NEURAL ACTIVATION PATTERNS IN CHRONIC STROKE PATIENTS WITH APHASIA. THE ROLE OF LESION SITE, LESION SIZE AND TASK DIFFICULTY

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NEURAL ACTIVATION PATTERNS IN CHRONIC STROKE PATIENTS WITH APHASIA. THE ROLE OF LESION SITE, LESION SIZE AND TASK DIFFICULTY

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Dedication

To my family, for their constant support and love.

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NEURAL ACTIVATION PATTERNS IN CHRONIC STROKE PATIENTS WITH APHASIA. THE ROLE OF LESION SITE, LESION SIZE AND TASK DIFFICULTY

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Functional neuroimaging research on language recovery in patients with aphasia due to left hemisphere damage has generated some intriguing results. However, it is still not clear what role the right hemisphere plays in supporting language functions in chronic phase for patients with different site and size of lesion when different tasks are used. The present study was aimed at exploring the role of perilesional, ipsilesional and contralesional regions in neural recovery in participants with aphasia with different site and size of lesion using three different language tasks. All patients in the present study were in the chronic stage who had achieved high levels of recovery. Functional magnetic resonance imaging (fMRI) was used to characterize cortical activation in eight stroke patients and eight age/gender matched controls during lexical decision, semantic judgment and picture naming. An event related design using jittered interstimulus intervals (ISIs) was employed to present the stimuli. The fMRI scans revealed differences in activation patterns across the three tasks. Normal control participants and participants

with aphasia mainly activated the left perisylvian region during the lexical decision task and the semantic judgment task. However, during the picture naming task, all participants activated bilateral posterior regions irrespective of the site or size of lesion. Subsequent regions of interest analysis and laterality index analysis revealed that patients with larger lesions produced greater right hemisphere activation than patients with smaller lesions during the picture naming task. The results of this study demonstrate that recovery is task, lesion site and lesion size specific. Further, the findings of the present study indicate a role for both homologous contralesional cortex and perilesional and ipsilesional regions as efficient mechanisms for supporting language functions in chronic stroke patients.

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Abbreviations

ANOVA	analysis of variance
BA	Brodmann's area
BNT	Boston Naming Test
BOLD	blood oxygen level dependent
DLPFC	dorsolateral prefrontal cortex
DWI	diffusion-weighted images
CLQT	Cognitive Linguistic Quick Test
fMRI	functional magnetic resonance imaging
FEAT	fMRI expert analysis tool
FLAME	FMRIB's linear analysis of mixed effect
FLIRT	FMRIB's linear image registration tool
FOV	field of view
FSL	FMRIB software library
FWHM	full width at half maximum
GLM	general linear model
LI	laterality index
LIFG	left inferior frontal gyrus
LPFC	lateral prefrontal cortex
LPPR	left posterior perisylvian region
MNI	Montreal Neurological Institute
PALPA	Psycholinguistic Assessment of Language Processing in Aphasia
PAPT	Pyramids and Palm Trees Test
PET	positron emission tomography
pIFG	posterior region of the left inferior frontal gyrus
PWI	perfusion weighted images
rCBF	regional cerebral blood flow
RIFG	right inferior frontal gyrus
RPPR	right posterior perisylvian region
ROI	regions of interest
SMA	supplementary motor area
SPGR	spoiled gradient recalled echo
TE	echo time
TMS	transcranial magnetic stimulation
TR	repetition time
WAB	Western Aphasia Battery

CHAPTER 1: INTRODUCTION

Aphasia is an acquired communication disorder caused by brain damage that impairs a person's ability to understand, produce and use language (La Pointe, 2005). Cerebrovascular accident or stroke in the left hemisphere is the most common cause of aphasia. Most individuals with aphasia show recovery of language functions following damage to the left hemisphere language zones (Holland, Fromm, & DeRuyter, 1996). An important, yet unanswered question about language recovery in aphasia is whether language reorganizes to the area surrounding the lesion (perilesional) or to other areas in the damaged hemisphere (ipsilesional), or whether it reorganizes to the previously non-dominant, usually right hemisphere areas.

This issue has been debated for well over a hundred years. As early as 1877, Barlow reported that a ten-year-old boy regained language after a lesion of Broca's area and lost language function again when its right-hemisphere counterpart was lesioned. Ten years later, Gowers (1887) also reported that some patients who recovered from aphasia after left-hemisphere stroke lost speech again after a right-hemisphere lesion. In both instances, it was suggested that some language functions reorganize to the right hemisphere. In the latter part of the 1900's, dichotic listening was also used as an indication of hemispheric lateralization of language perception in aphasia. While some studies suggested transfer of language comprehension to the right hemisphere for both Wernicke's and Broca's aphasics (Crosson & Warren, 1981; Johnson, Sommers, &

Weidner, 1977), others indicated that such lateralization may vary from patient to patient (Dobie & Simmons, 1971; Schulhoff & Goodglass, 1969; Shanks & Ryan, 1976; Sparks, 1970). More recent evidence from Wada tests has continued to indicate a role of the right hemisphere in language processing. Kinsbourne (1971) described some aphasic patients who lost language function when the right, but not the left, hemisphere was anesthetized during Wada tests. Basso, Gardelli, Grassi, and Mariotti (1989) reported patients who partially recovered from aphasia after a left-hemisphere lesion showed worsening of language functions during objective testing after subsequent right-hemisphere lesion.

More recently, the introduction of functional neuroimaging to aphasia research has contributed to a broader understanding of the neural mechanism underlying the recovery of language functions in aphasia. Functional neuroimaging techniques, such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET), have made it possible to begin to investigate recovery of functions at a systems level, i.e., by examining the role of integrated neural networks. Using several different methodologies, imaging studies have shown that the damaged adult brain reorganizes to compensate for the compromised linguistic functions. Some studies suggest that the right hemisphere regions can compensate for left hemisphere damage (Abo et al., 2004; Cappa et al., 1997; Fridriksson & Morrow, 2005; Ohyama et al., 1996; Thulborn et al., 1999; Weiller et al., 1995; Xu et al., 2004). However, others have indicated that language functions in aphasia are subserved primarily by restoration of perilesional regions or

ipsilesional region in the left hemisphere, claiming that right hemisphere activation is ineffective (Cardebat et al., 2003; Heiss et al., 1997; Karbe et al., 1998; Miura et al., 1999; Perani et al., 2003; Postman-Caucheteux et al., 2010; Saur et al., 2006; Warburton et al., 1999).

Although a number of research studies have investigated the neural mechanism of recovery of language functions, the results still remain inconclusive. The discrepancy regarding the participation of right hemisphere versus left hemisphere regions in language recovery could be attributed to methodological variability. Studies can vary widely on several variables including: the site/size of the lesion, time post stroke onset, and the type and severity of aphasia. In addition, the specific language behaviors being measured and the patient's relative ability to successfully perform the task(s) will also affect the results of imaging studies (Price & Friston, 1999). However, the association between the site and extent of the lesion, time after stroke and the type of task utilized, in relation to the involvement of the left and right language network to recovery from aphasia remains largely unclear.

The current study arose from a need to systematically examine these variables in order to understand the neural correlates of language recovery in post stroke aphasia. In the present study, the relationship between task difficulty (lexical decision, semantic judgment, and picture naming), varying lesion site/size (anterior, posterior, and antero-posterior), and performance accuracy (whether the responses were accurate or inaccurate)

was examined in eight chronic patients and eight normal control participants. This study will contribute to advancing our knowledge regarding the recovery of language functions in stroke patients with aphasia in two ways. First, since no study to date has comprehensively explored the relationship between task difficulty, varying lesion site/size, and performance accuracy in chronic stroke participants with aphasia, the results of the present study will answer crucial questions about the contributions of perilesional and contralesional brain areas in language recovery. Second, better understanding of this relationship could aid researchers in developing treatment programs that target the re-activation of either the left or the right-hemisphere regions while decreasing activity considered detrimental for recovery.

In the following chapters, I review relevant literature pertaining to functional neuroimaging in aphasia, including the tasks utilized to study language recovery in aphasia, theoretical basis for using those tasks, the stages involved in language recovery after stroke, and the role of the dominant and non-dominant hemispheres in language recovery.

CHAPTER 2: TASKS

2.1. TASKS USED TO EXAMINE LANGUAGE RECOVERY IN PATIENTS WITH APHASIA

The effect of stroke on the language system may involve an extensive range of linguistic deficits. As a result, studies have employed a wide variety of tasks in order to evaluate the mechanisms underlying language recovery following a stroke. The tasks that are typically used in neuroimaging experiments to investigate language recovery include: lexical decision (e.g., Zahn et al., 2004), word repetition (e.g., Abo et al., 2004; Karbe et al., 1998), word generation (e.g., Miura et al., 1999; Weiller et al., 1995), semantic judgment (e.g., Fernandez et al., 2004), sentence comprehension (e.g., Thulborn et al., 1999), and picture naming (e.g., Postman-Caucheteux et al., 2010). Each of these tasks involves a specific aspect of language processing. However, not all studies explain the underlying rationale for selecting a specific task to examine recovery. It is clear that different tasks place different demands on the language processing system; therefore, in order to understand the effect of any task on the recovery process, it is very important to know about the underlying cognitive-linguistic framework and the associated functional anatomy of the task. In the present study, three tasks, each involving the processing and retrieval of a single word, were utilized. These are: oral picture naming, word/semantic meaning judgment, and word lexical decision. The neural substrates underlying each of these tasks are described based on functional neuroimaging and lesion studies. The cognitive-linguistic components of each task are described using the Ellis and Young

Model of Psycholinguistic Processing (Ellis & Young, 1988).

2.1.1. Ellis and Young Model

This model applies a psycholinguistic approach to the interpretation of the processes concerned with the recognition, comprehension and production of spoken and written words and sentences. In this model, input streams are shown at the top and output streams are shown at the bottom. Spoken language is shown to the left and written language to the right (See Figure 1). Between the spoken and written language is the representation of objects and pictures. This gives four distinct processing routes, namely speech perception, reading, speech production, and writing. Following is a brief description of all the components involved in the model.

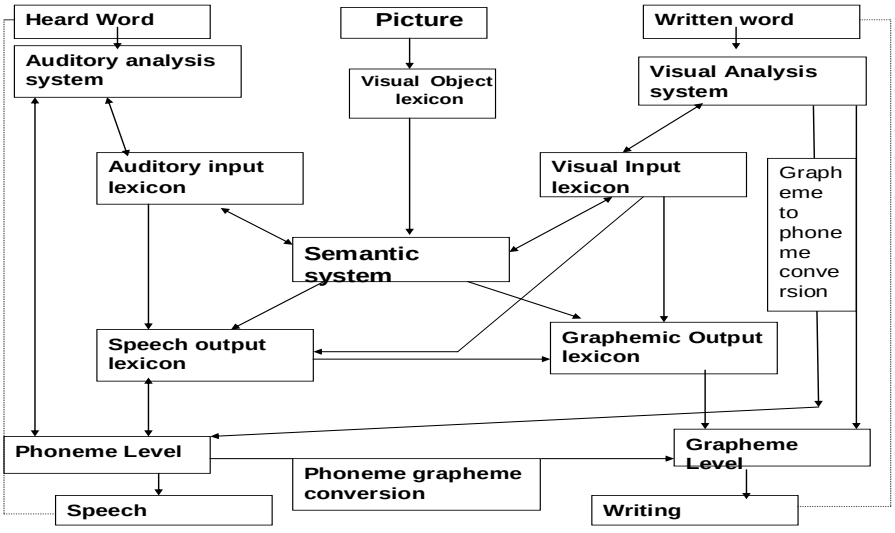


Figure 1: Ellis and Young Model. (From Ellis and Young, 1988).

1. The function of the auditory analysis system is to extract individual speech sounds (mostly phonemes) from the speech wave. The system does this despite differences in accent, voice, speech rate, etc. and so must have the flexibility to cope with these variations. Auditory analysis system has connection to the auditory input lexicon.

2. The function of the auditory input lexicon is to recognize familiar spoken words. It simply signals that a word has been heard before. To know what the word means requires subsequent activation of its semantic representation in the semantic system.

3. The visual object recognition system helps to form the visual feature maps that encode for lines, angles, and edges to a stored description of each seen object's structure and to access the stored structural description of an object, analogous to the lexicon of stored word.

4. The visual analysis system identifies letters in written words (or non-words or letter strings) and encodes each letter for its position within the word.

5. The function of the visual input lexicon in reading is analogous to that of the auditory input lexicon in speech perception. It identifies strings of letters that form familiar written words.

6. The semantic system is the store of all the word meanings that an individual is familiar with and this is one of the most important components of the model. It is assumed that the same store of word meanings is involved regardless of the modality of presentation of a word (spoken, written, or pictorial) and regardless of the modality of production (spoken or spelled). The semantic system has link to the auditory input lexicon, visual input

lexicon, visual object lexicon, speech output lexicon, and grapheme output lexicon. The link between the auditory input lexicon and the semantic system allows an individual to identify a heard word as 'familiar' and to access its meaning from the semantic system. The link between the visual input lexicon and the semantic system allows the individual to identify a written word as familiar and to access its meaning in the semantic system. The link between visual object input lexicon and the semantic system allows the individual to recognize a viewed object as familiar and to access its meaning. The link between speech/grapheme output lexicon and the semantic system allows the individual to identify familiar spoken and written words and to access their meaning during spoken word production or writing.

7. The function of the speech output lexicon is to make the spoken form of a word available to a speaker.

8. Individual distinctive speech sounds are represented at the phoneme level. The phoneme level receives inputs from the auditory analysis system, the speech output lexicon, and the grapheme phoneme conversion.

9. The provision of a direct link between the auditory analysis system and the phoneme level provides a mechanism that enables a person to repeat unfamiliar words without comprehension or recognition.

10. A direct connection is present between the auditory input lexicon and the speech output lexicon. This route helps to complete a whole-word route from auditory input to speech output that by-passes the semantic system. Similarly, there is a route from the

visual analysis system to the speech output lexicon that does not depend on words being recognized as familiar by the visual input lexicon.

11. The function of the graphemic output lexicon is to store the spellings of familiar words and make them available in the process of writing.

12. A connection exists between entries in the speech output lexicon and the graphemic output lexicon. This is due to the fact that normal writers will occasionally produce involuntary "slips of the pen", where an intended word is miswritten as another identically sounding real word (e.g., writing scene for seen, or surge for search).

13. The grapheme level consists of abstract representations of each of the letters used in English. These representations are abstract because it is assumed that the upper-case and lower-case versions of a letter will be represented by a single entry at the grapheme level.

14. The provision of a direct connection between the visual analysis system and the grapheme level allows words or non-words to be copied without being recognized or understood. Making the connection between the visual analysis system and the grapheme level provides a two-way mechanism whereby subjects might image visually retrieved words from the graphemic output lexicon or image words assembled by the phoneme-grapheme conversion.

The Ellis and Young model has been successfully used to describe and account for selective impairment in each of the modules in patients with aphasia (Kiran, 2005; Kiran, Thompson, & Hashimoto, 2001). The present study examined three tasks that are based on the processes described in the Ellis and Young model, namely, lexical decision,

semantic judgment, and picture naming. In addition to relatively clear predictions about the processes involved, there is extensive neuroimaging data from normal individuals validating the premise of the model. Following is a detailed explanation of the three tasks utilized in the present study. Each of these tasks is explained based on the Ellis and Young model and using data from functional neuroimaging and lesion studies.

2.2. COGNITIVE-LINGUISTIC AND NEURAL STRUCTURES UNDERLYING THE VARIOUS TASKS.

2.2.1. Lexical decision task

In the lexical decision task, participants are presented with strings of letters and asked to decide as rapidly as possible whether the letter strings constitutes a word or not. Based on the Ellis and Young model, lexical decision involves (1) recognition of the letters of the word by the visual analysis system and (2) selection of the correct lexical entry by the visual input lexicon. The neuroanatomical correlates of lexical decision have been well established (Binder et al., 2003; Carreiras et al., 2007; Fiebach et al., 2002; Ischebeck et al., 2004; Mummery, Shallice & Price, 1999; Price et al., 1994). The activation associated with viewing real words compared to viewing non-words involves the left middle temporal gyrus, angular gyrus, fusiform gyrus, pars opercularis, tempero-occipital junction, and bilateral insulae.

Lesion studies have also demonstrated an association between lesions in the left temporo-parietal regions, especially in the angular gyrus, and impairment in written word

recognition (Benson, 1979; Black & Behrmann, 1994). Furthermore, Hillis and colleagues found that in patients with hyperacute stroke, impairments at the level of visual input lexicon (recognizing the letters of a word) was significantly associated with hypoperfusion (reduced blood flow) of the left angular gyrus and the middle temporal gyrus (Hillis, Wityk, & Tuffiash, 2001).

2.2.2. Semantic decision task

Several studies have examined the neural correlates associated with different semantic processing tasks. Posner (1998) reported the involvement of the dorsolateral prefrontal cortex (DLPFC) while producing a semantically associated verb for a presented noun. Thompson-Schill, D'Esposito, Aguirre, and Farah (1997) tried to specifically delineate the semantic operations or functions associated with the DLPFC. Using sets of semantic judgment tasks that differed in the number of possible correct choices, they suggested that the left inferior frontal gyrus (LIFG) was involved in the selection of semantic knowledge among alternative choices. This selection role is likely to be a component in the manipulations necessary to perform a variety of semantic tasks (Thompson-Schill et al., 1997, 1998). This interpretation is supported by other neuroimaging studies that found activation in the LIFG during different tasks that required semantic retrieval, such as living/nonliving classification and abstract/concrete word decisions (Binder et al., 1997; Demb et al., 1995; Gabrieli et al., 1996; Kapur et al., 1994).

In the semantic judgment task employed in the present study, participants are presented with stimulus triplets and they are required to decide which of the two items are semantically related. In order to make a meaning judgment, the participant has to go through the (1) visual analysis system, (2) visual input lexicon, and (3) access the meaning of the words by the semantic system.

Lesion studies have also been productive in localizing regions involved in semantic processing and its associated correlates. These results generally support the fMRI findings. Thompson-Schill et al. (1998) studied fourteen patients with focal frontal lesions. Patients were divided into three groups on the basis of the location of their lesions. In the first group, four patients had lesions in the posterior region of the left inferior frontal gyrus (pIFG). In the second group (controls), five patients had lesions in the left prefrontal cortex that spared the left pIFG. The final group (right controls) was comprised of five patients with lesions in the right prefrontal cortex. Participants were asked to generate a verb from a concrete noun. There were two types of nouns: high selection nouns (with many competing responses) and low selection nouns (with few competing responses). Compared to the control patients, patients with lesions that encompassed the left pIFG showed impairment in generating semantically appropriate verbs for concrete high selection nouns but not for low selection nouns. Control patients did not have trouble generating a verb from a concrete noun. Furthermore, patients with lesions in the pIFG made more errors than the control group did during the verb generation task. According to the authors, the impairment observed in patients with

damage to the left pIFG allows one to conclude the necessity of this region for cognitive functioning, namely, that the left pIFG is necessary for the selection of competing semantic knowledge. Gold and Kertesz (2000) also reported similar results in their patients who had left frontal lesions.

2.2.3. Picture naming task

Picture naming involves (1) visual perceptual processing, i.e. formation of a perceptual representation of the picture by the visual analysis system, (2) visual recognition of an object by the visual object recognition system, (3) semantic processing, (4) phonological planning and retrieval of the word by the speech output lexicon, and (5) speech initiation and articulation. The neuroanatomical correlates of picture naming have also been well established. The brain activations observed when subjects retrieve the name of a visually presented stimulus reflects complex cognitive processes involving visual perceptual processing, semantic processing, lexical retrieval, and speech production. The visual perceptual processing involves the lateral-posterior occipital lobe and the bilateral posterior fusiform gyri (Cohen et al., 2002; Malach et al., 1995; Xue et al., 2006). Semantic processing during picture naming involves the left posterior temporal lobe (Abrahams et al., 2003; Cannestra et al., 2000; DeLeon, et al., 2007; Grabowski et al., 2003; Moore & Price, 1999; Mummery, Patterson, Hodges, & Wise, 1996; Price et al., 1996). Activation of phonology and word retrieval involves the left posterior temporal lobe, left precentral sulcus and the primary sensorimotor cortex (Zatorre et al.,

1992). Lexical retrieval and speech production involves the supplementary motor area and the motor cortex (Kertesz, 1999; Rosen et al., 2000; Zelkowicz et al., 1998).

Ojemann (1991) studied the neural correlates of impaired naming using direct cortical stimulation intra-operatively in patients undergoing neurosurgery. While the patient was performing a simple naming task, a very weak electric current was applied to the exposed cortical tissue. Naming disturbances were observed in stimulation sites ranging from middle temporal to superior temporal areas, as well as from inferior to superior frontal regions in the motor, premotor, and dorsolateral prefrontal parts of the frontal cortex. Amongst these areas, stimulations of the middle and posterior parts of the left temporal lobe have most consistently led to interruption in visual object naming.

In a recent study, Damasio et al. (2004) conducted an extensive MRI based lesion study on object recognition and naming in 139 patients with left and right cerebro-vascular accident. Naming and comprehension of pictures were probed by asking the patients to name objects from five different categories: famous faces, animals, tools/ utensils, fruits/vegetables, and musical instruments. If the patient failed to name the picture, the patient was prompted to provide a description of the object that was then scored for object recognition. The results indicated that more than half of the patients exhibited below normal naming in at least one of the object categories. A voxel-based rendering of the lesion overlap in patients with naming deficits indicated that maximum lesion overlap was in the classical language areas- inferior parietal and temporo-parietal regions. In the brain damaged patients with preserved naming abilities, the voxel-based

overlap was in the right hemisphere. This indicated that the left posterior regions (Wernicke's area and the inferior parietal regions) were critical for naming.

Taken together, the cognitive-linguistic, neuroanatomical and lesion data findings suggest that language processing is a complex function that involves the interplay of a distributed network in the frontal, temporal and parietal regions. These areas are hierarchically organized and activated according to the complexity of the specific language task. For example, processing in the lexical decision paradigm does not reflect higher-level phonological or semantic processing that is usually involved in tasks such as word naming or semantic judgment. Picture naming, on the other hand, requires higher level phonological and semantic processing that involves the functional integrity of extensive left hemisphere areas, forming a closely interconnected system. The knowledge that the degree of involvement of the left hemisphere regions varies for different language components in the normal human brain is relevant for interpreting the data of participants with aphasia and understanding the recovery process.

