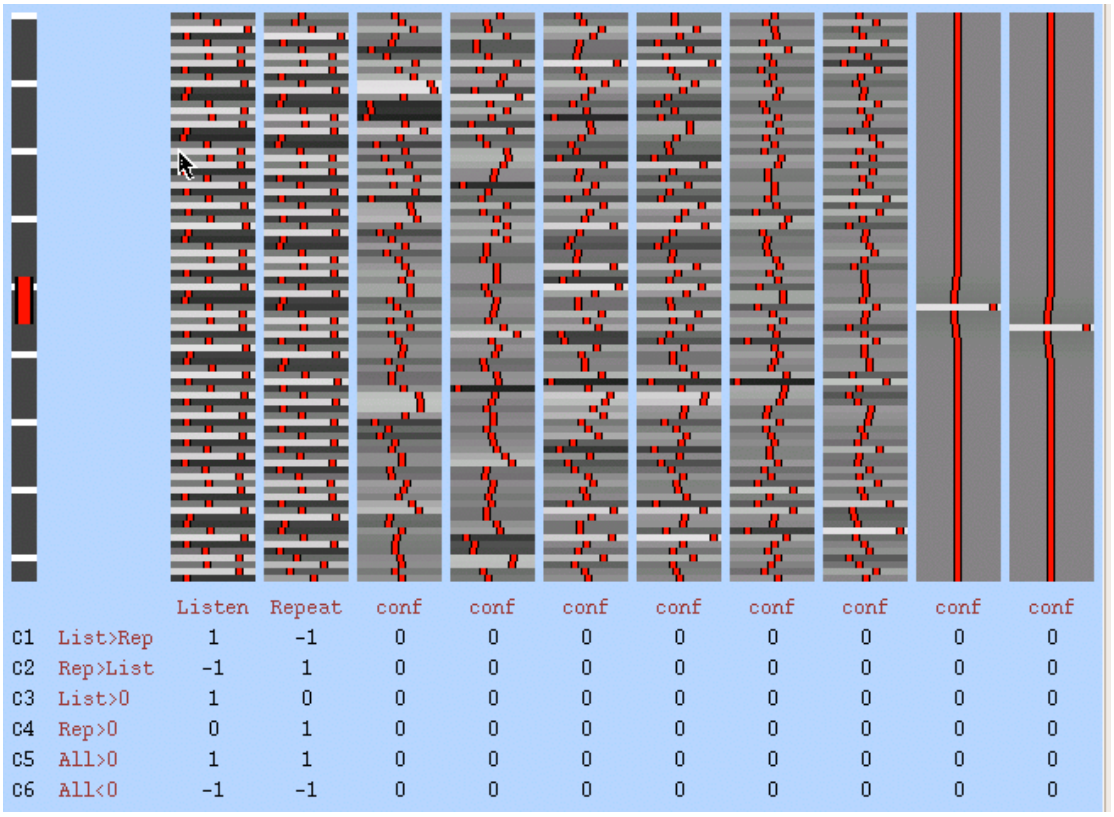
9.2 Appendix 2: Examples of design matrices

In all the design matrices the following key refers to the name of the specific explanatory variable or interaction:

A) Session
B) Task
C) Intelligibility
D) Session by Task interaction
E) Session by Intelligibility interaction
F) Task by Intelligibility interaction
G) Session by Task by Intelligibility interaction

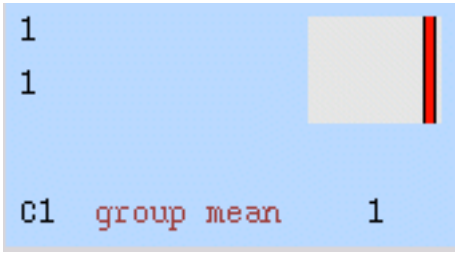
On the top part of the design matrices shown, time is represented on the y- axis and each black, white and red column is a different (real) explanatory variable (*e.g.* stimulus type). The grey, red and white columns represent each individual subjects contribution to the model. Below this is shown the requested contrasts; each row is a different contrast vector and each column refers to the weighting of the relevant explanatory variable. Thus each row will result in a *Z*- statistic image.