CHAPTER 3: LANGUAGE RECOVERY IN STROKE PATIENTS

3.1. RECOVERY OF LANGUAGE FUNCTIONS AFTER STROKE

Recent advances in technology, especially in functional imaging, have contributed substantially to our understanding of mechanisms and patterns of language recovery in stroke patients with aphasia. The study of aphasia with functional imaging can help us not only to understand how language functions are organized after damage to the dominant hemisphere, but also to determine how different factors such as site and size of the lesion influence the recovery process. Recent studies using functional imaging demonstrate that most patients make substantial recovery in language functions following stroke (Abo et al., 2004; Cardebat et al., 2003; Heiss et al., 1997; Perani et al., 2003; Postman-Caucheteux et al., 2010; Saur et al., 2006). Recovery from brain damage due to stroke occurs in several stages. This chapter is divided into two parts. Part I describes the stages involved in language recovery after stroke and part II describes the literature on functional imaging in aphasia.

3.1.2. Phases in language recovery

Hillis (2005a) suggests that recovery of language functions after stroke occurs in three overlapping phases, each with a unique set of underlying neural mechanisms. The initial phase is called the acute phase and lasts for about two weeks after the onset of the lesion. The second phase is the subacute phase and this usually lasts up to six months post onset. Finally, chronic phase begins months to years after stroke and it may continue

for the remainder of the person's life.

3.1.2.1. The acute phase

In acute stroke, the restoration of blood circulation in the area of the ischemic penumbra area is the main mechanism for recovery of language functions. Ischemic penumbra is the area surrounding the core infarct that is getting enough blood to survive but not to function (Olsen et al., 1983). The ischemic threshold of cerebral perfusion for membrane failure is around 8 ml/100 g brain tissue/minute, in contrast to the normal blood flow of 20 ml/100g/minute. Therefore, damage can be reversed if blood flow is elevated above anoxic values. Reperfusion (restoring blood flow) is usually done by using one of the following methods: (1) temporary blood pressure elevation with fluids, (2) urgent carotid endarterectomy, (3) intra-arterial thrombolysis, and (4) internal carotid stenting. The size of the ischemic penumbra can be estimated by comparing magnetic resonance imaging changes reflecting core infract size with the large areas of ischemia including the ischemic penumbra demonstrated by diffusion-weighted images (DWI) and perfusion-weighted images (PWI).

In a series of studies, Hillis and colleagues (Hillis & Heilder, 2002; Hillis et al., 2008) investigated the relationship between reperfusion of the ischemic penumbra and language recovery. Hillis and Heilder (2002) investigated the relationship between word comprehension impairment and hypoperfusion (low blood flow/ischemic penumbra) in the Wernicke's area (BA 22). They examined a series of hundred patients with acute left

hemisphere ischemic stroke within 24 hours of onset or worsening of symptoms, and three days after onset, using PWI, DWI, and a battery of lexical tasks, including spoken word/picture verification. A subset of eighteen patients with impaired spoken word comprehension on Day 1 were included in the study. All patients underwent reperfusion of the ischemic penumbra. The results revealed that improvement in word comprehension was significantly associated with reperfusion of Brodmann's area 22 (Wernicke's area), but not with reperfusion of other Brodmann areas.

In a recent study, Hillis et al. (2008) used diffusion-perfusion mismatch to estimate salvageable tissue and to predict potential for recovery in acute stroke. *Diffusion–perfusion mismatch* refers to the difference between volume of perfusion abnormality on perfusion-weighted imaging (PWI) and volume of diffusion abnormality on diffusion-weighted imaging (DWI). One hundred and five patients with acute left hemisphere ischemic stroke underwent diffusion-weighted imaging, perfusion-weighted imaging, a picture naming test, and other language tests twice, first at admission and the second two to four days after admission. Linear regression was used to determine whether diffusion–perfusion mismatch in any Brodmann's area in language cortex predicted degree of improvement in naming by days three to five. Results revealed that diffusion–perfusion mismatch in the left Brodmann's area 39 (angular gyrus) predicted the potential for recovery in picture naming. Based on the results of the linear regression, a subset of eighty seven patients underwent medical or surgical intervention to restore or improve

blood flow in ischemic tissue near BA 39. Reperfusion of the left BA 39 in those with mismatch in BA 39 was almost certainly critical for improvement in naming. There was a significant difference between the naming abilities of the patients who got treatment and that of those who did not. The data indicated that reperfusion of area 39 resulted in improved naming. These studies illustrate that reperfusion of the hypoperfused area is a critical component of the underlying acute recovery process.

3.1.2.2. The subacute phase

In most cases, reperfusion can only salvage the ischemic penumbra for the first few days following ischemia. Eventually, in the absence of an intervention to reperfuse the ischemic penumbra, the hypoperfused area often progresses to infarction (Hillis et al., 2004). Nevertheless, language recovery continues in the subacute phase, often at a rapid rate, throughout the following weeks to months after stroke. The main mechanism that has been suggested for mediating language recovery in the subacute phase involves resolution of diaschisis. The term 'diaschisis', established by Von Monakow in 1914, indicates a condition in which there is hypometabolism (reduced neuronal metabolism) of structurally normal cortical regions situated distant from the infarct. This hypometabolism is caused due to disruption of functional pathways between normal cortical regions and the infarcted region. The phenomenon of diaschisis has been widely accepted and subsequently elaborated with biochemical and physiological supporting evidence.

Several studies suggest that resolution of diaschisis results in the improvement of language functions in patients with aphasia (Cappa et al., 1997; Price et al., 2001). Cappa et al. (1997) studied eight patients with unilateral left hemisphere stroke using PET in the acute phase after stroke (within two weeks) and six months later. All patients had substantial recovery of language functions at follow up. Analysis of regional glucose metabolism in the acute phase showed hypometabolism in structurally unaffected regions both in the left and the right hemisphere. Glucose metabolism increased significantly on both sides in all patients at the second PET study. Regional analysis showed significant positive correlations between changes in metabolic values in several cortical regions in the right hemisphere and changes in language performance at follow up. According to the authors, language recovery in the first months after aphasia is associated with regression of functional depression (diaschisis) in structurally unaffected regions, particular those in the right hemisphere.

In another study, Price et al. (2001) investigated the distant effect of lesion using PET in four patients with aphasia. All patients had lesions in the Broca's area (BA 44, 45) and were at least six months post onset. All patients had speech output deficits but relatively preserved comprehension. They were scanned while viewing words relative to consonants. In the normal subjects, activation was observed in the left posterior inferior frontal, middle temporal, and posterior inferior temporal cortices. Each patient activated normally in the middle temporal region but abnormally in the damaged posterior inferior

frontal cortex and in the undamaged posterior inferior temporal cortex. In the damaged frontal regions, activity was insensitive to the presence of words but in the undamaged posterior/inferior temporal regions, activity decreased (hypometabolism) in the presence of words rather than increasing as it did in the normal individuals. The authors proposed that, in patients, posterior temporal responses are abnormal when they depend upon inputs from the damaged inferior frontal cortex. This abnormal activity or hypometabolism was attributed to neuronal diaschisis.

3.1.2.3. The chronic phase

Following the end of the changes in the subacute phase, many patients are still able to improve their language skills. The chronic phase continues months or even years after injury. During this phase, recovery of language functions is achieved by learning new ways to retrieve language representations and establishing compensatory strategies by recruiting (a) ipsilateral physiologically and anatomically connected structures, or (b) contralateral homologous cortical areas. Some of the theories that explain how language recovery takes place in the chronic stage are summarized below.

Redundancy recovery

This theory suggests that built into each organism, is a biological protective mechanism that anticipates injury. Redundancy provides structures that can substitute for the damaged functions. Fritsch and Hitzig first proposed this theory in 1870. The authors suggested that regions of the brain previously not occupied could assume certain

functions. Language impairments can be compensated for, to some extent, by intact areas of the language network normally subserving closely related functions (Zahn et al., 2004). Thus, recovery mechanisms extend beyond the perilesional regions (area surrounding the lesion) in the left hemisphere to other areas that are normally involved in the language network. For example, Zahn et al. (2004) studied seven patients with left middle cerebral artery (MCA) infarction and partial recovery of comprehension atleast six months after presentation with global aphasia on acute assessment. Lateralization of activation did not differ significantly between patients and controls. The most consistent regions of activation included the left extrasylvian posterior temporal and the right posterior parietal cortex. Recovery of language comprehension was associated predominantly with activations in regions that were also activated in several normal subjects. They suggested that redundancy recovery mechanism within multiple representations of closely related functions served as the basis of recovery of word comprehension in their patients with extensive left hemispheric damage.

Reorganization

According to the theory of reorganization, the homologous area in the undamaged hemisphere is assumed to take responsibility for mediating the lost or impaired function (Benton & Tranel, 2000; Finger, Buckner, & Buckingham, 2000). The role of the undamaged hemisphere in the recovery of motor functions in rats after stroke has been investigated in experimental neuroscience studies (Jones & Schallert, 1994; Jones, Kleim,

& Greenough, 1996) and in post-stroke motor recovery studies in humans using functional imaging (TMS) (Liepert et al., 2000b; Netz et al., 1997; Rossini et al., 2003; Schallert et al., 1997; Traversa et al., 2000). The role of undamaged (right) hemisphere in language recovery has also been investigated by several authors (Abo et al., 2004; Cappa et al., 1997; Fridriksson & Morrow, 2005; Ohyama et al., 1996; Thulborn et al., 1999; Weiller et al., 1995; Xu et al., 2004). These studies suggest that language impairments can be compensated by intact regions in the right hemisphere.

In summary, reorganization of language functions after stroke is a complex process and it involves several mechanisms. The first two stages of language recovery occur very rapidly. However, the third stage takes place over a period of months or years after the injury. Functional imaging has played a significant role in helping us understand the recovery process. This is discussed in detail in the following section.

3.2. REVIEW AND EVALUATION OF LITERATURE ON FUNCTIONAL IMAGING IN APHASIA

In this section, I review the functional neuroimaging literature on language processing in patients with aphasia. Functional neuroimaging has been used to address a number of different questions that concern how neuronal activation changes after a left hemisphere stroke and aphasia. Researchers have primarily focused on whether patients compensate for their neurological and functional loss by increasing the level of language-related brain activation, and if so, whether the activation is in the left or in the right hemisphere. Indeed, there has been much theoretical debate on the relative contributions

of the left hemisphere regions and the right hemisphere regions to recovery of language functions. Some studies underlined the role of left hemisphere regions in recovery mechanisms (Blasi et al., 2002; Cardebat et al., 2003; Karbe et al., 1998; Heiss et al., 1997; Miura et al., 1999; Perani et al., 2003; Postman-Caucheteux et al., 2010; Saur et al., 2006; van Oers et al. 2010; Warburton et al., 1999; Winhuisen et al., 2007). However, others have implicated areas of the right hemisphere in compensatory functions (Abo et al., 2004; Blank et al., 2003; Cappa et al., 1997; Fridriksson & Morrow, 2005; Ohyama et al., 1996; Thulborn et al., 1999; Weiller et al., 1995; Xu et al., 2004). The literature review on functional imaging studies of stroke patients that follows is therefore, divided according to whether the authors support the role of right hemisphere or left hemisphere regions in language recovery.

3.2.1. Role of the nondominant hemisphere (right) in supporting language recovery

Many functional imaging studies have indicated that patients with lesions in the left hemisphere regions show activation in the homologous areas of the left hemisphere during language tasks (Abo et al., 2004; Blank et al., 2003; Cappa et al., 1997; Fridriksson & Morrow, 2005; Ohyama et al., 1996; Thulborn et al., 1999; Weiller et al., 1995; Xu et al., 2004). These studies have used a variety of tasks in order to examine the contribution of right hemisphere regions in recovery from aphasia. The tasks include: word generation, word repetition, semantic judgment, sentence comprehension, and picture word matching (see Table 1). One of the initial studies aimed at understanding the

neural correlates of language recovery in patients with aphasia was done by Weiller et al. (1995). Using PET and a word generation paradigm, they investigated six right-handed patients who had recovered from Wernicke's aphasia caused by an infarction that completely destroyed the left posterior perisylvian language zone (Wernicke's area). In the control subjects, strong regional cerebral blood flow (rCBF) increases were found not only in the left hemisphere in the posterior part of the superior and middle temporal gyrus (Wernicke's area) and in left lateral prefrontal cortex (LPFC), but also in the posterior part of the inferior frontal gyrus (Broca's area). There was a slight increase in activation in the right superior temporal gyrus and inferior premotor cortex. In participants with aphasia, clear right hemisphere activation in the superior temporal gyrus and the inferior premotor and lateral prefrontal cortices was found. Their findings support a theory of language recovery in which activation of remaining structures within a pre-existing, bilateral, distributed network is key.

Table 1: Role of right hemisphere in language recovery from aphasia

Studies	Method	Imaging task	Time since stroke	Mechanism of recovery	
				Left	Right
Cross sectional studies					
Weiller et al., 1995	PET	Verb generation task	Chronic		X
Ohyama et al., 1996	PET	Single word repetition	Acute (1-16 months)		X
Abo et al., 2004	fMRI	Word repetition and rest	Acute/Subacute (6-9 months)		X
Xu et al., 2004	fMRI	Covert semantic word generation and visual fixation	Acute (within weeks)		X
Blank et al., 2003	PET	Propositional speech	Chronic (19-134 months)		X
Fridriksson & Morrow, 2005	fMRI	Picture word matching task	Chronic (12-141 months)		X
Longitudinal studies					
Cappa et al., 1997	PET	Language battery	Acute 2 weeks, 6 months		X
Thulborn et al., 1999	fMRI	Written sentence comprehension	Acute Case 1: 76 hours, 6 months, Case 2: 3 months, 6 months		X

Extending the focus on the right hemisphere regions in aphasia recovery, Abo et al. (2004), Xu et al. (2004), and Ohyama et al. (1996) have suggested that for speech production tasks, the site of right hemisphere activation depends on the site of the lesion. Abo et al. (2004) illustrated how right hemisphere activation depends on the lesion site. They observed right frontal activation during auditory repetition in a patient with left frontal damage, but not in control subjects or in a patient with left temporo-parietal damage. Conversely, their patient with left temporo-parietal damage showed right

inferior parietal activation that was not observed in control subjects or in the patient with left frontal damage. Likewise, Xu et al. (2004) observed right inferior frontal activation during covert word generation in a patient with left frontal damage but not in two patients with left temporo-parietal damage. In another study, Ohyama et al. (1996) measured the changes in rCBF during a repetition task using PET in six normal subjects and sixteen aphasic patients. All patients had suffered a single cerebral infarction in the left hemisphere resulting in a lesion in either the frontal (non fluent aphasics), or the temporal (fluent aphasics), or the temporo-parietal (fluent aphasics) regions. The patients were studied at least one month post onset. The researchers observed increased rCBF in the right temporo-parietal regions for patients with lesions in the left temporo-parietal regions and increased CBF in the right posterior inferior frontal areas in patients with left frontal lesions.

Similarly, Blank, Bird, Turkheimer, and Wise (2003) suggested that right hemisphere areas were recruited during language production only when their left hemisphere counterparts were damaged. They used PET to study language production in seven chronic aphasic patients with left anterior perisylvian infarction (which included the pars opercularis) and seven chronic anterior aphasic patients whose infarcts spared the left pars opercularis. Patients performed a common propositional speech task during imaging. The authors found that during a narrative language task, aphasic patients with lesions to the left pars opercularis showed more pronounced activity in the right pars

opercularis, than that shown by healthy controls or by aphasic patients with little to no lesion in the left pars opercularis. Since the patients had already recovered language functions at the time of assessment, the authors suggested that the increased activity observed in the right pars opercularis was related to recovery from nonfluent aphasia.

A more recent study by Fridriksson and Morrow (2005) presented a finding that may shed light on the contribution of right hemisphere regions in aphasia recovery. They explored the relationship between changes in language task difficulty and cortical activation in patients with aphasia. Four aphasic patients who had suffered left middle cerebral artery ischemic strokes were recruited for the study. All of them were in the chronic stage (12- 141 months post onset). The task consisted of picture–word verification with two levels of difficulty. In the first level, participants were presented a series of two picture-word pairs (2-PWC) for 2 seconds each. In the second level, which was more difficult, participants were presented a series of three picture–word pairs (3-PWC) for 1.333 seconds each. Greater cortical activation was observed in three out of the four patients during the 3-PWC compared to the 2-PWC condition. Significant right hemisphere activation was observed for the three patients in the right superior temporal lobe. However, the functional scan of the fourth patient showed primarily left temporal lobe activation. In addition, compared to the 2-PWC, greater cortical activation extent and signal intensity was noted in the right Broca's area and right superior temporal lobe for patients with aphasia on the 3-PWC. The control subjects showed more activation

during the more difficult condition (3-PWC). The superior temporal lobe was activated in all four controls during both conditions, with greater signal intensity and extent of activation seen during the more difficult condition. The right Broca's area was activated in the difficult condition in all the patients. The authors suggested the importance of taking into consideration the difficult of the task while interpreting the role of right hemisphere regions in language recovery.

Further support for the importance of right hemisphere regions in language recovery comes from two longitudinal studies. Cappa et al. (1997) examined the contribution of the contralateral undamaged hemisphere in recovery from aphasia. Eight patients with unilateral left hemispheric stroke underwent a PET scan while they listened to an open conversation. Scanning was done in the period immediately after the stroke (within two weeks) and then six months later. All patients also underwent an extensive battery of language tests such as the Western Aphasia Battery (Kertez, 1982). In the first evaluation (two weeks post onset), they found extensive metabolic depression in both the hemispheres while the patients listened to the conversation. All patients had a substantial recovery of specific aspects of language functions at the follow-up. Glucose metabolism increased significantly on both sides in all patients at the second PET study. The metabolic value in the contralateral region was highly predictive of the recovery of auditory comprehension, indicating that the right hemisphere regions were crucial for recovery.

In another longitudinal study, Thulborn et al. (1999) used fMRI to map language comprehension in six normal adults and in two adult patients during recovery from acute stroke presenting with aphasia. Patient 1 had a lesion in the Broca's area and fMRI examination was performed at 76 hours and again at six months post onset. Patient 2 had a lesion in the Wernicke's area and fMRI was done at three and nine months post onset. In the normal subjects, language comprehension showed activation predominately in left-sided Wernicke's and Broca's areas. In the first patient, recovery of language occurred rapidly with a shift of activation to the homologous region in the right hemisphere within three days, with continued rightward lateralization over a period of six months. In the second patient, recovery of aphasia showed a similar increasing rightward shift in activation recruitment over nine months after the event. This study demonstrated a spontaneous redistribution of function to the right hemisphere that occurred within days and continued over months as performance normalized during recovery from aphasia.

In summary, all the above mentioned functional imaging studies suggest neurofunctional changes in the right frontal or temporal regions after a left hemisphere stroke. Right frontal activation is more likely to be observed after left frontal damage (Cappa et al., 1999; Thulborn et al., 1999; Xu et al., 2004), whereas right temporoparietal activation is more likely to be observed after left temporoparietal damage (Abo et al., 2004; Ohyama et al., 1996; Thulborn et al., 1999; Weiller et al., 1995). Right hemisphere changes do not; however, appear to reflect the level of recovery of language functions.

For example, the results of Xu et al. (2004) do not relate to recovery because their patients participated in the brain imaging study within a month of their stroke before they had recovered their language functions. This is also true of the study by Ohyama et al. (1996), Thulborn et al. (1999), and Cappa et al. (1999) who looked at language performance in the acute or subacute phase of recovery. These studies therefore, provide evidence that right hemisphere activation changes occur rapidly after cerebral infarction and do not reflect the level of recovery. The contribution of right hemisphere may, therefore, reflect ineffective neuronal reorganization rather than functional compensation. Nevertheless, the data of Fridriksson and Morrow (2005) suggest that right hemisphere does play a role in language recovery, especially when the difficulty of the task increases.

3.2.2. Role of the dominant hemisphere (left) in supporting language recovery

Many studies suggest that increased activation in the right hemisphere regions are related to ineffective neuronal reorganization that does not necessarily relate to recovery, whereas increased activation related to compensatory strategies in the left hemisphere may be critical for functional recovery (Blasi et al., 2002; Cardebat et al., 2003; Karbe et al., 1998; Heiss et al., 1997; Miura et al., 1999; Perani et al., 2003; Postman-Caucheteux et al., 2010; Saur et al., 2006; van Oers et al. 2010; Warburton et al., 1999; Winhuisen et al., 2007).

Several cross sectional studies support the role of left hemisphere regions in language recovery (Blasi et al., 2002; Perani et al., 2003; Postman-Caucheteux et al.,

2010; Rosen et al., 2000; Warburton et al., 1999). Warburton et al. (1999) used PET to compare regional brain activations in response to a word retrieval task in normal subjects and in five patients with aphasia who had shown at least some recovery and were able to attempt the task. All patients were scanned between six and fourteen months after the onset of aphasia. The activations associated with cued word retrieval were indistinguishable from those in the normal controls, except that in the presence of a lesion, the activations were perilesional. In the normal controls, the activation was exclusively left lateralized in the inferolateral temporal cortex, reflecting retrieval of words appropriate in meaning to the cue from the semantic system. This was also seen in four patients. However, the fifth patient proved to be very inefficient at retrieving verbs from the cues. There were limited right dorsolateral frontal activations in three of the five patients, but a similar pattern was also found in four of the nine normal subjects. These results support the role of left hemisphere regions in language recovery in patients with aphasia.

In another study, Rosen et al. (2000) used fMRI to examine the verbal performance of patients with infarcts centered in the left inferior frontal gyrus (LIFG). Two types of tasks were used: attention demanding lexical tasks and a simpler reading task. Results revealed that patients with damage to the LIFG were impaired on all attention-demanding lexical tasks, but were able to complete the word-reading task normally. The imaging study demonstrated an increased activity in the right inferior

frontal gyrus (RIFG). However, the level of activation in the RIFG did not correlate with verbal performance. In addition, a perilesional response within the damaged LIFG was localized in the two patients who gave the best performance in the word-stem completion task and showed the most complete recovery from aphasia.