9.2.1 First level example design matrix: Patients



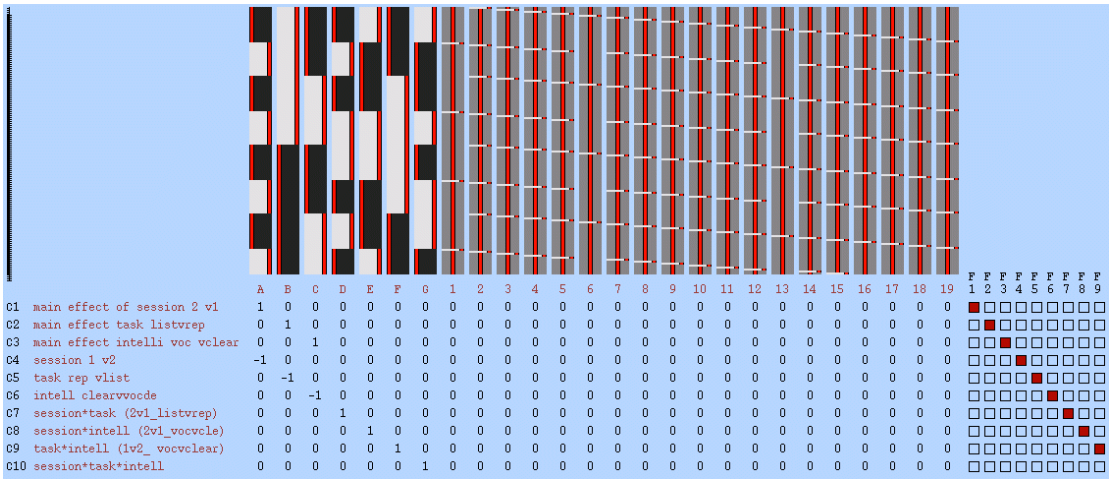
		Listen	Repeat	conf	conf	conf	conf	conf	conf	conf	conf
C1	List>Rep	1	-1	0	0	0	0	0	0	0	0
C2	Rep>List	-1	1	0	0	0	0	0	0	0	0
C3	List>0	1	0	0	0	0	0	0	0	0	0
C4	Rep>0	0	1	0	0	0	0	0	0	0	0
C5	All>0	1	1	0	0	0	0	0	0	0	0
C6	All<0	-1	-1	0	0	0	0	0	0	0	0