Table 2: Role of left hemisphere in language recovery from aphasia

Studies	Method	Imaging task	Time since stroke	Mechanism of recovery	
				Left	Right Inefficient/or large lesions
Cross sectional studies					
Warburton et al., 1999	PET	Word retrieval and rest		X	
Rosen et al., 2000	fMRI PET	Reading and word stem completion	Acute (6 months)	X	X
Blasi et al., 2002	fMRI	Word retrieval	6 months post onset	X	X
Perani et al., 2003	fMRI	Phonemic verbal fluency, semantic verbal fluency and rest	Subacute (6 months)	X	X
Postman-Caucheteux et al., 2010	fMRI	Picture naming	< 3years	X	

Table 2 (continued)

Longitudinal Studies					
Heiss et al., 1997	PET	Repeating words	4 weeks, 12-18 months	X	X
Karbe et al., 1998	PET	Repeating words	2 weeks, 1 year	X	
Miura et al., 1999	fMRI	Word generation	2 wks, wks, 7 months	X	
Cardebat et al., 2003	PET	Word generation	2 months, 11 months	X	
Fernandez et al., 2004	fMRI	Word picture rhyming, Word picture semantic matching	1 month, 12 months	X	X
Saur et al., 2006	fMRI DWI	Listening to spoken versus time reversed sentences	2, 12, 320 days	X	X
Winhuisen et al., 2007	PET, TMS	Verb generation disruption with repetitive TMS over Broca's area	10 days, 8 weeks	X	
van Oers et al., 2010	fMRI	Picture word matching, semantic decision, and verb generation	2 months, <1 year	X	X

Similar to Rosen et al. (2000), Blasi et al. (2002) investigated the role of the RIFG during a novel word retrieval task in eight patients with lesions involving the LIFG. All participants were partially recovered aphasics, with the acute event occurring at least six months back. The results indicated that patients with left frontal lesions and partially recovered aphasics learn, at a normal rate, a novel word retrieval task that requires the damaged cortex. Verbal learning was accompanied by specific response decrements in the RIFG. Further, they found that in patients with small lesions, there was evidence of

perilesional activation near the left frontal stroke. In patients with large left hemisphere lesions, they found persistent right hemisphere activation in the chronic stage. Similarly, Perani et al. (2003) found that in chronic patients with good recovery, the activation foci generally involved the perilesional or undamaged regions in the language dominant hemisphere during covert word production. Poor recovery was associated with right hemisphere activation. The results of Warburton et al. (1999), Rosen et al. (2000), Perani et al. (2003), and Blasi et al. (2002) provide evidence that intact perilesional tissue in stroke patients has an important impact on recovery from aphasia.

A recent study by Postman-Caucheteux et al. (2010) is notable for separating correct and incorrect responses from picture-naming trials during fMRI. They studied three patients with left hemisphere damage due to left middle cerebral artery infarction. Although all were initially globally aphasic, yet, as the standard naming batteries demonstrated, at the time of testing (at least three years post-onset), they had excellent comprehension but moderate language production impairment and word finding difficulties. In the age-matched control group, picture naming activated bilateral visual areas, posterior perisylvian areas and basal ganglia, and left-sided inferior frontal areas. For all three patients, while both correct and incorrect responses were associated with left-sided perilesional activation, incorrect responses were consistently associated with much greater contralesional activity. Most notably, incorrect responses elicited activation in the RIFG and middle frontal gyrus, which was not observed either for patients' correct

responses or controls' responses. The result that contralesional activation in the right frontal areas is largely driven by patients' inaccurate responses supports the hypothesis that it is not an effective mechanism for language recovery.

Further support for the role of left hemisphere regions in language recovery comes from several longitudinal studies. One of the first studies that looked at the contribution of left hemisphere regions in language recovery was conducted by Heiss et al. (1997). Using PET, they investigated six stroke patients with aphasia at four weeks and again at twelve to eighteen months post onset using a word repetition task. Three patients had small lesions in and around the temporo-parietal regions, whereas the other three patients had large lesions encompassing the entire perisylvian region. The three patients with small lesions showed improvement in language scores at the second evaluation. They showed significantly greater activation of left hemisphere speech areas, especially the left superior temporal gyrus, resulting from the repetition-rest comparison, than that shown by those without improved language scores. The patients with large lesions did not improve on their languages scores. Heiss et al. (1997) concluded that recovery from aphasia depends on the degree of functional integrity of speech areas of the dominant hemisphere. Right hemisphere activation was interpreted as a nonspecific involvement of the network activation in an effort to perform a complex task. Similar results were obtained by Karbe et al. (1998) during a repetition task. Using PET, they compared twelve patients within two weeks and one year post onset. The comparison between the initial and the follow up PET studies showed quite interesting changes in the

activation patterns. In the acute phase of aphasia, PET revealed impairments of metabolic activation within the left cerebral cortex. The left superior temporal and the left precentral metabolic activations were significantly reduced or even lost because of the ischemic brain damage. However, the corresponding right superior temporal and precentral areas showed the typical activation pattern due to the ongoing auditory and motor processing in the right hemisphere. The additional activation of right hemispheric regions that they observed in the acute phase of stroke, however, did not simply continue during the period of long-term reorganization of the speech-relevant network. Their results were comparable to that of Heiss et al. (1997) and they concluded that good long-term outcome depended mainly on the repair of left superior temporal cortex function.

Several other longitudinal studies also emphasize the role of left hemisphere regions in recovery of speech production in patients with aphasia (Miura et al., 1999; Cardebat et al., 2003; Fernandez et al., 2004; Winhuisen et al., 2007). Miura et al. (1999) used fMRI to study language recovery in a patient with Broca's aphasia. Two weeks after the onset of infarction, the fMRI signal was found to be absent from the left frontal lobe during verb generation task. Symptomatic improvement four weeks later was accompanied by an increased fMRI signal in the left frontal region. Finally, seven months post onset, when recovery was complete, the BOLD signal had recovered to a level seen in normal subjects. In another study, Cardebat et al. (2003) examined six healthy subjects and eight aphasic patients during a word generation task. Patients were studied twice (the

first PET was conducted two months post onset and the second eleven months post onset stroke). All patients had suffered a single ischemic stroke with different lesion sites (frontal in two cases, temporal in two cases, and subcortical in four cases). For each group, correlations between performance indexes and rCBF between the two sessions were analyzed. The results indicated that language performance improved in both groups. rCBF decreased from PET1 to PET2 in the healthy group and increased in the aphasic group in the perisylvian regions bilaterally. Decreased activation in the neural systems for the normal subjects suggested a familiarization effect. Correlations between performance and rCBF changes across sessions were similar in the two groups; positive correlations involved superior temporal cortex bilaterally, and negative correlations related to the right superior frontal and medial temporal regions. Their results indicated that left hemisphere regions are important in supporting language recovery in chronic phase.

Winhuisen et al. (2007) used positron emission tomography (PET) to study the contribution of the RIFG in language processing in patients with aphasia. They applied repetitive TMS to these regions in order to temporarily disrupt their function and thus test the functional significance of the activations. They studied nine patients (again a mixture of aphasia types) at ten days and eight weeks after stroke, applying repetitive TMS to the LIFG and RIFG as identified in each patient's PET scan. Repetitive TMS adversely affected language function in all patients at both time points when applied over the LIFG, strongly implicating this region as supporting the verb generation task. On the right,

repetitive TMS only disrupted verb generation in four out of the nine patients at ten days after stroke and in only two of them at eight weeks after stroke. This suggests that the RIFG probably does not 'take over' the function of the left IFG after stroke, but probably helps to support left language function. Thus, the findings of Miura et al. (1999), Cardebat et al. (2003), and Winhuisen et al. (2007) suggest that recovery of word generation is mainly associated with left frontal regions. Similarly, Fernandez et al. (2004) reported activation for rhyme decisions (which involve identifying whether the name of a picture rhymes with a heard word) in a patient with a large left temporo-parietal lesion at two different time points in the recovery period (one month and one year after stroke). Irrespective of the recovery stage, the patient showed increased right temporoparietal activation when compared with ten control subjects. Left hemisphere changes were only observed a year after stroke when performance had improved. This suggests that left rather than right hemisphere changes were important for long-term recovery.

A complementary but slightly more complex perspective is offered by Saur et al. (2006). The authors used repeated fMRI examinations with parallel language testing to examine the reorganization in the language system from the acute to the chronic stage in fourteen patients with aphasia and an age-matched control group with an auditory comprehension task. Control subjects were scanned once, whereas patients were scanned repeatedly at three consecutive dates. All patients recovered clinically as shown by a set

of aphasia tests. In the acute phase (mean: 1.8 days post-stroke (dps)), patients' group analysis showed little early activation of non-infarcted left hemispheric language structures. However, in the subacute phase (mean: 12.1 dps) a large increase of activation in the bilateral language network was observed with peak activation in the right Broca's area. A direct comparison of both examinations revealed that the strongest increase of activation was in the right Broca's area and supplementary motor area. In the chronic phase (mean: 321 dps), a normalization of activation with a re-shift of peak activation to left-hemispheric language areas was observed, associated with further language improvement. Their data suggest that brain reorganization during language recovery proceeds in three phases. In the first (acute) phase, the activation of the left language areas is strongly reduced. In the second (upregulation) phase, there is an upregulation of the entire language network with recruitment of homologue language zones. In the third phase, fMRI activation normalizes and peak activation're-shifts' to the left hemisphere. Activation normalization correlated with language improvement, possibly reflecting consolidation in the language system.

In a recent longitudinal study, van Oers et al. (2010) examined the relative contribution of dominant and non-dominant language networks towards recovery from aphasia in thirteen patients using three language tasks (picture word matching, semantic decision, and verb generation) at two different stages of recovery: two months after stroke and at least one year after stroke . All patients also underwent an extensive battery of language tests including the Aachen Aphasia Test, Boston Naming Task, and Token

Test at two months and one year post onset. The results indicated that language recovery from the subacute phase to the chronic phase after stroke was associated with increased activation in the left compared to right perisylvian areas. Recovery of naming was only associated with activity in the LIFG. By contrast, improvement on the Token Test was positively correlated with activation in both the left and right inferior frontal gyrus during semantic decision and verb generation tasks indicating that the RIFG contributed more during auditory sentence comprehension than during picture naming. The increased activation observed in the RIFG was attributed to increased demand on working memory during the Token Test. The results of this study underlined the importance of restoration of the pre-morbid language network in the dominant left hemisphere for recovery from aphasia for linguistic functions such as object naming and sentence comprehension, while the RIFG may contribute through non-linguistic processing related to increased demand on working memory or executive control reflecting task difficulty or learning.

In summary, the above mentioned studies indicate that good recovery of language functions in aphasia is accompanied by greater perilesional than right hemisphere reorganization, whereas poor recovery of language functions is accompanied by greater right hemisphere than perilesional reorganization (Cao et al., 1999; Heiss et al., 1999; Karbe et al., 1998; Rosen et al., 2002; Perani et al., 2003; Fernandez et al., 2004). Indeed, the data of Heiss et al. (1997) indicate a link between large lesions and right hemisphere activation. According to the authors, larger lesions encompassing the fronto-temporo-parietal regions are associated with poor recovery of language functions and

reorganization to the right hemisphere. Thus, lesion site/size appears to be one potential factor that may account for some of the variability seen in the neuroimaging literature in stroke patients with aphasia.

In addition to lesion site/size, another potential factor that might influence the neural activation patterns in patients is the phase of recovery. Most of the studies that support the role of 'right hemisphere mechanism' in recovery were done in either the acute or subacute stage (Cappa et al., 1997; Ohyama et al., 1996; Thulborn et al., 1999; Xu et al., 2004), whereas most studies that support the role of left hemisphere mechanisms were done in the chronic phase (Karbe et al., 1998; Heiss et al., 1997; Miura et al., 1999; Perani et al., 2003; Postman-Caucheteux et al., 2010; Warburton et al., 1999). However, it should be noted some studies found right hemisphere activation in chronic aphasic patients many years after stroke onset suggesting that both right and left hemispheres supports language recovery in chronic stage, particularly in patients with large left hemisphere lesions (Blasi et al., 2002; Heiss et al., 1997). This suggests that it is important to consider the phase of recovery while interpreting the role of left versus right hemisphere in language recovery.

Besides the phase of recovery and the lesion site/size, there are two other potential factors that might account for the observed variability in right and left hemisphere activity in functional neuroimaging literature. These factors include performance accuracy and difficulty of the task and are often overlooked in experimental studies

dealing with language recovery in aphasia. As mentioned earlier, Weiller et al. (1995) reported right temporal activation during a verb generation task in patients with left temporal lesion in the chronic phase, whereas Fernandez et al. (2004) reported activation in the perilesional region during a rhyme judgment task in a chronic patient with left tempero-parietal damage. It should be noted that the participants in both these studies had relatively homogeneous lesions in the left temporal lobe, yet one favored the 'role of right hemisphere' in recovery and the other the 'role of left hemisphere' in recovery. Verb generation is arguably more complex than rhyme judgment, which may be why Weiller et al. (1995) found activation in the right hemisphere and Fernandez et al. (2004) did not. This is in line with Fridriksson and Morrow (2005), who suggest that greater task difficulty results in increased activation in the right hemisphere regions for patients with aphasia. Analyzing performance accuracy may also help to resolve this discrepancy. It is likely that patients in Weiller et al's study made more errors than the patient in Fernandez's study, leading to the increased involvement of the right hemisphere regions in Weiller et al's study. Postman- Caucheteux et al. (2010) provide support for this argument; they found that correct responses are associated with left hemisphere processing and incorrect responses are associated with right hemisphere processing. Such an explanation would be speculative because both Weiller et al. (1995) and Fernandez et al. (2004) did not analyze the data by separating the correct and incorrect responses.

Task difficulty and performance accuracy may also vary as a function of lesion

site. Since both Weiller et al. (1995) and Fernandez et al. (2004) included only patients with small lesions restricted to posterior (temporo-parietal) regions, it is not clear whether there would be a difference in activation for an easy versus a difficult task and for correct versus incorrect responses in patients with left fronto-temporo-parietal lesions. The data of Heiss et al. (1997) indicate that large lesions are associated with poor recovery of language functions and reorganization to the right hemisphere. However, Heiss et al. (1997) did not look at the role of performance accuracy or task complexity.

Finally, the type of data analysis (single subject analysis versus group analysis) has also complicated comparison of results and generalization of conclusions. For example, the results of Saur et al. (2006) and van Oers et al. (2010) indicate that participation of right hemisphere structures may be greater in the initial stages of language recovery followed by normalization of activation to the left hemisphere regions. However, both these studies utilized a group analysis approach, where a cohort of patients is analyzed as a group. This procedure is problematic because information about individual patterns of activation can be lost through averaging of patient brain images resulting in gross underestimation of right hemisphere and perilesional activations (Crosson et al. 2007b).

CHAPTER 4: PURPOSE

An in depth examination of the neuroimaging literature suggests that the recovery of language functions in aphasia is a more complex process than a simple reversal of normal left hemisphere lateralization (i.e., transferring language functions as a whole to the right hemisphere) or exclusive recruitment of left perilesional and other language areas. The key variables that influence the patterns of activation include the: lesion site/size, task difficulty, phase of recovery, and performance accuracy. To date, no studies have systematically examined the interactions between these variables within the context of language recovery in aphasia. This could lead to better understanding and characterization of the nature of cortical reorganization supporting language recovery in patients with aphasia. Therefore, the present study attempted to explore the contribution of left hemisphere and right hemisphere regions in language recovery by including the following key variables.

4.1. KEY VARIABLES

4.1.1. Phase of recovery

This study addressed this issue by recruiting participants with aphasia in the chronic stage (nine months post onset). Recent fMRI studies suggest a temporary contribution of the right hemisphere regions in the early phase post-stroke, which is absent or more modest in the chronic phase (Saur et al., 2006; Winhuisen et al., 2007). Functional recovery is associated with emerging activation of perilesional tissue, which is

achieved through improvement of metabolic rate, regression of diaschisis, and neuroplastic reorganization with time. Thus, it is important to examine patients in the chronic phase to maximize the contribution of left hemisphere regions in neural recovery associated with stroke.

4.1.2. Site/size of lesion

The results of Abo et al. (2004), Blasi et al. (2002), and Heiss et al. (1997) indicate that lesion site/size influences the role of left versus right hemisphere participation in neural recovery. In the present study, participants with varying site/size of lesion were recruited to understand the effect of site/size of lesion on language recovery. The present study included participants with anterior (frontal) lesions, posterior (temporal, parietal, or temporo-parietal) lesions, and antero-posterior/posterior-subcortical lesions (fronto-temporal, fronto-temporo-parietal, temporo-parietal-occipital-subcortical). The site of lesion criteria was deliberately kept general because there is no consensus of measuring precise sites of lesions. One current approach is to use voxel based lesion mapping, but this approach is an arduous undertaking and can be the focus of a separate research project.

4.1.3. Tasks with varying processing demands

This study addressed this issue by selecting three different paradigms that vary in the level of difficulty. The three tasks are lexical decision, semantic judgment, and

picture naming. Task difficulty was modulated by manipulating the processing demands involved in each task. Lexical decision task requires basic phonological processing, whereas semantic judgment task requires higher level semantic processing. Picture naming task requires both higher level phonological and semantic processing. Additional considerations of the chosen tasks were that the underlying cognitive-linguistic components and their associated functional anatomy have been well established.

4.1.4. Group analysis versus single subject analysis.

Group analysis is problematic because information about individual patterns of activation can be lost through averaging of patient brain images (Crosson et al., 2007b). Therefore, analysis of individual cases is likely to be critical for fully appreciating the details of activation patterns when lesions are present. This is the approach taken in the present study.

4.1.5. Performance accuracy

The results of Postman-Caucheteux et al. (2010) indicate a link between error processing and right hemisphere activation. Therefore, the present study addressed this issue by separating correct and incorrect trials during analysis. Correct versus incorrect analysis was carried out only when response accuracy was less than 70%, in order to ensure adequate number of events for response analysis.

4.2. SPECIFIC RESEARCH QUESTIONS ADDRESSED

The following specific research questions were addressed by this study:

(a) What are the differences in the patterns of activation between the three tasks for the normal control participants? Is there a relationship between task difficulty and cortical activation?

(b) What are the differences in the patterns of activation between the three tasks for participants with aphasia? Is there an interaction between lesion site/size and task difficulty in participants with aphasia?

(c) Do participants with aphasia recruit the same brain regions as normal control participants or do they recruit novel brain regions to compensate for their structural deficits?

(d) What are the differences in patterns of activation between correct and incorrect responses? Is the right hemisphere differentially involved in trials with incorrect responses?

4.3. HYPOTHESES

It has been noted above that the neural correlates of language recovery in post stroke aphasia is not well understood. Nonetheless, based on the growing literature, with regards to the previously outlined specific research questions, the following hypotheses were made:

Hypothesis 1

This research question was addressed by using three different kinds of analyses: whole brain analysis, regions of interest analysis, and laterality index analysis.

(a) Whole brain analysis. Based on previous functional neuroimaging work that explored lexical decision, semantic judgment, and picture naming (e.g., Abrahams et al., 2003; Binder et al., 2003; Carreiras et al., 2007; Cohen et al., 2002; Kapur et al., 1994; Thompson-Schill et al., 1997), it was hypothesized that normal control participants would activate the left middle temporal gyrus (BA 21), angular gyrus (BA 39), supramarginal gyrus (BA 40), fusiform gyrus (BA 37), and occipital cortex (BA 18/19) during the lexical decision task. Semantic judgment task was expected to activate the left inferior frontal gyrus (BA 44/45). Picture naming task was expected to activate a broad bilateral network (more left than right lateralized) including the left inferior frontal gyrus (BA 44/45), bilateral superior/middle temporal gyrus (BA 22/21), left precentral gyrus (BA 4), left postcentral gyrus (BA 3), left supramarginal gyrus (BA 40), and bilateral occipital cortex (BA 17/18/19).

(*b) Regions of interest analysis*. It was hypothesized that the mean percent BOLD signal change would be modulated by task difficulty. BOLD signal change would be extracted from two main regions of interest: anterior perisylvian regions and posterior perisylvian regions. Greater mean percent BOLD signal change would be associated with the picture naming task compared to the semantic judgment task and the lexical decision task. Further, greater mean percent BOLD signal change would be associated with the

semantic judgment task compared to the lexical decision task.

(c) Laterality index analysis. The laterality index reflects the degree of activation in a left hemisphere ROI in relation to the right hemisphere ROI. It was hypothesized that there would be positive laterality index (left lateralized) for all the three tasks, although to a lesser extent for the picture naming task.

Hypothesis 2

This research question was addressed by using three different kinds of analyses: whole brain analysis, regions of interest analysis, and laterality index analysis.

(a) Whole brain analysis. It was hypothesized that during the lexical decision task, participants without lesions involving the left posterior regions would activate the left temporo-parietal regions similar to that expected in the normal control participants. Participants with left posterior lesions would either activate the perilesional posterior regions and/or the ipsilesional frontal/occipital regions. During the semantic judgment task, participants without lesions involving the left frontal regions (inferior frontal gyrus) would activate the left inferior frontal gyrus similar to that expected in the normal control participants. Participants with left frontal lesions would activate perilesional regions in the frontal lobe, ipsilesional temporal and/or contralesional right hemisphere regions. For the picture naming tasks, participants with left frontal lesions would activate perilesional frontal and/or contralesional frontal, bilateral temporal and occipital regions. Participants with temporal and/or parietal lesions would activate perilesional temporal, right temporal, left frontal, and bilateral occipital regions. Participants with lesions involving the frontal

and temporal regions would activate remaining non-lesioned tissue in the left hemisphere and right frontal and temporal regions.

(b) Regions of interest analysis (ROI). It was hypothesized that the mean percent BOLD signal change would be modulated by task difficulty. Greater mean percent BOLD signal change would be associated with the picture naming task compared to the semantic judgment task and the lexical decision task. Further, greater mean percent BOLD signal change would be associated with the semantic judgment task compared to the lexical decision task. It was also hypothesized that there would be greater BOLD signal change in the right hemisphere regions as the lesion volume increases.

(c) Laterality index analysis. It was hypothesized that the laterality index would be positive (left lateralized) for all the three tasks for patients with anterior or posterior lesions. For patients with antero-posterior lesions, laterality index would be positive (left lateralized) for the lexical decision task and the semantic judgment task and negative (right lateralized) for the picture naming task. Finally, it was hypothesized that the laterality index would shift from positive to negative as the lesion volume increases.

Hypothesis 3

This research question was addressed by comparing the activations (patient versus controls) from the whole brain analysis. It was predicted that patients with anterior and posterior lesions would activate more ipsilesional and contralesional right hemisphere regions than activated by the normal control participants. It was predicted that patients with antero-posterior lesions would activate more novel regions (regions traditionally not

activated by language tasks) than activated by the normal control participants.

Hypothesis 4

This research question was addressed by comparing the activations for correct versus incorrect responses from the whole brain analysis. Based on the results of Postman-Caucheteux et al. (2010), it was hypothesized that correct responses would be associated with perilesional, ipsilesional, and contralesional right hemisphere activations, whereas incorrect responses would be associated with contralateral right frontal and bilateral cingulate activations.

CHAPTER 5: METHODOLOGY

5.1. PARTICIPANTS

Eight monolingual, English speaking participants with aphasia were involved in the experiment (age range 40-79 years). All patients had suffered an ischemic stroke with the exception of P4 who had suffered a cerebral hemorrhage. Strokes were generally in the distribution of the left middle cerebral artery and affected primarily posterior and/or anterior cortical areas, although P8 showed evidence of some subcortical involvement. All participants were at least 24 months post onset (mean 48.25 MPO1[1]). Some participants had concomitant medical problems such as heart disease, or diabetes; however, at the time of participation, they were medically and neurologically stable and at least wheelchair ambulatory. All participants with aphasia were premorbidly right handed and had completed at least a high school education (See Appendix 1). Localization of lesion was determined by an experienced Neuroradiologist based on each participant's T-1 weighted MRI slices. Please see Table 3 for details of participant information and Figures 2-4 for lesion locations.

Eight monolingual, English speaking, normal controls (age range 40-82 years) were also recruited for the experiment. All normal control participants were matched for age (±3 years) and gender (see Table 4). Groups were matched for age (±3 years) because age has been found to considerably affect brain activation for language and other

[1] Months Post Onset

functions (Fridriksson, Morrow, Moser, & Baylis, 2006). The normal control participants had normal hearing and either normal or corrected to normal vision. All normal control participants were screened using a medical history questionnaire (See Appendix 2) in order to rule out individuals who had a history of neurological disease, head trauma, psychiatric disease, development speech, language or learning disability. All normal control participants were right handed as determined by the handedness and language inventory (Oldfield, 1971). *The Mini Mental Status Exam* (MMSE) (Folstein et al., 1975) was administered to the normal control participants in order to ensure that they did not have any cognitive impairment. All participants gave informed consent according to the University of Texas at Austin Human Subjects Protocol. Participants also completed fMRI screening forms to verify eligibility to participate in the scanner (see Appendix 3).

The experiment consisted of three sessions. The first session involved collecting participant medical history and administering the standardized language tests for the patients. For the normal control participants, the *Mini Mental status Exam* (MMSE) was administered. The second session consisted of participant training. Training trials were similar to the experimental trials (Please see section 5.3 for details). The training trials used the same stimuli as utilized in the imaging experiment. Training trials, which took place approximately 2-3 days before the fMRI experiment, were conducted at the Aphasia Research Laboratory at the University of Texas on a DELL PC using the 7 and 8 number keys for lexical and semantic decisions. For the picture naming task, oral responses were recorded using a SONY digital recorder. On average, patients performed

the training task one to two times before high accuracy scores (90 % or above) were achieved. The third session consisted of the fMRI experiment.

Table 3: Demographic details, lesion site, and lesion volumes for participants with aphasia

Participant	Age	Sex	Education	MPO	Site of Lesion	Lesion Volume (mm^3)
Anterior Lesions						
P1	62	M	J.D.	52	Left frontal (pars opercularis of Broca's area and primary motor cortex), insula extending into the white matter	37331
P2	53	M	Master's Degree	38	Left frontal including the motor cortex and part of the pars opercularis of Broca's area, SMA, insula extending into the white matter	42127
Posterior Lesions						
P3	56	M	High School	36	Left temporo-parietal region	31887
P4	40	F	Bachelor's Degree	30	Left temporo-parietal region	23488
P5	79	M	J.D.	56	Left temporal and insula	28838

Table 3 (continued)

Antero-Posterior/subcortical Lesions						
P6	60	F	2 years college	78	Left frontal (excluding broca's area) temporal and insular region	37813
P7	70	M	High School	36	Left frontal, temporo-parietal extending into the white matter	43384
P8	60	F	High School	60	Left temporo-parietal, insula, lateral occipital cortex, and left putamen	45203

Table 4: Demographic details for normal control participants

Participant	Age	Gender	Education	MMSE
NC1	64	M	Master's Degree	30/30
NC2	51	M	Bachelor's Degree	30/30
NC3	55	M	Master's Degree	30/30
NC4	40	F	Bachelor's Degree	30/30
NC5	82	M	Doctorate	30/30
NC6	60	F	Bachelor's Degree	30/30
NC7	73	M	Master's Degree	30/30
NC8	60	F	Bachelor's Degree	30/30

Note: MMSE-Mini Mental Status Exam.

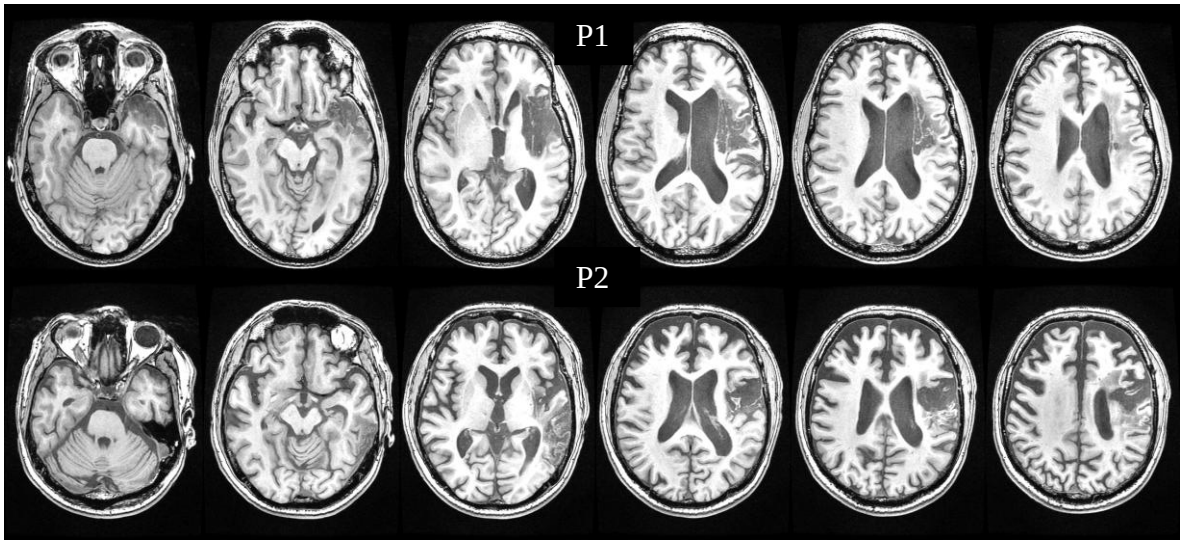


Figure 2: Structural T1-weighted axial images for participants with anterior lesions (P1 and P2). Images are in radiological orientation with the right side of the brain to the left and the left side to the right.

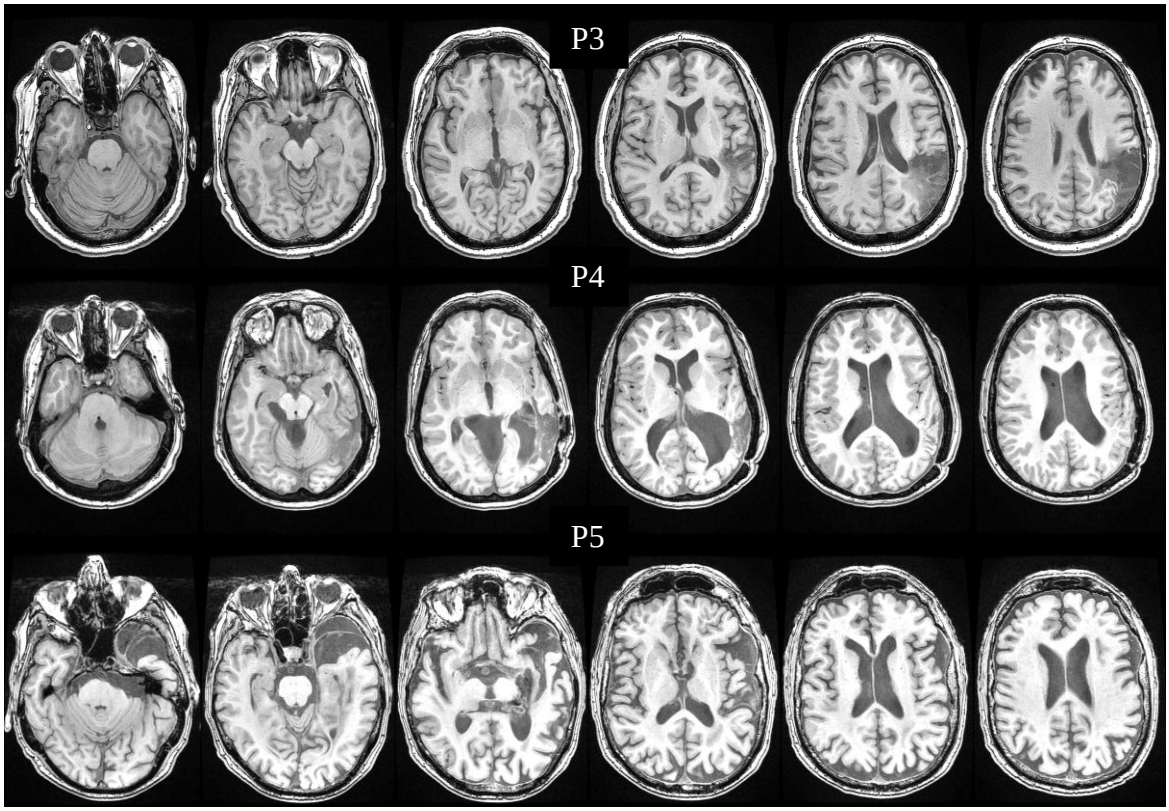


Figure 3: Structural T1-weighted axial images for participants with posterior lesions (P3, P4 and P5). Images are in radiological orientation with the right side of the brain to the left and the left side to the right.

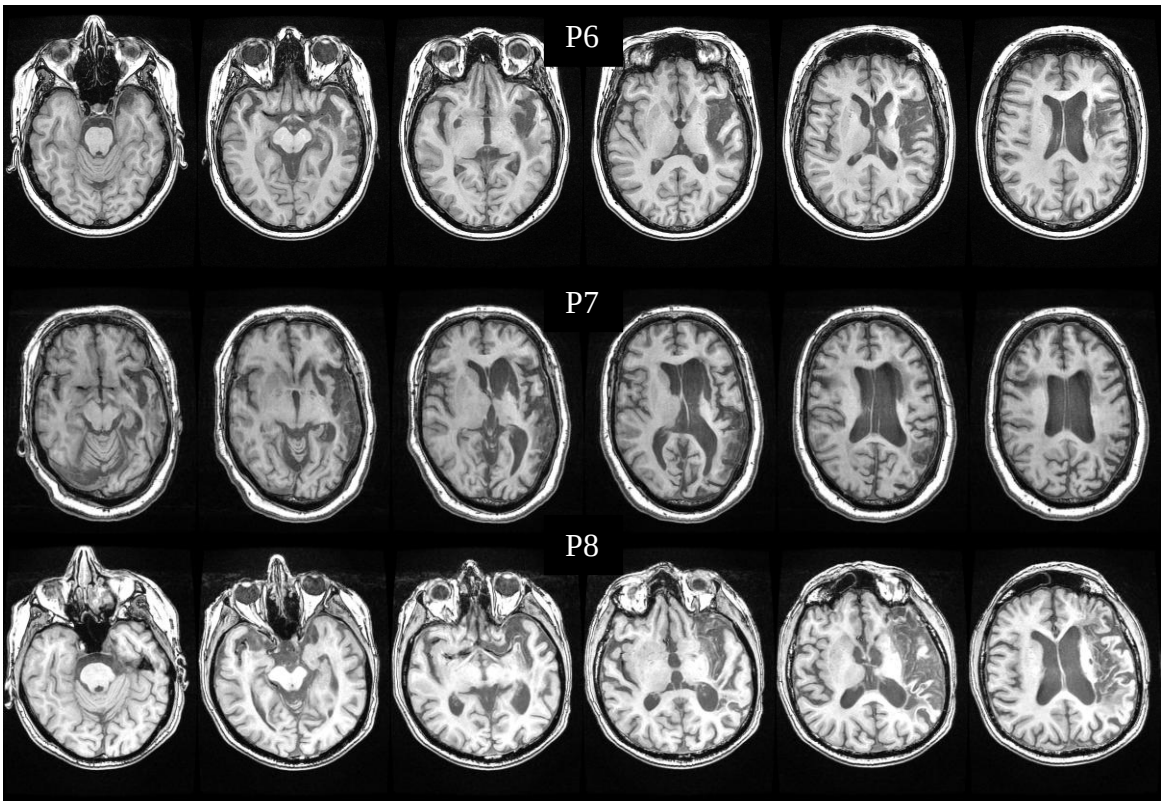


Figure 4: Structural T1-weighted axial images for participants with antero-posterior/ subcortical lesions (P6, P7 and P8). Images are in radiological orientation with the right side of the brain to the left and the left side to the right.

5.2. PATIENTS LANGUAGE PROFILE

The following standardized language tests were administered to each patients: *Western Aphasia Battery* (WAB) (Kertesz, 1982), *Boston Naming Test* (BNT) (Kaplan, Goodglass, & Weintraub, 1983), portions of the *Psycholinguistic Assessment of Language Processing in Aphasia* (PALPA) (Kay, Lesser, & Coltheart, 1992), *Pyramids and Palm trees test* (PAPT) (Howard & Patterson, 1992), and *Cognitive Linguistic Quick Assessment* (CLQT) (Helm-Estabrooks, 2001). Please see Table 5 for the language test scores.

Based on the results of the WAB, six patients were classified as anomic (P2, P4, P5, P6, P7 and P8) and two patients were classified as non-aphasic (P1 and P3). All patients scored 7 or higher (on a scale of 10) on each of the WAB fluency, auditory comprehension and repetition subtests. Six patients (P1, P2, P3, P4, P5 and P6) scored 8 or higher (on a scale of 10) on the WAB naming subtest. P7 scored 6.8/10 on the WAB naming and P8 scored 5.2/10 on the WAB naming subtest. On the BNT, two patients (P1 and P3) scored above average, three patients (P2, P5 and P6) had mild difficulty with naming, P4 had mild-moderate difficulty with naming, and P7 and P8 had moderate-to-severe difficulty with naming. On the PAPT, all patients scored above average. Results from selected subtests of the PALPA indicated that all patients scored perfect or nearly perfect on each of the PALPA-VLD, PALPA-SWPM, and PALPA-WWPM subtests. Five patients (P1, P2, P3, P5 and P6) scored above average of the PALPA-WSJ/ASJ.

Three patients (P4, P7 and P8) scored below average on the PALPA-WSJ/ASJ. On the CLQT, all patients performed within functional limits on attention, memory, and visuospatial skills. Two patients (P1 and P3) performed within functional limits on executive function and language skills. Four patients' (P2, P4, P5 and P6) performance on the CLQT indicated a mild impairment on executive function and language skills. Two patients' (P7 and P8) performance on the CLQT indicated a mild impairment on execute function and moderate impairment on language skills.

Table 5: Test scores for participants with aphasia

Participant	WAB FL (M=10)	WAB AC (M=10)	WAB REP (M=10)	WAB NAM M=10)	WAB AQ (M=100)	BNT (M=60)	PAPT (M=52)	PALPA VLD (M=60)	PALPA SWPM (M=40)	PALPA WWPM (M=40)	PALPA WSJ (M=60)	PALPA ASJ (M=60)
P1	10	10	9.8	8.3	96.2	58	51	60	40	40	59	58
P2	8	9.4	7.6	8.4	84.8	42	49	60	40	40	57	56
P3	10	10	9.6	10	97.8	59	52	60	40	40	59	59
P4	9	10	9.2	8.4	93.2	35	50	60	40	40	53	54
P5	9	9.25	8.8	8.5	91.1	40	49	59	40	40	56	56
P6	9	10	8.6	8.8	91	46	52	60	40	40	59	58
P7	8	8	7.5	6.8	78.4	13	49	58	40	40	51	51
P8	8	8.75	8	5.2	74	13	47	59	40	40	47	50

Note: M-Maximum score; WAB FL-WAB Fluency; WAB AC-WAB Auditory comprehension; WAB REP-WAB Repetition; WAB NAM-WAB Naming; WAB AQ-WAB Aphasia Quotient; PALPA VLD-PALPA Visual lexical decision; PAPLA SWPM-PALPA Spoken word to picture matching; PALPA WWPM-Written word to picture matching; PALPA WSJ-PALPA Written synonym judgment; PALPA ASJ-PALPA Auditory synonym judgment.

5.3. STIMULI AND TASK

Each of the experimental tasks was designed to help us understand the effect of task processing demands on brain activation patterns in chronic stroke patients with aphasia. The order of presentation of the tasks was counterbalanced across participants in order to minimize the effect of task.

5.3.1. Lexical decision task

The first task was a lexical decision task (see Figure 5). This procedure involved measuring how quickly the participants classify stimuli as words or non-words. This task consisted of 60 word stimuli and 60 non-words stimuli. The word stimuli were selected from the MRC Psycholinguistic Database (Coltheart, 1981b). The control condition consisted of non-pronounceable English letters (non-words). The use of non-words instead of pseudo words minimizes segmental phonological and automatic lexical-semantic processing. The non-words were selected from the ARC non-word database (Rastle, Harrington, & Coltheart, 2002). ARC non-word database is a web-based psycho-linguistic resource that can be used to select non-words and pseudo homophones on the basis of a number of psycholinguistic dimensions. The control condition was expected to require the same amount of visual and non-segmental phonological processing. Brain activation observed in the lexical decision paradigm does not involve higher-level phonological or semantic processes that are usually involved in tasks such as picture naming or semantic judgment. It was hypothesized that the direct comparison of words

with non-words would result in activations associated with the mapping of orthographic representations of perceived words onto stored word form representations.

5.3.2. Semantic decision task

The second task was a semantic judgment task (see Figure 6). The stimuli for this task were taken from the Pyramids and Palm Tree task (Howard & Patterson, 1992). The experimental design is similar to that utilized in Chee et al. (2000) and Kurland et al. (2004). In the semantic judgment task, word triplets were presented on the screen and participants had to match one item closer in meaning (presented on top of the screen) to one of the two items presented at the bottom of the screen. This task required analysis of visual stimuli, comparison of two choices with the target in terms of semantic relatedness and subsequent selection of the choice that best matched the target. There were 48 word triplets. The control condition consisted of symbol triplets. One of the items was 8% smaller than the sample item presented at the top of the screen and the other one was 16% larger than the sample item. Participants had to choose the item that was closest in size to the sample item presented at the top of the screen. It was assumed that the control task and the experimental task had a number of common characteristics in terms of visual processing and response selection. Thus, it was intended as a "tight" comparison for the purpose of fMRI analysis. It was hypothesized that subtraction of the experimental condition from the control condition would identify regions involved in semantic processing.

5.3.3. Picture naming task

The third task was an oral picture naming task (see Figure 7). This task required visual processing of the stimulus, followed by integration of semantic and phonological information and subsequent retrieval of the phonological word form. The oral picture naming task consisted of 60 gray scale pictures taken from the international picture naming project database (Bates et al., 2003). Photos sized 4x6 inches were selected for each target example. The control condition consisted of viewing gray scaled scrambled pictures and saying "*pass*". The scrambled pictures were derived by pixelating photographs from the naming task using Adobe PhotoShop7.0. This control task has now been examined in several word retrieval studies (e.g., Meltzer, et al., 2009; Wierenga, et al., 2008). The scrambled pictures were selected as a control for visual complexity of the pictures and did not bear any resemblance to the stimuli used for the picture naming task. Viewing the scrambled pictures was expected to require the same level of visual processing as required by the oral picture naming task. Further, saying pass was expected to require the same level of articulatory processing as the oral picture naming task. It was hypothesized that subtraction of the picture naming task from the control condition (viewing scrambled pictures) would identify regions involved in semantic-phonological integration and phonological retrieval.

5.3.4. Psycholinguistic properties of the stimuli

All stimuli in the three tasks were concrete nouns controlled for syllable length,

frequency of occurrence (Frances & Kucera, 1983), imageability (Gilhooly & Logie, 1980), familiarity (Toglia & Battig, 1978; Gilhooly & Logie, 1980) and concreteness (Gilhooly & Logie, 1980). In order to ensure that there were no differences in the psycholinguistic properties of the stimuli for the three tasks selected for the experiment, a 3 X 5 ANOVA was performed between Task (*lexical decision, semantic judgment, picture naming*) and Psycholinguistic properties (*concreteness, familiarity, imageability, frequency, syllable length*). Results revealed no significant main effects for task ($F(2, 482) = 1.76$, $p = .24$) and psycholinguistic properties ($F(4, 168) = 2.76$, $p = .34$).The mean values of the psycholinguistic properties of the stimuli for the three tasks are shown in Table 6.