9.2.2 Second level example design matrix

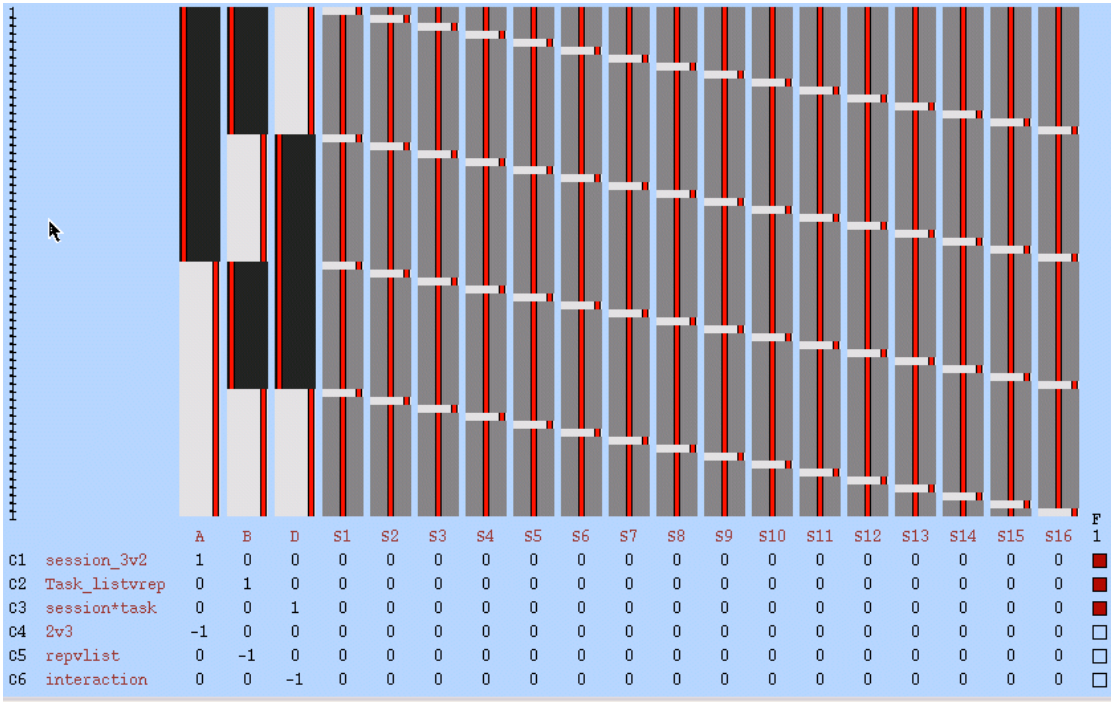


9.2.3 Third level example design matrices: within group

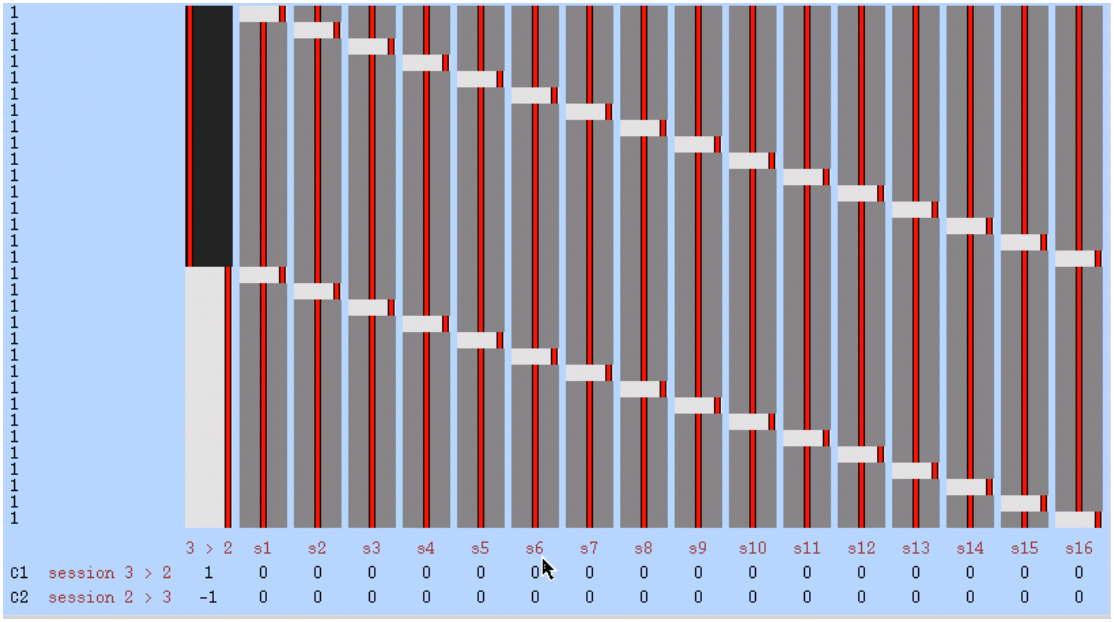
9.2.3.1 Task by Session by Intelligibility ANOVA in healthy volunteers



9.2.3.2 Task by Session ANOVA in Patients



9.2.3.3 Paired samples T-test: session 3 vs. session 2 in Patients (ListNorm)



9.2.4 Third level example design matrices: between group

9.2.4.1 Unpaired 2 sample T-test: Patients versus Healthy volunteers