Table 6: Psycholinguistic properties of the stimuli

Task	Concreteness	Familiarity	Imageability	Frequency	Syllable length
Lexical Decision	589	544.1	585.7	23	1.2
Semantic Judgment	593.2	547.8	587.5	28.7	1.2
Picture Naming	589	497.4	585.2	18.8	1.7

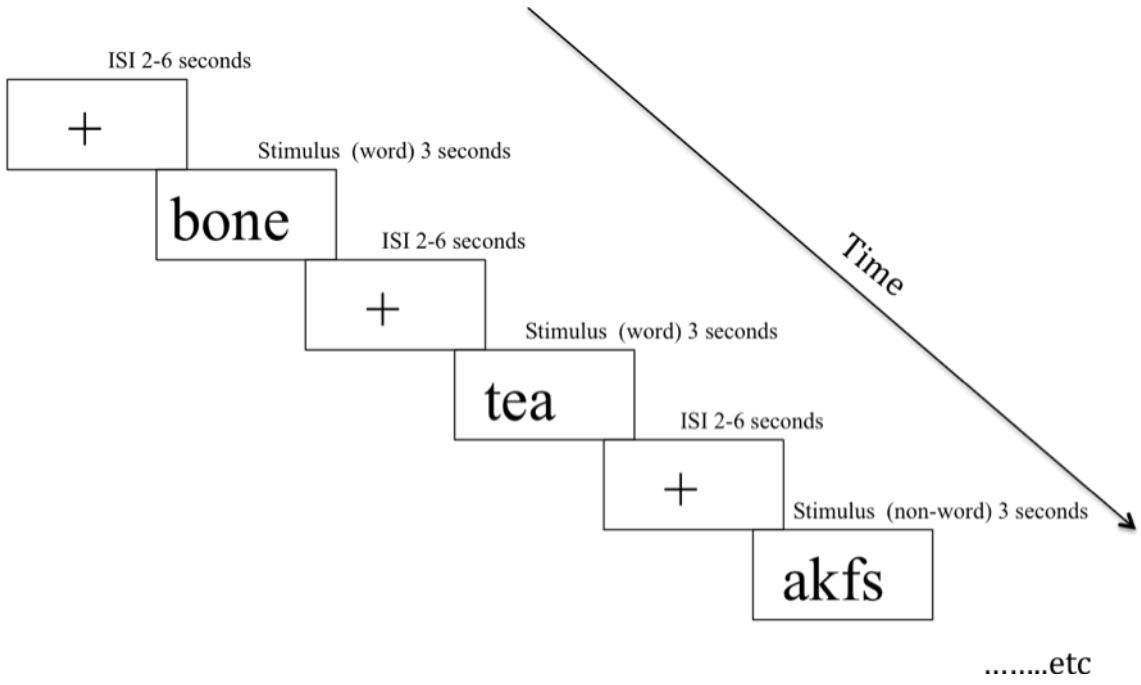


Figure 5: Examples of stimuli used for the lexical decision task. Sample timings of the fixation, word and non-word condition are also shown.

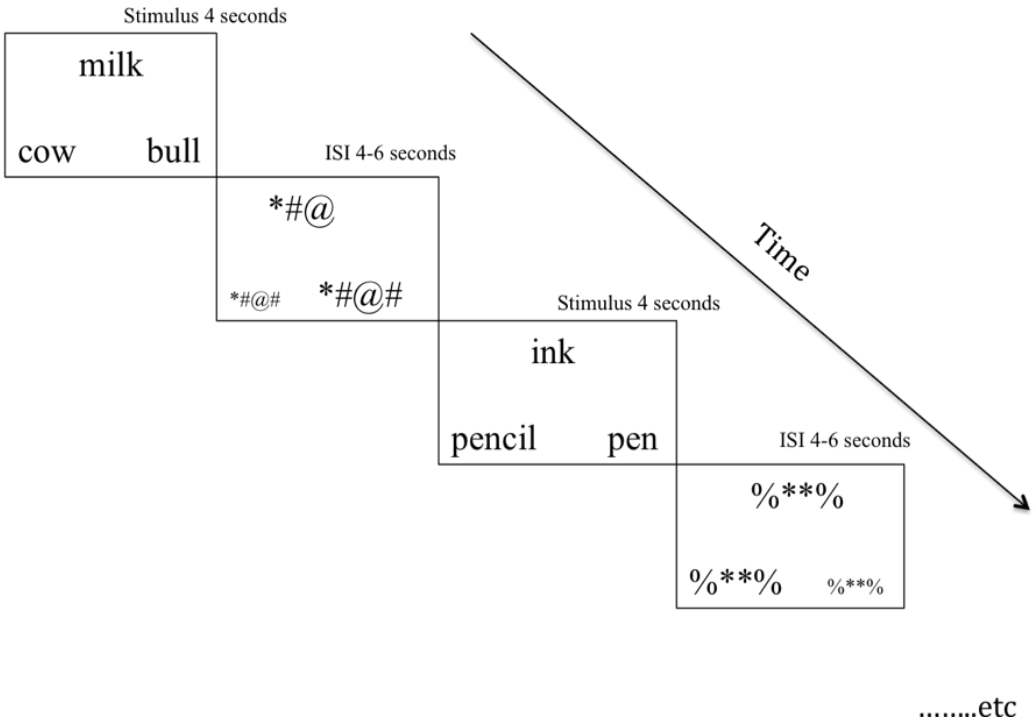


Figure 6: Examples of stimuli used for the semantic judgment task. Sample timings of the semantic and size judgment condition are also shown.

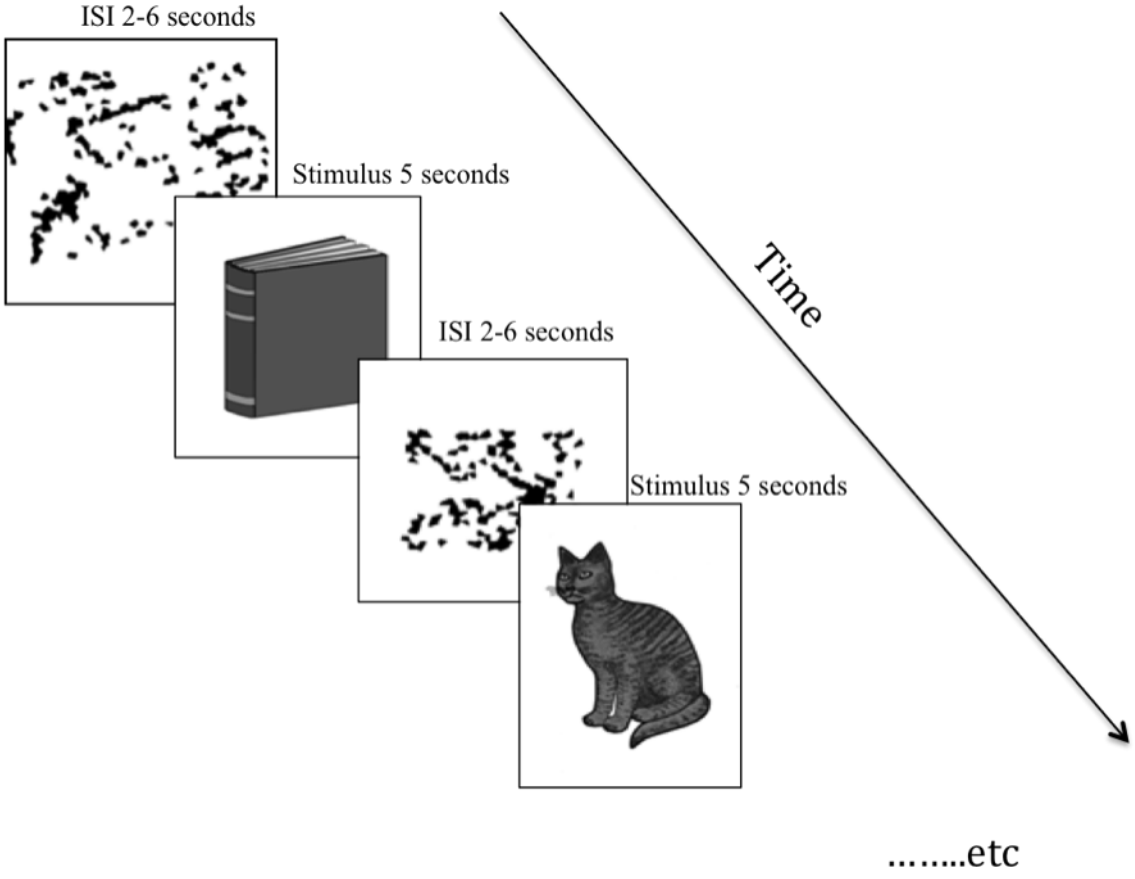


Figure 7: Examples of stimuli used for the picture naming task. Sample timings of the experimental and control (scrambled picture) condition are also shown.

5.4. EXPERIMENTAL DESIGN

An event related design using pseudo-randomized inter-stimulus intervals (ISIs) was employed in this study. This method involves randomly intermixing short stimuli from different experimental conditions and/or pseudo-randomizing different ISIs. Event related paradigms have been increasingly used for the localization of function in tasks involving overt speech since they allow maximization of detection of function while

minimizing task induced motion artifacts (Binder et al., 2003; Birn, Cox, & Bandettini, 2004; de Zubicaray, Wilson, McMahon, & Muthiah, 2001). In addition, event-related fMRI has the ability to segregate correct responses from incorrect ones, which helps us in evaluating the relationship between performance accuracy and brain activation patterns in patients with aphasia.

The control condition was presented during the ISI (see Table 7). For the lexical decision task, the ISI consisted of the visual fixation. For the semantic judgment task, the ISI consisted of the size judgment task. For the picture naming task, the ISI consisted of passively viewing the scrambled pictures and saying "pass". The timing and order of stimulus presentation were optimized for estimation efficiency using Optseq2 (Greve, 2002). In the lexical decision task, each stimulus was presented for three seconds. In the semantic judgment task, each stimulus was presented for four seconds. In the picture naming task, each stimulus was presented for five seconds. The ISI varied from two to six seconds for the lexical decision and picture naming tasks. For the semantic judgment task, the ISI varied from four to six seconds. Both picture naming and semantic judgment tasks were divided into two runs. For the picture naming task, each run consisted of thirty items. For the semantic judgment task, each run consisted of twenty four items. Lexical decision task was divided into three runs. Each run consisted of twenty words and twenty non-words. The stimulus duration and the ISI utilized in the present study is in line with several fMRI studies that have examined language processing in normal participants and participants with aphasia (Chee et al., 2000; Eaton et al., 2008;

Fridriksson et al., 2006; Meltzer et al., 2008).

Table 7: Details of the stimuli and task employed in the fMRI experiment

	Lexical Decision	**Semantic Judgment**	**Picture Naming**
Response Type	Button Press	Button Press	Oral Response
Pseudo randomized ISI	2,4 and 6	4 and 6	2,4 and 6
Total ISI Duration	480sec	484sec	480sec
#Run, #Items per run	3 Runs, 60 items per run	2 Runs,48 items per run	2 Runs, 60 items per run
Stimulus Duration	60X3X3sec=480sec	48X2X4sec=384sec	60X2X5sec=600sec
Total Time	960sec	868sec	960sec

5.5. STIMULUS PRESENTATION AND RESPONSE COLLECTION

The stimuli were presented with EPrime (Psychology Software Tools, Inc.), which uses an InVivo system to project the images on a screen fitted to the head coil of the MRI scanner. Corrective optical lenses were used to correct visual acuity. The picture naming task required the participant to orally name the picture stimuli. Microphone output from the scanner room was run through the penetration panel and connected to a Dell Inspirion Laptop Computer in the scanner control room. The Audacity software on the computer recorded verbal responses from each scanning run. These responses were scored for accuracy and reaction time off-line. Scanner noise cancellation software was used to remove the scanner noise from the subject's response.

For the lexical decision task, participants responded by pressing the middle finger of their left hand for non-words ("no responses") and left index finger for words ("yes responses"). For the semantic judgment task, participants responded by pressing the middle finger of their left hand if they matched the stimuli on the right and the index finger if they matched the stimuli on the left. Before all the runs began, a baseline fixation condition was presented for eight seconds to ensure that the scans had reached equilibrium.

5.6. DATA COLLECTION

Magnetic resonance images were acquired at the University of Texas Imaging Research Center on a 3 Tesla GE MRI scanner. Participants were in the supine position and wore earplugs to reduce the disturbance caused by the scanner noise. When required, corrective optical lenses were used to correct visual acuity. Once a subject took his/her position in the scanner, the magnet was shimmed to achieve maximum homogeneity. Scout images (4s) were obtained to determine the proper angle for subsequent structural and fMRI data acquisitions. This was followed by one high-resolution T1 SPGR scan lasting 5 minutes and 44 seconds (128 1 mm sagittal slices, FOV 240 X 240 mm, flip angle=20, bandwidth=31.25, phase encoding=A-P, TR = 9.5 ms, TE = 6.1 ms). Blood-oxygen-level-dependent (BOLD) sensitive functional images were collected using a gradient echo-planar pulse sequence (TR =2,000 ms, TE = 35 ms, 64 _ 64 matrix, 24x24cm FOV, flip angle 90, 31 oblique slices covering the whole brain, 3-mm-thick,

0.3-mm inter slice gap).

5.7. DATA ANALYSIS

5.7.1. Behavioral tasks

The data were analyzed in terms of accuracy and reaction times for all the three tasks. Naming latencies were measured from recorded sound files as the duration between the offset of the control condition and the onset of the participant's response. For the lexical decision task and the semantic judgment task, the latency and accuracy of response were recorded based on the button press. Only correct responses were considered for the reaction time analysis. Statistical analysis of the behavioral data was performed using STATISTICA 6.0 (StatSoft Tulsa, OK). Univariate analysis of variance was used to compare reaction time and accuracy means for normal controls and participants with aphasia.

5.7.2. Imaging

All fMRI data were analyzed using the Oxford Center for Functional MRI of the Brain (FMRIB)—FMRIB's software library (FSL) version 5.9 (Smith et al. 2004; Woolrich et al., 2009). Image preprocessing was performed to remove nonbrain tissues and to correct image intensity fluctuations and RF inhomogeneities The following pre-statistics processing were applied: motion correction (Jenkinson, Bannister, & Smith, 2002), non-brain removal (Smith, 2002), spatial smoothing using a Gaussian kernel of FWHM 5 mm, mean-based intensity normalization of all volumes by the same factor, and

highpass temporal filtering using Gaussian-weighted LSF straight line fitting, with sigma = 120.0 s. After preprocessing, statistical analyses were performed at the individual level (for both control subjects and patients) within FSL (FEAT, FMRI Expert Analysis Tool). The task timing was convolved with the standard gamma function implemented in FSL (lag, 6 s; width, 3 s), and the fMRI signal was then linearly modeled on a voxel-by-voxel basis using a general linear model (GLM) approach, with local autocorrelation correction (Woolrich et al., 2001).

Stimulus trials were separated into correct and incorrect responses. Only correct responses were included in the data analysis. For the lexical decision task, contrasts examined differences in activation between word decision versus fixation, fixation versus word, non-word decision versus fixation, fixation versus non-word, non-word decision versus word decision, and word decision versus non-word decision. For the semantic judgment task, contrasts examined differences in activation between semantic judgment versus size judgment and size judgment versus semantic judgment. For the picture naming task, contrasts examined differences in activation between picture naming versus scrambled picture viewing and scrambled picture viewing versus picture naming. In a contrast, e.g., semantic judgment versus size judgment, the comparison would reveal which brain regions were significantly more activate during the semantic judgment task than the size judgment task.

Registration of the fMRI images to the MNI standard space was carried out using a linear image registration tool included in FSL. For patients, the cost function masking

method of normalization was employed (Brett et al., 2001), in which a hand-drawn stroke mask, derived from the T1 MRI scan, prevents the normalization algorithm from interpreting the infarct's edge as part of the brain surface. T1-weighted images from each patient were also normalized into MNI space using the cost function masking method found in FLIRT (Jenkinson & Smith, 2001). Higher level analysis, i.e., analysis across runs for the same subject was carried out using fixed effects. *Z* (Gaussianised *T*/*F*) statistic images were thresholded using clusters determined by $Z>3.5$ and a (corrected) cluster significance threshold of $p=0.05$ (Worsley, 2001). Group analysis was carried out only for control participants using FLAME.

5.7.3. Comparison between patients and normal control participants

In order to further understand the difference in activation patterns between the patient group and the control group with regards to the three tasks, a comparison analysis was carried out using FMRIB's Local Analysis of Mixed Effects (Beckmann et al, 2003; Woolrich, Behrens, Beckmann, Jenkinson, & Smith, 2004). This analysis was carried out to determine whether patients recruit the same brain regions as normal control participants or whether they recruit novel brain regions to compensate for their structural deficits. In this analysis, each patient's statistical activation map was directly compared to that of the normal control participants' average.

5.7.4. Regions of Interest Analysis

Regions of interest analysis (ROI) were carried out to determine the relationship between task difficulty and neural activation patterns. The two main regions of interest included the: anterior perisylvian regions and posterior perisylvian regions. These areas were selected because they all serve different aspects of language function (e.g., Binder et al. 2009; Indefrey & Levelt, 2004) and have been associated with recovery in aphasia (e.g., Abo et al., 2004; Blank et al., 2003; Heiss et al., 1997). The anterior perisylvian regions included the left inferior frontal gyrus (LIFG) (pars opercularis and pars triangularis) and the posterior perisylvian regions (PPR) included the: posterior part of the superior temporal gyrus (pSTG), posterior part of the middle temporal gyrus (pMTG), angular gyrus, and supramarginal gyrus. Homologous areas on the right side were chosen as ROIs in the right hemisphere. The mean intensity of signal change associated with each task in these four main regions of interest [left inferior frontal gyrus (LIFG), right inferior frontal gyrus (RIFG), left posterior perisylvian regions (LPPR), and right posterior perisylvian regions (RIFG)] was extracted. The anatomical mask for each ROI was created using fslmaths (part of FSL) and the Harvard-Oxford cortical structural atlas was used as a guide for defining anatomical landmarks. In patients with lesions affecting the regions of interest, ROI maps from the perilesional regions not more than 5 mm from the lesion in three axes were developed (Bonakdarpour, Parrish, & Thompson, 2007). The mean activation within each region associated with each task for each participant was obtained using the Featquery tool, which is part of FSL (FMRIB's Software Library,

www.fmrib.ox.ac.uk/fsl). Lesion volumes were calculated for each patient in order to determine whether there was any relationship between lesion volume and BOLD signal change in the four ROIs. Using the T_1 MRI images, the location and extent of each lesion was drawn by the author and verified by a Neuroradiologist. Lesion volumes and the number of damaged voxels were obtained using fslmaths, which is part of FSL. MRICRON software was used for qualitative display of lesion overlap maps (MRIcron: http://www.sph.sc.edu/comd/rorden/mricron/). Please refer Figure 8 for lesion overlay maps and Figure 9 for ROI maps.

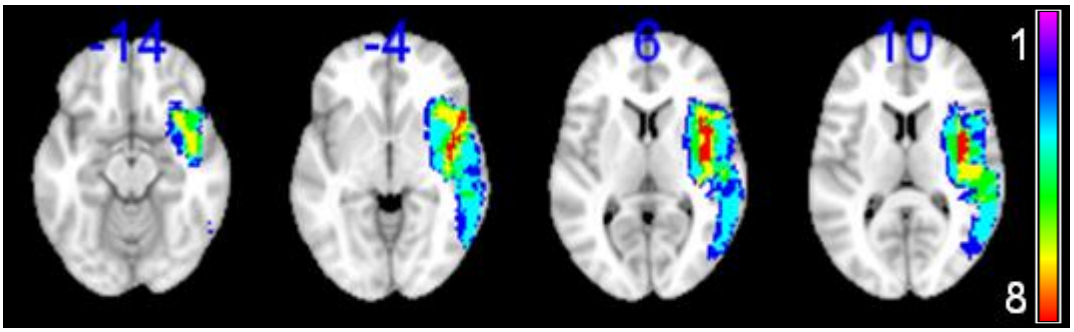


Figure 8: Lesion overlap maps for eight participants with aphasia. Lesion overlaps are displayed on the MNI template brain. The color scale indicates the number of patients contributing to the average lesion image. Images are in radiological orientation with the right side the brain to the left and the left side to the right.

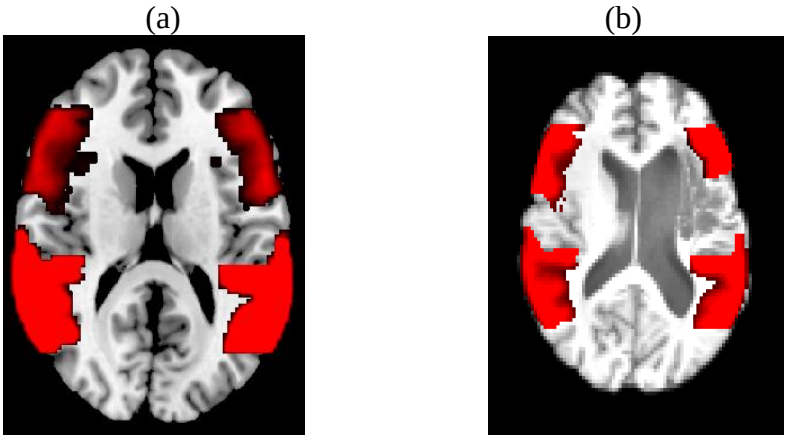


Figure 9: (a) Regions of interest for normal participants. The anterior regions included the left inferior frontal gyrus-pars opercularis and left inferior frontal gyrus-pars triangularis. The posterior regions included the pSTG, pMTG, left angular gyrus and left supramarginal gyrus. Homologues of the same areas were used as ROIs in the right hemisphere, and (b) Regions of interest for Patient P1. In the anterior regions remaining tissue in inferior frontal gyrus (Broca's area, pars triangularis) and the middle frontal gyrus was examined. The posterior regions included the pSTG, pMTG, left angular gyrus and left supramarginal gyrus. Homologues of the same areas were used as ROIs in the right hemisphere.

5.7.5. Laterality Index Analysis

The laterality index analysis was another measure utilized to determine the relationship between task difficulty and neural activation patterns. The laterality index reflects the degree of activation in a left hemisphere ROI in relation to its right hemisphere ROI. To determine the extent to which particular brain regions are involved in the three tasks, the intensity, spatial extent and number of activations were obtained to compute an intensity weighted area of activation (defined as the integral of intensity over that significantly activated region including intensity and spatial extent for that area).

These intensity-weighted volumes were then combined to calculate the lateralization index (LI). The intensity-weighted volumes of the significant activations were calculated for the following ROIs: inferior/middle frontal gyrus, superior temporal gyrus, middle temporal gyrus, angular gyrus and supramarginal gyrus for both left and right hemispheres. An LI was computed for each individual participant from these areas by the following equation (Binder et al., 1995; Desmond et al., 1995): $LI = (\sum sl(i) - \sum sr(i)) / (\sum sl(i) + \sum sr(i))$, where sl(i) and sr(i) refer to the intensity-weighted areas of activations in the i^{th} left and right side ROIs. The value of the LI can range from +1 to -1. A negative value indicates right-hemispheric dominance, a positive value indicates left-hemispheric dominance and a value near zero indicates no dominant hemisphere (or indeterminant).

CHAPTER 6: RESULTS

The purpose of the present study was to examine the neural activation patterns in eight chronic stroke participants with aphasia and eight normal control participants. All participants with aphasia were well recovered and/or had made significant progress in language functions. Further, the site/size of the lesion was different for different patients (anterior lesions, posterior lesions and antero-posterior lesions). fMRI images were obtained while the participants were performing three tasks (lexical decision, semantic judgment and picture naming) that had varying levels of difficulty. Behavioral results are reported first, followed by the results from the whole brain analysis, the regions of interest analysis, and finally the laterality index analysis. For both the normal control participants and the participants with aphasia response accuracy was greater than 70% for all the three tasks. Therefore, performance accuracy based analysis was not carried out.

6.1. BEHAVIORAL RESULTS

Behavioral data are reported for individual participants and by group, i.e., normal control participants and participants with aphasia for both accuracy and reaction times (RTs). The mean accuracy rates and mean RTs for the three tasks for normal control participants are shown in Figures 10 and 11 respectively. The mean accuracy rates and mean RTs for the three tasks for participants with aphasia are shown in Figures 12 and 13 respectively. Only correct responses were included in RT analysis.

6.1.1. Behavioral results for normal control participants

The mean accuracy for the word judgment task was 99.5% and 97.25% for the non-word judgment task. The mean accuracy for the semantic judgment task was 91.7% and 94.15% for the size judgment task. The mean accuracy for the picture naming task was 99.5%. A one-way ANOVA for mean accuracy rates showed a significant main effect for task [F (2, 1299) =33.585, MS_e =0.79, *p=0*.00000]. Lexical decision was significantly more accurate than semantic judgment ($p<0.001$) and picture naming was significantly more accurate than semantic judgment ($p<0.001$). There was no significant difference between the lexical decision task and the picture naming task.

The mean RT for the word judgment task was 940.69msec and 998.65msec for the non-word judgment task. The mean RT for the semantic judgment task was 2062.33msec and 1530.85msec for the size judgment task. The mean RT for the picture naming task was 2427.37msec. A one-way ANOVA for mean RT showed a significant main effect for task [F (2, 1241) =832.11, MS_e=2.79, p=0.0000]. Lexical decision was significantly faster than semantic judgment ($p<0.001$) and picture naming ($p<0.001$) and semantic judgment was significantly faster than picture naming ($p<0.001$). Please see Appendix 4 for mean accuracy, RT, and standard deviation for each individual control participant.

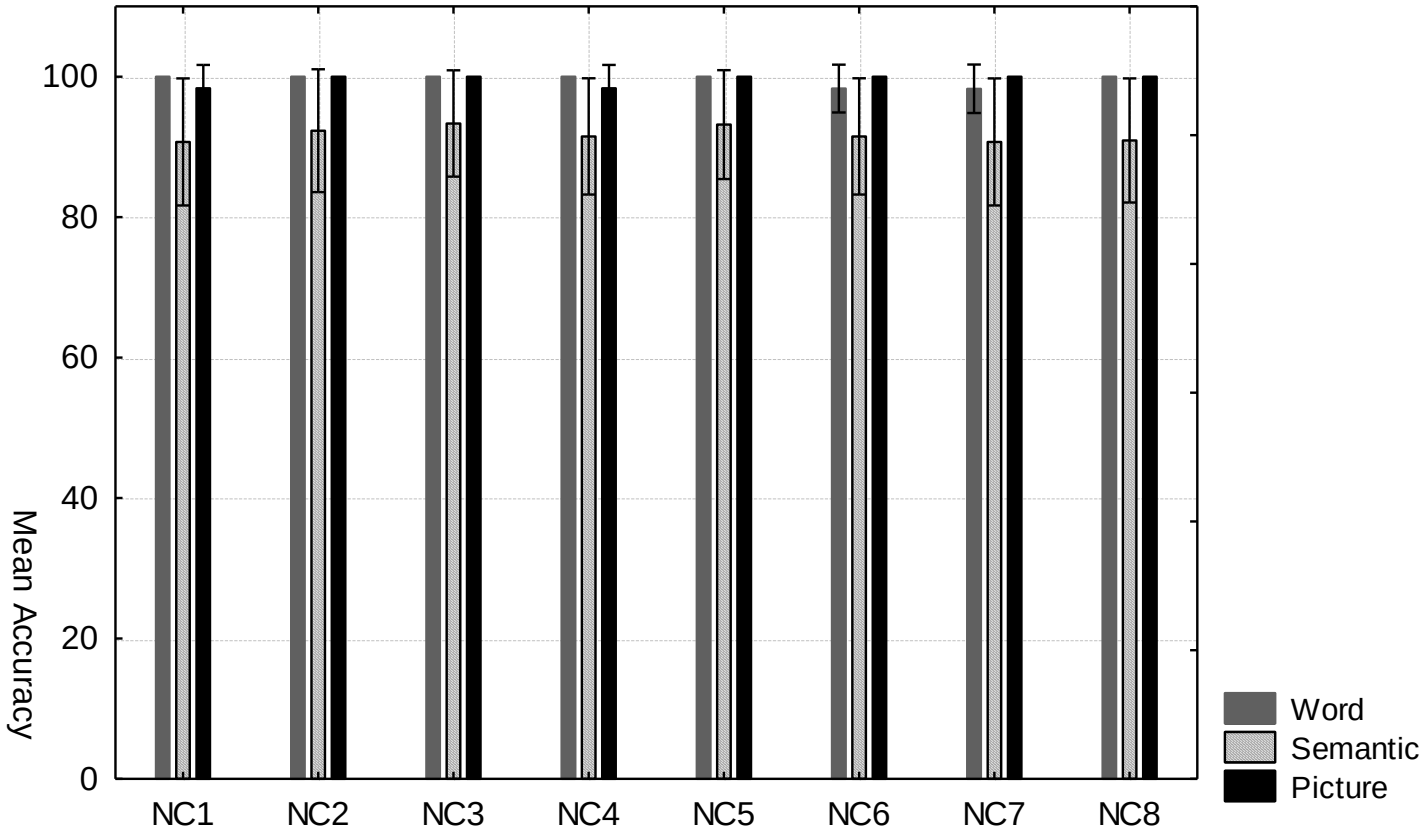


Figure 10: Mean accuracy for normal control participants for the three tasks.

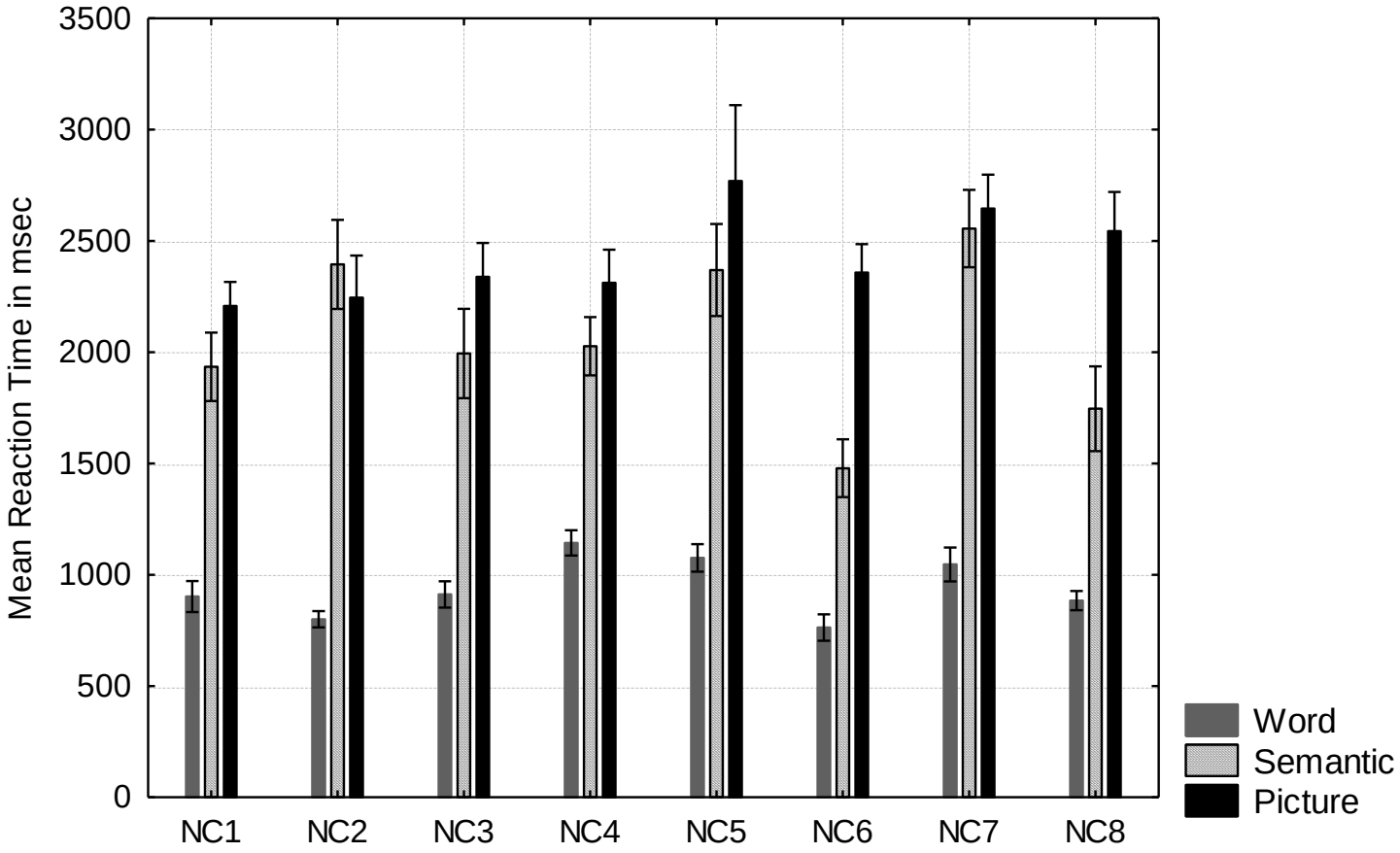


Figure 11: Mean RT for normal control participants for the three tasks.

6.1.2. Behavioral results for participants with aphasia

For participants with aphasia, the mean accuracy for word judgment was 98.7% and 96.2% for non-word judgment. The mean accuracy for semantic judgment was 84.5% and 91.5% for size judgment. The mean accuracy for picture naming task was 88.74%. A one-way ANOVA for the accuracy rates showed a significant main effect for task [F (2, 1232) =29.926, MS_e =2.47 *p*=. 0000]. Lexical decision was significantly more accurate than semantic judgment (*p*<0.001) and picture naming (p<0.001) and picture naming was significantly more accurate than semantic judgment (p<0.001).

For participants with aphasia, the mean RT for word judgment was 958.63 and 965.57msec for non-word judgment. The mean RT for semantic judgment was 2700.45msec and 1520.62msec for size judgment. The mean RT for picture naming was 2945.19msec. A one-way ANOVA for mean RTs showed a significant main effect for task [F (2, 1145) =1093.3, MS_e =4.67 *p*=0.000]. Lexical decision was significantly faster than both semantic judgment (*p*<0.001) and picture naming (p<0.001) and semantic judgment was significantly faster than picture naming (p<0.001). Please see Appendix 5 for mean accuracy, RT, and standard deviation for each participant with aphasia.

Normal control participants were significantly more accurate than patients for the semantic judgment task [t (14) =-3.56, *p* = 0.003] and the picture naming task [t (14) =-3.44, *p* = 0.003]. No significant difference was found between normal control participants and patients in their accuracy rate for the lexical decision task [t (14) =-1.36, *p* = 0.17]. Further, normal control participants were significantly faster than patients for the

semantic judgment task [t (14) =3.66, p = 0.002] and the picture naming task [t (14) =3.22, *p*=0.006]. However, no significant difference was found between normal control participants and patients in RTs for the lexical decision task [t (14) =-1.03, *p* = 0.30].

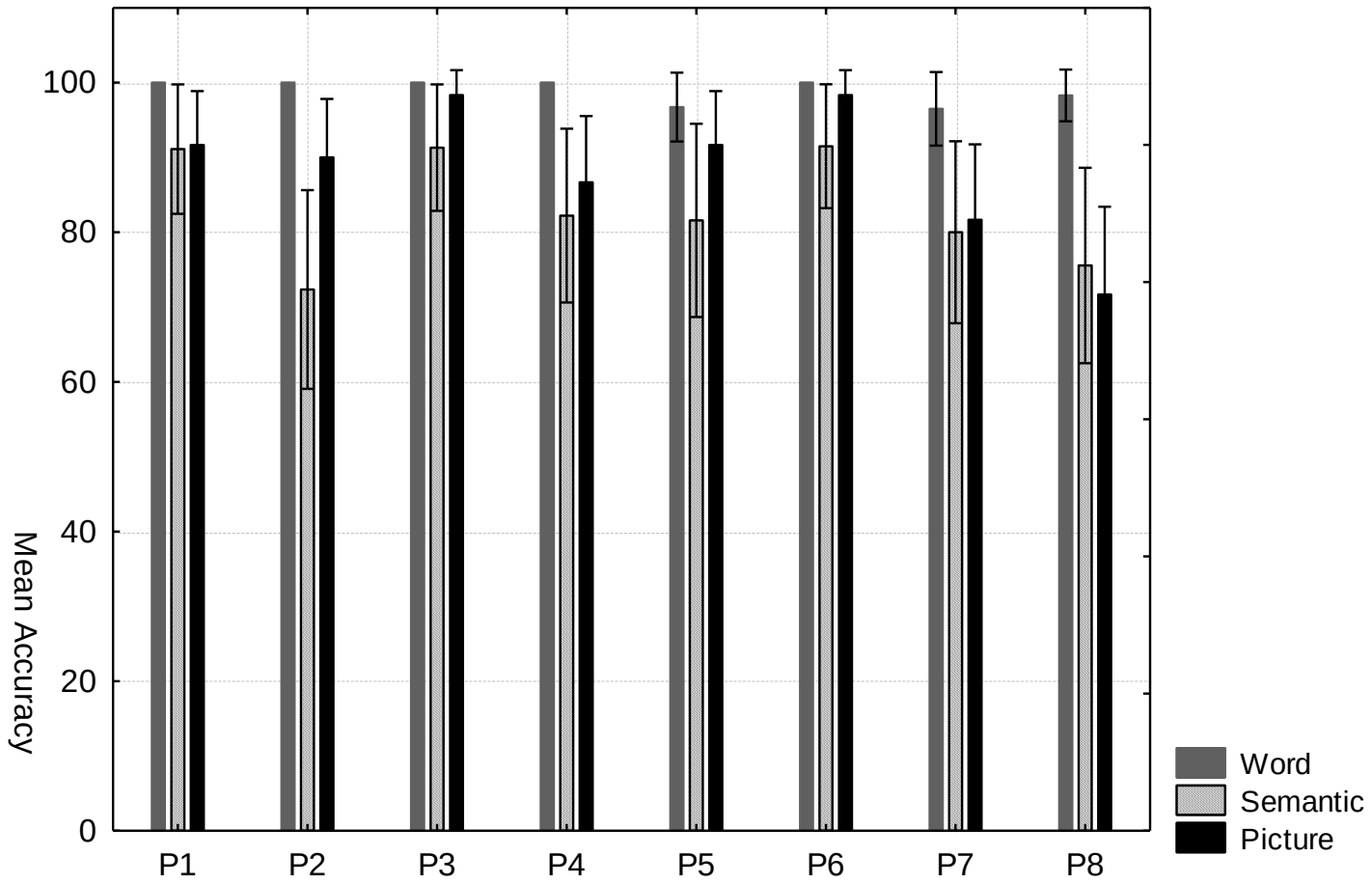


Figure 12: Mean accuracy for participants with aphasia for the three tasks.

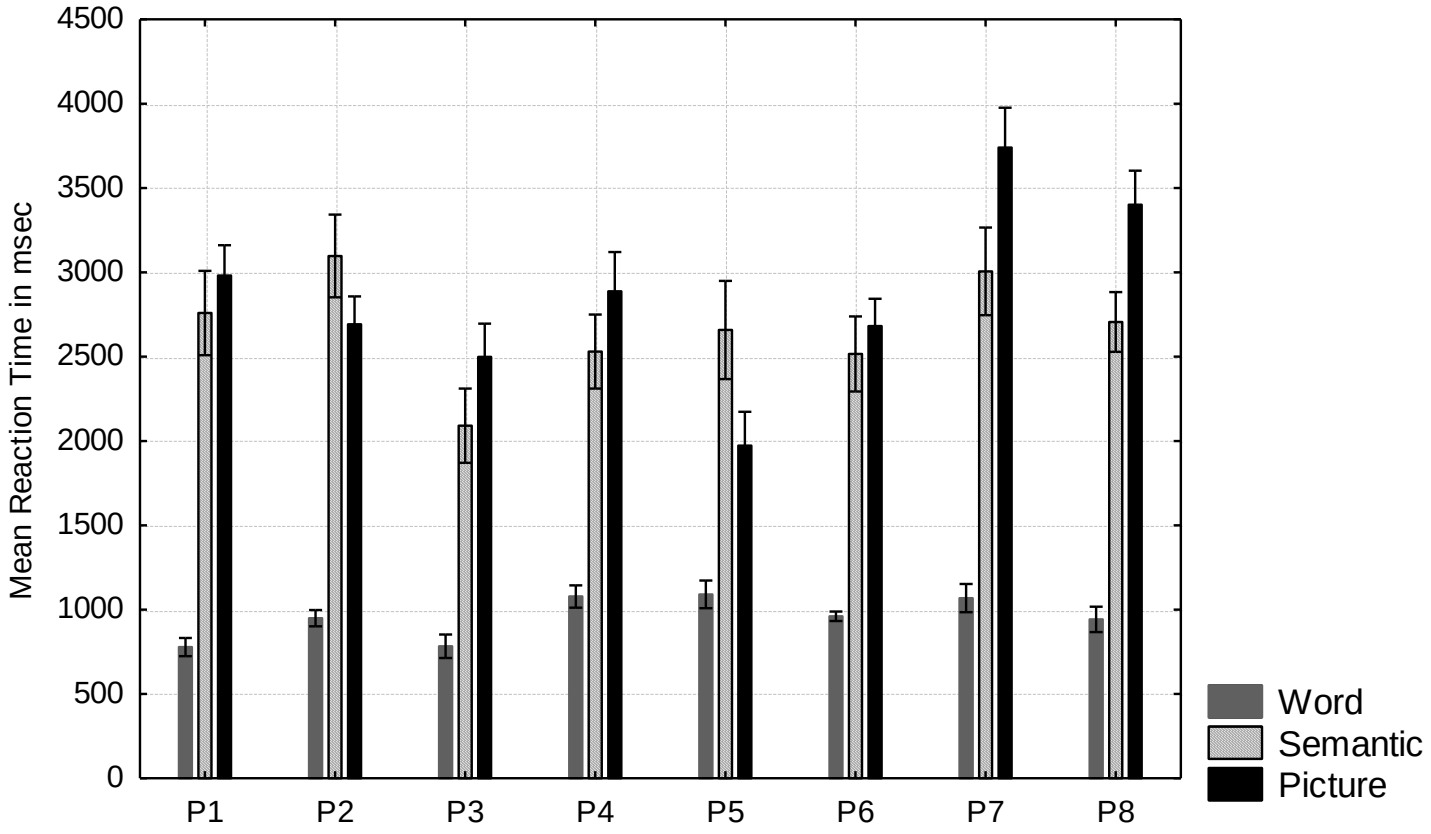


Figure 13: Mean RT for participants with aphasia for the three tasks

2. IMAGING RESULTS (WHOLE BRAIN ANALYSIS)

The results of the whole brain analysis are presented first, followed by the regions of interest analysis, and finally the laterality index analysis. Group data are presented for normal control participants. Individual data are presented for each participant with aphasia. Please see Appendix 6-13 for individual data for each normal control participant. Before discussing fMRI data for patients it is important to understand performance by normal control participants. The data from normal control participants are presented first, followed by data from participants with aphasia.

For each task data from two contrasts are presented. For the lexical decision task the two contrasts are: word vs. non-word and non-word vs. word. The result from the contrast word vs. fixation is presented only when the result from the contrast word vs. non-word is not significant. For the semantic judgment task the two contrasts are: semantic vs. size and size vs. semantic. For the picture naming task the two contrasts are: picture vs. scrambled picture and scrambled picture vs. picture. The contrasts examining the activation patterns for the experimental conditions (word, semantic, and picture) are presented first, followed by the contrasts examining the activation patterns for the control conditions (non-word, size, and scrambled picture).

6.2.1. Normal control participants

6.2.1.1. Lexical decision task

In general, there was a great deal of inter-subject variability in cortical activation patterns for the lexical decision task for the normal control participants. As predicted, four participants (NC1, NC3, NC4 and NC7) activated the left posterior regions for word processing compared to non-word processing. However, some participants (NC1, NC3, NC4 and NC6) also activated the right posterior regions and the left anterior regions (NC3 and NC6). The activation for the contrast word vs. non-word did not reach statistical significance in three normal control participants (NC5, NC7 and NC8). Further, the mean group activation for the contrast word vs. non-word did not reach statistical significance in the normal control participants. Therefore, the mean group activation for the contrast word vs. fixation is presented. Group analysis revealed activations in the bilateral supramarginal gyrus and precentral gyrus. As expected, the control condition (non-word vs. word) mostly activated the visual regions. The mean statistical map representing brain activation in the normal control participants for the lexical decision task is shown Figure 14 and the activation coordinates are shown in Table 8.

6.2.1.2. Semantic judgment task

As predicted, robust activation was observed in all participants in the left inferior frontal gyrus for the contrast semantic vs. size. In addition, some participants also

activated the left middle temporal gyrus (NC2, NC6, NC7 and NC8). Bilateral occipital activation was observed for the control condition (size vs. semantic). The mean statistical map representing brain activation in the normal control participants for the lexical decision task is shown Figure 14 and the activation coordinates are shown in Table 8.

6.2.1.3. Picture naming task

As predicted, picture naming task activated a broad bilateral network (more left than right). All participants activated the bilateral superior temporal gyrus and middle/inferior occipital gyrus. Other activated regions included the left middle/inferior temporal lobe (NC1, NC2, NC3 and NC6), left inferior frontal gyrus (NC1, NC3, NC4, NC6 and NC7), left precentral gyrus (NC7), left supramarginal gyrus (NC1 and NC8), and right supramarginal gyrus (NC8). Bilateral occipital activation was observed for the control condition (scrambled vs. pictures). Additional activation was also observed in the parieto-occipital regions for the control condition. The mean statistical map is shown Figure 14 and the activation coordinates are shown in Table 8.

Table 8: Mean activation coordinates and significance (Z statistics) for normal control participants for the three tasks.

Region	Lexical Decision				Semantic Judgment				Picture Naming			
	Z	**x**	**y**	**z**	**Z**	**x**	**y**	**z**	**Z**	**x**	**y**	**z**
Left Frontal												
Inferior frontal gyrus, BA 45					6.3	-44	48	18	5.1	-52	28	24
Inferior frontal gyrus, BA 44					4.2	-40	16	18	3.5	-42	18	22
Precentral gyrus, BA 4	3.8	-52	2	34					3.5	-50	2	26
Left Temporal												
Middle temporal gyrus, BA 21					3.6	-56	-38	-10				
Superior temporal gyrus, BA 22									5.8	-50	-36	6
Left Parietal												
Supramarginal gyrus, BA 40	3.6	-46	-32	34					3.7	-56	-44	12
Left Occipital												
Occipital gyrus, BA 17	4.5	-16	-96	-10					3.5	-26	-80	24
Right Frontal												
Precentral gyrus, BA 4	3.9	48	8	28								
Right Temporal												
Superior temporal gyrus, BA 22									5.0	64	-22	4
Middle temporal gyrus, BA 21									3.5	52	-36	-2
Right Parietal												
Supramarginal gyrus, BA 40	4.2	50	-24	34								
Right Occipital												
Lingual gyrus, BA 18					3.5	6	-78	4				

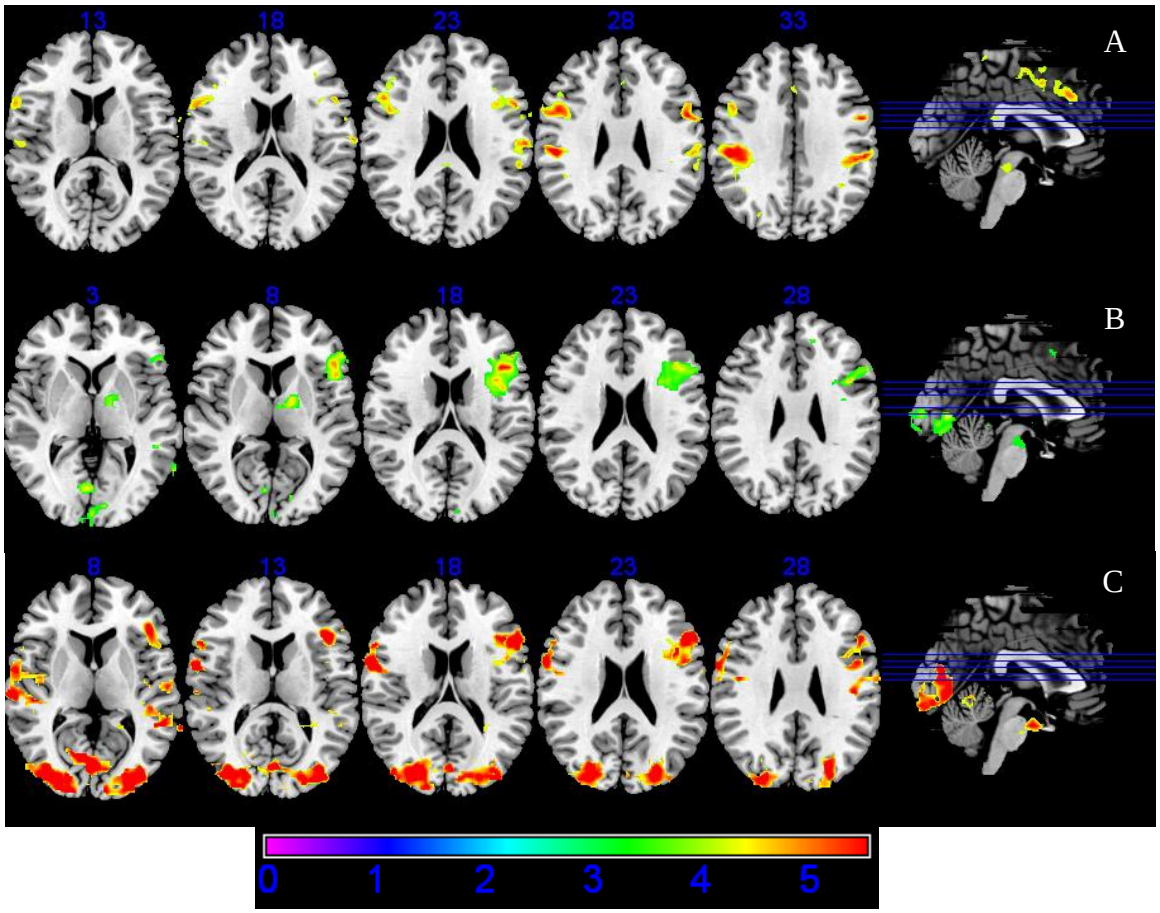


Figure 14: Mean activation maps for normal control participants for (a) lexical decision task determined by the contrast word vs. fixation, (b) semantic judgment task determined by the contrast semantic vs. size judgment, and (c) picture naming task determined by the contrast picture naming vs. scrambled picture viewing. Statistical maps are thresholded by using clusters determined by $Z > 3.5$ and a (corrected) cluster significance threshold of $p = 0.05$. Images are in radiological orientation with the right side of the brain to the left and the left side to the right.

6.2.2. Participants with aphasia

Statistical threshold were not met for the contrast word vs. non-word for all participants with aphasia. This was likely the result of similar activations for words and non–words. Therefore, the result of the contrast word vs. fixation is presented. Further, there was a great deal of inter-subject variability in patients for the contrast word vs. fixation. For participants with aphasia, the activation data are presented based on the site of lesion. Activation data for participants with anterior lesions are presented first, followed by activation data for participants with posterior lesions, and finally activation data for participants with antero-posterior lesions are presented.

6.2.2.1. Participants with anterior lesions

Both P1 and P2 sustained left frontal lesions. Visual inspection of P1's and P2's data revealed primarily a left lateralized network for the lexical decision task and the semantic judgment task. Bilateral posterior activation was observed for the picture naming task. Activation patterns were similar in both the patients for the semantic judgment task and the picture naming task. However, there was some variability in activation patterns for the lexical decision task. Right hemisphere activation was only observed in P2's data for the lexical decision task. Cortical activations observed in P1's and P2's data closely matched the data observed in the normal control participants. However, some differences were also present, such as the recruitment of perilesional region (left inferior frontal gyrus, pars triangularis) for the semantic judgment and the

picture naming tasks and contralesional region (right inferior frontal gyrus) for the semantic judgment task.

6.2.2.1.1. Participant P1

Activation maps for P1 are shown in Figure 15 and activation coordinates are shown in Table 9. For word decision vs. fixation, activation was observed in the left supramarginal gyrus, left angular gyrus, left middle temporal gyrus, left postcentral gyrus, and left middle occipital gyrus. For semantic judgment vs. size judgment, activation was observed in left inferior frontal gyrus, left middle frontal gyrus, left superior and middle temporal gyrus, and left inferior parietal lobe. Contralesional right hemisphere activation (right inferior frontal gyrus) was noted during the semantic judgment task. For picture naming vs. scrambled picture viewing, activation was observed in the left superior/middle temporal gyrus, left superior parietal lobe, left middle frontal gyrus, and left inferior frontal gyrus. Significant right posterior activation (superior/middle temporal gyrus) was also noted for the picture naming task.

The control conditions mainly activated the bilateral occipital regions. Activation did not reach statistical significance for the contrast fixation vs. word. For size judgment vs. semantic judgment, activation was observed in the right middle and superior occipital gyrus, right middle temporal gyrus, and left temporal fusiform cortex. For scrambled picture viewing vs. oral picture naming, activation was observed in the left lingual gyrus, right cuneus, and right angular gyrus.

Table 9: Activation coordinates for P1

Region	Lexical decision				Semantic Judgment				Picture Naming			
	Z	**x**	**y**	**z**	**Z**	**x**	**y**	**z**	**Z**	**x**	**y**	**z**
Left Frontal												
Inferior frontal gyrus, BA 45					3.6	-42	36	6	4.6	-44	36	0
Middle frontal gyrus, BA 46					5.8	-28	52	8				
Left Temporal												
Superior temporal gyrus, BA 22					5.0	-64	-22	-6	5.4	-60	-22	-6
Middle temporal gyrus, BA 21	3.5	-48	-60	8	3.9	-54	-42	-6	5.3	-58	-52	4
Left Parietal												
Postcentral gyrus, BA 3	3.4	-38	-18	42					5.2	-54	-18	40
Supramarginal gyrus, BA 40	3.2	-60	-26	24	4.5	-54	-48	22	5.6	-54	-48	20
Angular gyrus, BA 39	3.0	-42	-56	20								
Left occipital												
Middle occipital gyrus, BA 18	3.5	-26	-76	20								
Right Frontal												
Inferior frontal gyrus, BA 44/45					4.0	42	16	22				
Right Temporal												
Superior temporal gyrus, BA 22									5.0	60	-22	2
Middle temporal gyrus, BA 21									5.1	58	-42	2
Right Occipital												
Middle occipital gyrus, BA 18									3.5	32	-82	22

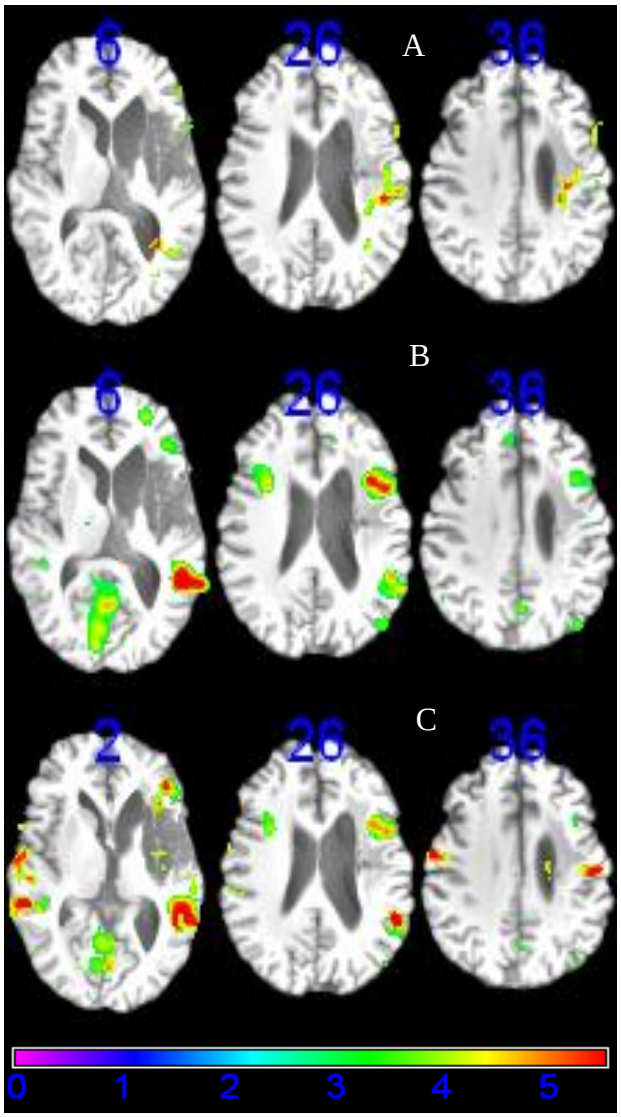


Figure 15: Activation maps for P1 for (a) lexical decision task, (b) semantic judgment task, and (c) picture naming task. Statistical maps are thresholded by using clusters determined by $Z > 3.5$ and a (corrected) cluster significance threshold of $P = 0.05$. Images are in radiological orientation with the right side of the brain to the left and the left side to the right.

6.2.2.1.2. Participant P2

Activation maps for participant P2 are presented in Figure 16 and activation coordinates are presented in Table 10. Language recruitment of the right hemisphere regions were present for all the three tasks, but to a lesser extent for the lexical decision and the semantic judgment tasks. Robust perilesional activation was also observed for P2. Activation was observed in the left angular gyrus, bilateral supramarginal gyrus, left inferior occipital gyrus, and right middle occipital gyrus for word decision vs. fixation. For semantic judgment vs. size judgment, activation was observed in the left inferior frontal gyrus (pars triangularis), left superior frontal gyrus, left superior temporal gyrus, and right inferior frontal gyrus. For picture naming vs. scrambled picture viewing, activation was observed in the left inferior frontal gyrus (pars triangularis), left supramarginal gyrus, right middle temporal gyrus, bilateral superior temporal gyrus, and bilateral inferior occipital gyrus. Activation data did not reach statistical significance for any of the control conditions.

Table 10: Activation coordinates for P2

Region	Lexical decision				Semantic Judgment				Picture Naming			
	Z	**x**	**y**	**z**	**Z**	**x**	**y**	**z**	**Z**	**x**	**y**	**z**
Left Frontal												
Inferior frontal gyrus, BA 45					5.7	-48	22	20	5.8	-46	28	12
Superior frontal gyrus, BA 46					3.5	-16	58	16				
Left Temporal												
Superior temporal gyrus, BA 22					4.0	-58	-52	20	4.9	-46	-32	-4
Middle temporal gyrus, BA 21												
Left Parietal												
Supramarginal gyrus, BA 40	4.7	-56	-38	38					4.3	-60	-34	30
Angular gyrus, BA 39	4.6	-46	-58	50								
Left occipital												
Middle occipital gyrus, BA 18	4.2	-32	-82	20								
Inferior Occipital gyrus, BA 17									5.5	-22	-96	-4
Right Frontal												
Inferior frontal gyrus, BA 45					3.5	40	30	8				
Right Temporal												
Superior temporal gyrus, BA 22									6.1	54	-14	6
Middle temporal gyrus, BA 21									4.1	50	-34	-4
Right Parietal												
Supramarginal gyrus, BA 40	6.2	52	-44	48								
Right Occipital												
Middle occipital gyrus, BA 18	4.4	26	-82	20					6.1	30	-90	-18

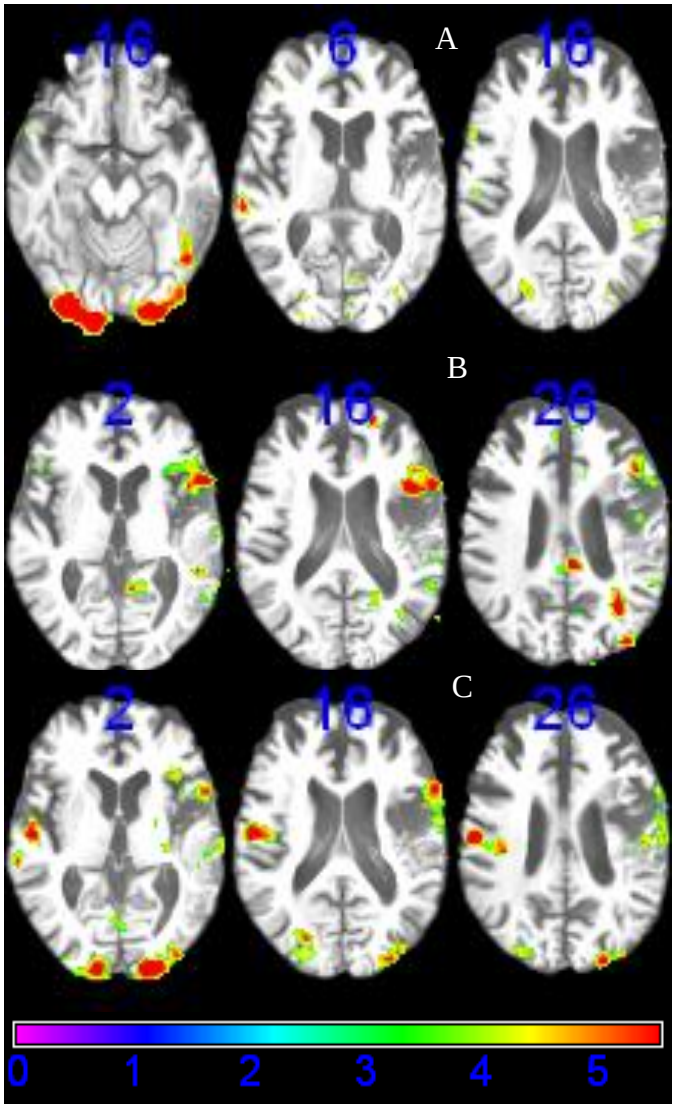


Figure 16: Activation maps for P2 for (a) lexical decision task, (b) semantic judgment task, and (c) picture naming task. Statistical maps are thresholded by using clusters determined by $Z > 3.5$ and a (corrected) cluster significance threshold of $P = 0.05$. Images are in radiological orientation with the right side of the brain to the left and the left side to the right.

6.2.2.2. Participants with posterior lesions

P3 and P4 sustained lesions involving the left temporo-parietal regions. P5 sustained a lesion involving the left temporal lobe and insula. There was great variability in activation patterns for the lexical decision task. Robust left inferior frontal gyrus activation was observed for the three participants for the semantic judgment task. Right posterior activation was observed for the picture naming task for the three participants. Similar to P1 and P2, the greatest amount of activation was observed for the picture naming task. Cortical activations observed for P3, P4, and P5 closely matched the data observed for the normal control participants. However, some differences were also present, such as activation in the perilesional temporal/parietal regions for the picture naming task.

6.2.2.2.1. Participant P3

Activation maps for patient P3 are presented in Figure 17 and activation coordinates are presented in Table 11. For word decision vs. fixation, activation was observed in the left fusiform gyrus, left inferior occipital gyrus, right middle occipital gyrus, and right angular gyrus. For semantic judgment vs. size judgment, activation was observed in the left precentral gyrus, left inferior/middle frontal gyrus and right occipital gyrus. For picture naming vs. picture viewing, activation was observed in the left inferior/middle frontal gyrus, left middle temporal gyrus, right inferior frontal gyrus, and

right superior/middle temporal gyrus.

Activation did not reach statistical significance for the control condition fixation vs. word decision. For size judgment vs. semantic judgment, activation was observed in bilateral fusiform gyrus and bilateral supramarginal gyrus. For scrambled picture vs. oral picture naming, activation was observed in the right angular gyrus and left frontal pole.

Table 11: Activation coordinates for P3

Region	Lexical Decision				Semantic Judgment				Picture Naming			
	Z	**x**	**y**	**z**	**Z**	**x**	**y**	**z**	**Z**	**x**	**y**	**z**
Left Frontal												
Inferior frontal gyrus, BA 44/45					5.2	-50	26	18	6.7	-44	22	2
Middle frontal gyrus, BA 46					5.7	-54	22	26				
Precentral gyrus, BA 4					6.0	-48	-8	58	5.3	-54	-4	18
Left Temporal												
Superior temporal gyrus, BA 22												
Middle temporal gyrus, BA 21									5.3	-50	-32	-10
Left Parietal												
Postcentral gyrus, BA 3									5.3	-54	-6	16
Fusiform gyrus, BA37	3.5	-48	-56	-14								
Left occipital												
Inferior Occipital gyrus, BA 17	3.6	-26	-98	-4								
Right Temporal												
Superior temporal gyrus, BA 22									5.1	52	-20	-4
Middle temporal gyrus, BA 21									5.3	50	-32	-10
Right Parietal												
Angular gyrus, BA 39	3.5	36	-52	38								
Right Occipital												
Middle occipital gyrus, BA 18	3.6	34	-84	2	3.6	36	-88	4	5.0	16	98	-2

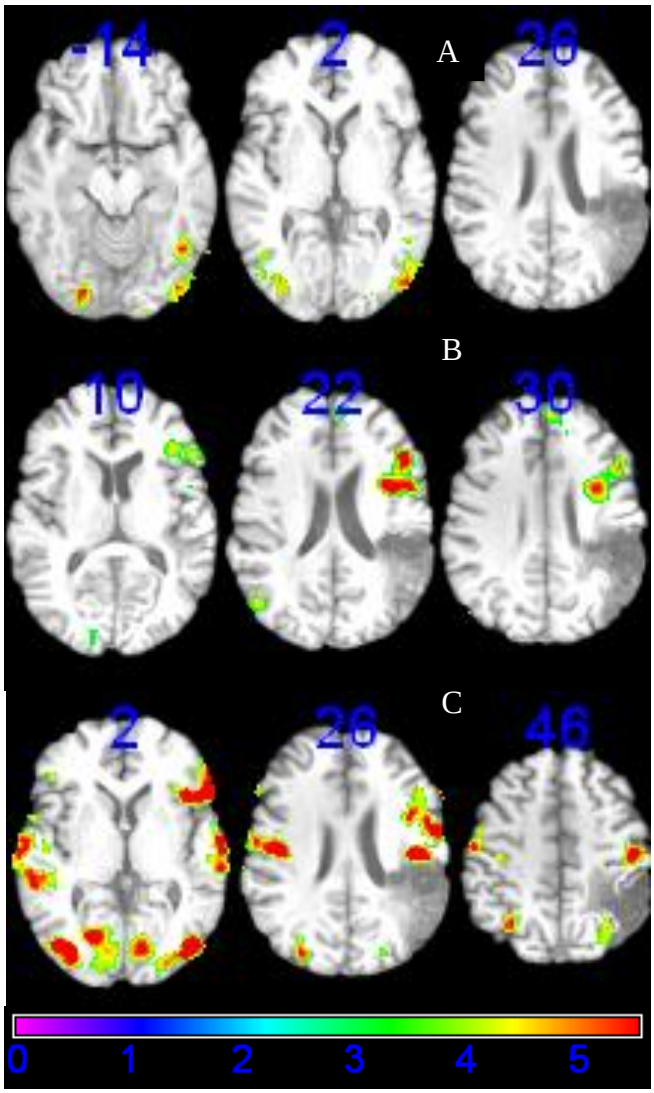


Figure 17: Activation maps for P3 for (a) lexical decision task, (b) semantic judgment task, and (c) picture naming task. Statistical maps are thresholded by using clusters determined by Z > 3.5 and a (corrected) cluster significance threshold of P = 0.05. Images are in radiological orientation with the right side of the brain to the left and the left side to the right.

6.2.2.2.2. Participant P4

Activation maps for participant P4 are presented in Figure 18 and activation coordinates are presented in Table 12. P4's activation was left lateralized for the semantic judgment task. Bilateral activation was observed for both lexical decision and picture naming tasks, although to a greater extent for the picture naming task. For word judgment task vs. visual fixation, activation was observed in bilateral supramarginal gyrus, bilateral precentral gyrus, and right inferior occipital gyrus. Semantic judgment task vs. size judgment task activated the left precentral gyrus, left inferior frontal gyrus, and left occipital cortex. Oral picture naming vs. scrambled picture viewing activated the left middle frontal gyrus, left inferior frontal gyrus, bilateral precentral gyrus and postcentral gyrus, and bilateral middle occipital gyrus. Activation data did not reach statistical significance for any of the control conditions.

Table 12: Activation coordinates for P4

Region	Lexical Decision				Semantic Judgment				Picture Naming			
	Z	**x**	**y**	**z**	**Z**	**x**	**y**	**z**	**Z**	**x**	**y**	**z**
Left Frontal												
Inferior frontal gyrus, BA 44/45					7.7	-40	22	18	6.7	-50	14	24
Middle frontal gyrus, BA 46									3.5	-42	22	38
Precentral gyrus, BA 4	4.9	-60	0	34	6.0	-46	0	40	6.5	-64	0	24
Left Temporal												
Superior temporal gyrus, BA 22												
Middle temporal gyrus, BA 21												
Left Parietal												
Postcentral gyrus, BA 3									3.5	-60	-20	24
Supramarginal gyrus, BA 40	5.7	-58	-28	38								
Left occipital												
Middle occipital gyrus, BA 18					3.6	-40	-74	-5	3.5	-44	-90	8
Right Frontal												
Precentral gyrus, BA 4	4.3	60	2	34					4.2	62	-4	22
Right Parietal												
Postcentral gyrus, BA 3									3.5	-54	-12	34
Supramarginal gyrus, BA 40	4.9	40	-34	46								
Right Occipital												
Inferior occipital gyrus, BA 17	3.9	38	-78	-4					4.1	44	-82	-8

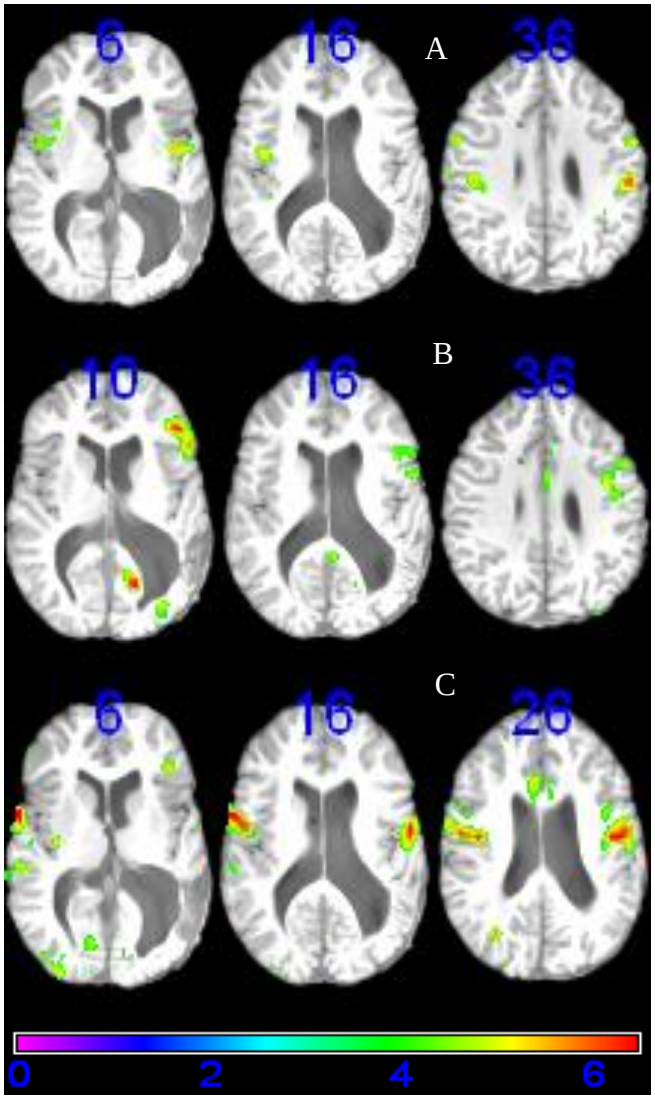


Figure 18: Activation maps for P4 for (a) lexical decision task, (b) semantic judgment task, and (c) picture naming task. Statistical maps are thresholded by using clusters determined by $Z > 3.5$ and a (corrected) cluster significance threshold of $P = 0.05$. Images are in radiological orientation with the right side of the brain to the left and the left side to the right.

6.2.2.2.3. Participant P5

Activation maps for participant P5 are presented in Figure 19 and activation coordinates are presented in Table 13. P5 showed activation mainly in the left ipsilesional frontal and/or perilesional temporal regions for all the three tasks. However, perilesional activation was not observed for the lexical decision task. Activation was also observed in the right hemisphere regions including the temporal and visual cortex. The activation patterns were comparable to that observed in the normal control participants. Further, the activation patterns were also comparable to that observed in the other two patients with posterior lesions. For word judgment vs. visual fixation, activation was observed in the left inferior frontal gyrus, left middle occipital gyrus, and bilateral frontal pole. Semantic judgment vs. size judgment activated the left inferior frontal gyrus, left precentral gyrus, and superior occipital gyrus. Oral picture naming vs. scrambled picture viewing activated the left inferior, middle and superior frontal gyrus, left middle temporal gyrus, bilateral superior occipital gyrus, right superior temporal gyrus, and right postcentral gyrus.

Fixation vs. word decision activated the bilateral occipital gyrus and the left fusiform gyrus. Size judgment vs. semantic judgment activated the left supramarginal gyrus, left superior occipital gyrus, right angular gyrus, and right superior frontal gyrus. The activation for scrambled picture viewing vs. oral picture naming was not significant.

Table 13: Activation coordinates for P5

Region	Lexical Decision				Semantic Judgment				Picture Naming			
	Z	**x**	**y**	**z**	**Z**	**x**	**y**	**z**	**Z**	**x**	**y**	**z**
Left Frontal												
Inferior frontal gyrus, BA 44/45	3.1	-44	22	10	3.8	-44	20	10	3.9	-48	30	0
Middle frontal gyrus, BA 46									4.0	-34	44	18
Superior frontal gyrus, BA 8									3.9	-14	52	18
Frontal pole	2.8	-20	68	2								
Precentral gyrus, BA 4					3.6	-58	0	6				
Left Temporal												
Middle temporal gyrus, BA 21									3.6	-64	-22	-6
Left Parietal												
Postcentral gyrus, BA 3									3.9	-54	-12	28
Left occipital												
Middle occipital gyrus, BA 18	2.9	-32	-80	20								
Superior Occipital gyrus, BA 19	3.5	-32	-76	24	3.9	-30	-76	20	3.8	-20	-82	28
Right Frontal												
Frontal pole	2.6	-4	68	4								
Right Temporal												
Superior temporal gyrus, BA 22									5.9	64	-30	14
Right Parietal												
Postcentral gyrus, BA 3									4.5	54	-14	28
Right Occipital												
Inferior occipital gyrus, BA 17									5.9	46	-80	-10
Superior occipital gyrus, BA 19									5.6	39	-74	-6

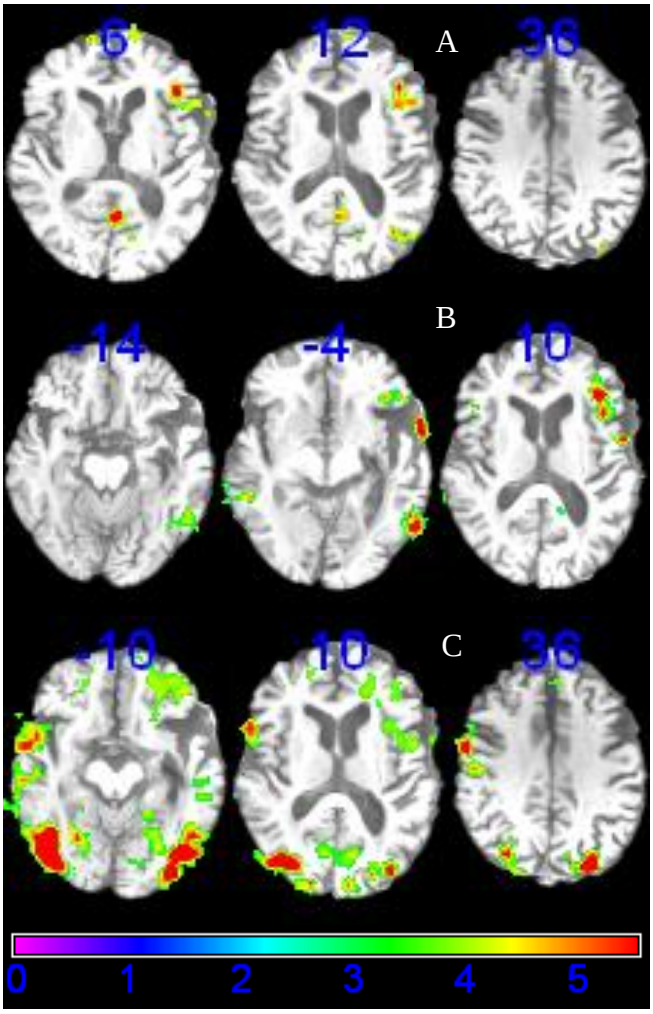


Figure 19: Activation maps for P5 for (a) lexical decision task, (b) semantic judgment task, and (c) picture naming task. Statistical maps are thresholded by using clusters determined by $Z > 3.5$ and a (corrected) cluster significance threshold of $P = 0.05$. Images are in radiological orientation with the right side of the brain to the left and the left side to the right.

6.2.2.3. Participants with antero-posterior lesions

P6 sustained a lesion involving the left frontal, temporal and insular regions. P7 sustained a lesion involving the left temporo-parietal regions and left motor cortex extending into the white matter and P8 sustained a lesion involving the left posterior cortex, insular and subcortical regions. There was great variability in activation patterns for the lexical decision task for all the three participants. This variability was similar to that observed in participants with anterior and posterior lesions. It should be noted that all the three participants' lesions spared the left inferior frontal gyrus. Thus, robust activation was observed in the left inferior frontal gyrus for the semantic judgment tasks. Bilateral activation was observed for the picture naming tasks for the three participants. Although P6 sustained an antero-posterior lesion, her activation patterns were very similar to participants with posterior lesions (P4, P5 and P6). P7's and P8's activation patterns were strikingly different from P6's activation patterns for the picture naming task. No perilesional temporal/ parietal activation was observed for the picture naming task. Large right hemisphere activations were observed for the picture naming task. In addition, activation was observed in the cingulate cortex for P7 and P8.

6.2.2.3.1. Participant P6

Activation maps for P6 are presented in Figure 20 and activation coordinates are presented in Table 14. Bilateral activation was observed for the picture naming task.

Robust perilesional and ipsilesional activations were observed. For P6, activation was observed in left middle temporal gyrus, bilateral middle occipital gyrus, and left middle frontal gyrus for word decision vs. fixation. For semantic judgment vs. size judgment, activation was observed in left inferior frontal gyrus, left middle frontal gyrus, left middle temporal gyrus, and left middle occipital gyrus. For picture naming vs. scrambled picture viewing, activation was observed in the left inferior frontal gyrus, left supramarginal gyrus, left middle temporal gyrus, right precentral gyrus, right lingual gyrus, and right superior temporal gyrus.

For the control conditions, activation was mainly observed in the bilateral visual cortex. Fixation vs. word decision activated the bilateral occipital gyrus, left angular gyrus, and the left fusiform gyrus. For size judgment vs. semantic judgment, activation was observed in the left middle and inferior occipital gyri, left middle temporal gyrus, bilateral angular gyrus, right inferior and superior occipital gyri, and left postcentral gyrus. For scrambled picture viewing vs. oral picture naming, activation was observed in the left superior occipital gyrus and right middle temporal gyrus.

Table 14: Activation coordinates for P6

Region	Lexical Decision				Semantic Judgment				Picture Naming			
	Z	**x**	**y**	**z**	**Z**	**x**	**y**	**z**	**Z**	**x**	**y**	**z**
Left Frontal												
Inferior frontal gyrus, BA 44/45					5.7	-40	22	18	5.3	-46	34	2
Middle frontal gyrus, BA 46	3.4	-44	40	24	5.6	-46	6	46				
Left Temporal												
Middle temporal gyrus, BA 21	3.9	-54	-44	-6	5.2	-56	-30	-7	4.2	-58	-20	-8
Left Parietal												
Postcentral gyrus, BA 3									5.2	-60	-8	16
Supramarginal gyrus, BA 40									4.5	-56	-42	12
Left occipital												
Middle occipital gyrus, BA 18	4.1	-28	-94	4	3.8	-8	-94	20				
Right Frontal												
Precentral gyrus, BA 4									5.2	48	-4	42
Right Temporal												
Superior temporal gyrus, BA 22									6.2	62	-28	-2
Middle temporal gyrus, BA 21									4.0	32	-88	8
Right Occipital												
Middle occipital gyrus, BA 19	5.0	40	-82	-6					5.8	42	-80	-6

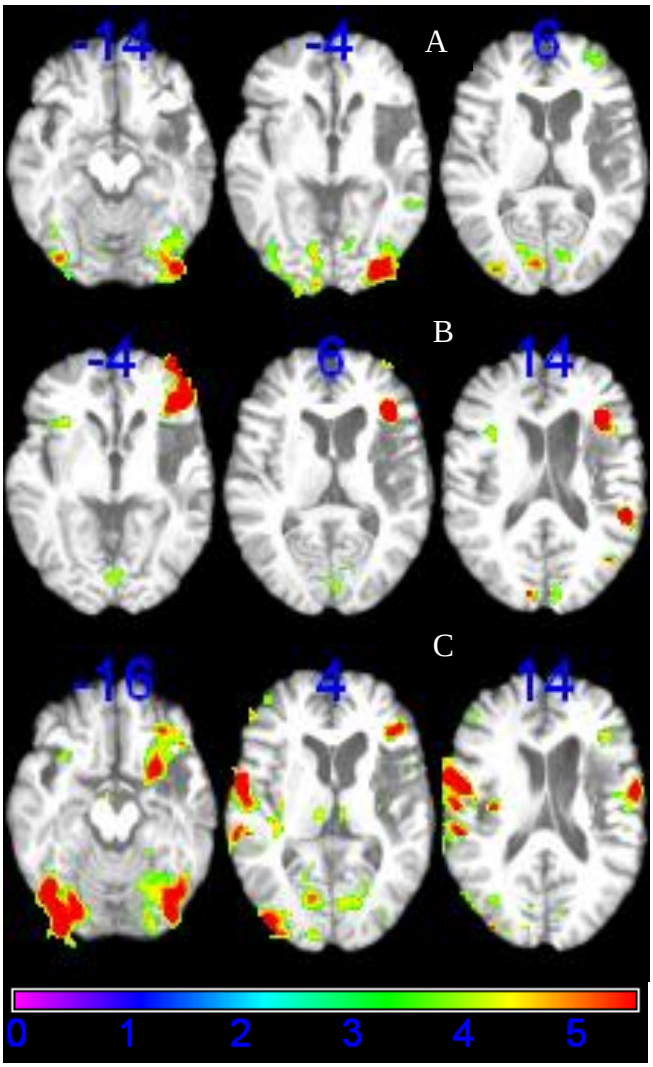


Figure 20: Activation maps for P6 for (a) lexical decision task, (b) semantic judgment task, and (c) picture naming task. Statistical maps are thresholded by using clusters determined by $Z > 3.5$ and a (corrected) cluster significance threshold of $P = 0.05$. Images are in radiological orientation with the right side of the brain to the left and the left side to the right.

6.2.2.3.2. Participant P7

Activation maps for P7 are presented in Figure 21 and activation coordinates are presented in Table 15. P7's lesion did not extent into the left inferior frontal gyrus. Thus, robust activation was observed in the left inferior frontal gyrus for the semantic judgment task. Activation was observed in the left precentral gyrus, bilateral inferior occipital gyrus, and right planum temporal for word vs. fixation. For semantic judgment vs. size judgment, activation was observed in the left inferior and middle frontal gyrus and left superior occipital gyrus. For oral picture naming vs. scrambled picture viewing, activation was observed in the bilateral inferior frontal gyrus, bilateral cingulate gyrus, left superior frontal gyrus, right precentral gyrus, right postcentral gyrus, right supramarginal gyrus, and right middle frontal gyrus.

Fixation vs. word decision activated the bilateral occipital gyrus, right angular gyrus, and the left fusiform gyrus. Activation was observed in the left supramarginal gyrus, left superior occipital gyrus, right angular gyrus, and right superior frontal gyrus for size judgment compared to semantic judgment. Activation was not significant for scrambled picture viewing compared to oral picture naming

Table 15: Activation coordinates for P7

Region	Lexical Decision				Semantic Judgment				Picture Naming			
	Z	**x**	**y**	**z**	**Z**	**x**	**y**	**z**	**Z**	**x**	**y**	**z**
Left Frontal												
Inferior frontal gyrus, BA 45/44					6.2	-52	22	16	4.2	-46	18	18
Middle frontal gyrus, BA 46					4.1	-34	50	14	4.1	-36	38	16
Superior frontal gyrus, BA 8									3.6	-22	54	18
Precentral gyrus, BA 4	5.2	-42	0	32								
Left occipital												
Superior occipital gyrus, BA 19					4.7	-30	-56	32				
Inferior occipital gyrus, BA 17	6.2	-24	-98	-8								
Left Cingulate												
Cingulate gyrus, BA 24									3.5	-16	42	8
Right Frontal												
Inferior frontal gyrus, BA 44/45									5.2	48	22	6
Precentral gyrus, BA 4									3.6	52	10	8
Right Temporal												
Planum temporale	4.9	52	-24	10								
Right Parietal												
Postcentral gyrus, BA 3									3.5	48	-22	38
Supramarginal gyrus, BA 40									3.9	52	-20	26
Right Occipital												
Inferior occipital gyrus, BA 17	6.5	28	-98	-8								
Right Cingulate												
Cingulate gyrus, BA 24									3.6	16	40	12

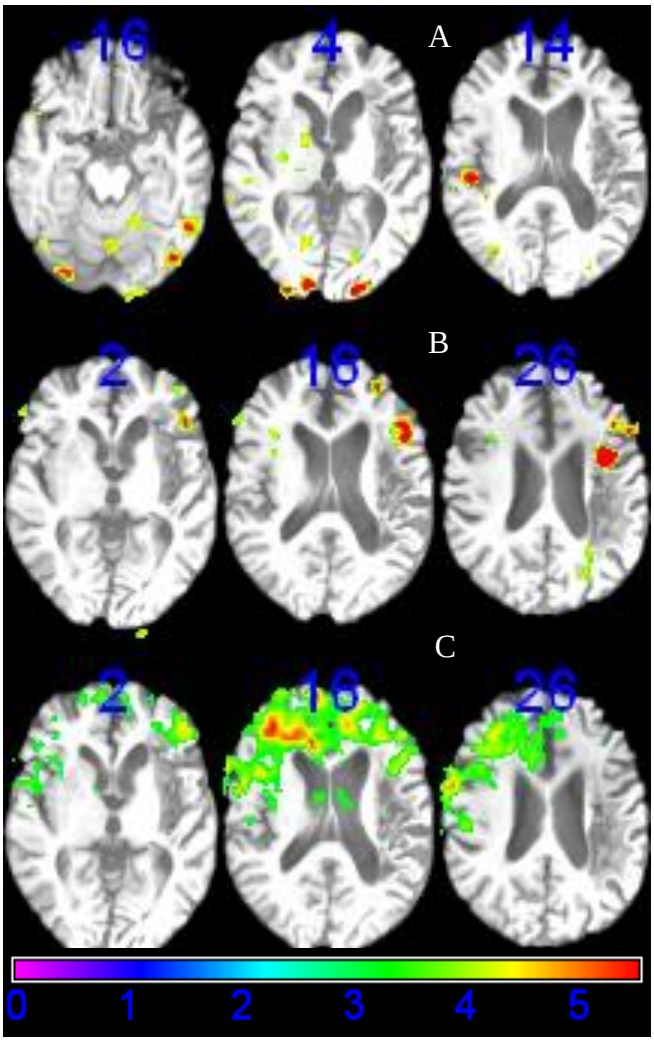


Figure 21: Activation maps for P7 for (a) lexical decision task, (b) semantic judgment task, and (c) picture naming task. Statistical maps are thresholded by using clusters determined by $Z > 3.5$ and a (corrected) cluster significance threshold of $P = 0.05$. Images are in radiological orientation with the right side of the brain to the left and the left side to the right.

6.2.2.3.3. Participant P8

Activation maps for P8 are presented in Figure 22 and activation coordinates are presented in Table 16. P8's activation patterns were very similar to that of P7's activation patterns. No perilesional temporal and parietal activations were observed for the picture naming task. Large right hemisphere activation was observed for the picture naming task. Activation was also observed in the cingulate cortex during picture naming. For word decision vs. fixation, activation was observed in the left precentral gyrus and bilateral supramarginal gyrus. For semantic judgment vs. size judgment, activation was observed in the left inferior and middle frontal gyrus and left precentral gyrus. For oral picture naming vs. scrambled picture viewing, activation was observed in the left inferior and middle frontal gyrus, right superior and middle temporal gyrus, right inferior frontal gyrus, right superior and middle occipital gyrus, and right parahippocampal gyrus.

For the control conditions, activation was only significant for the contrast size judgment vs. semantic judgment. For size judgment vs. semantic judgment, activation was observed in the right middle temporal gyrus and inferior occipital gyrus.

Table 16: Activation coordinates for P8

Region	Lexical Decision				Semantic Judgment				Picture Naming			
	Z	**x**	**y**	**z**	**Z**	**x**	**y**	**z**	**Z**	**x**	**y**	**z**
Left Frontal												
Inferior frontal gyrus, BA 45					5.4	-46	16	12	3.5	-48	30	8
Middle frontal gyrus, BA 46					5.3	-46	8	42	4.2	-40	52	8
Precentral gyrus, BA 4	3.5	-46	-8	30	3.5	-44	6	32				
Left Parietal												
Supramarginal gyrus, BA 40	3.7	-62	-32	24								
Left occipital												
Superior occipital gyrus, BA 19									3.5	-36	-86	32
Left Cingulate												
Cingulate gyrus, BA 24									5.0	-12	18	42
Right Frontal												
Inferior frontal gyrus, BA 44/45									3.5	48	34	0
Right Temporal												
Superior temporal gyrus, BA 22									5.9	64	-26	0
Middle temporal gyrus, BA 21									4.0	54	-18	-16
Right Parietal												
Supramarginal gyrus, BA 40	3.5	54	-20	26								
Right Occipital												
Middle occipital gyrus, BA 17									3.5	44	-78	6
Superior occipital gyrus, BA 19									3.5	32	-88	36
Parahippocampal gyrus, BA 32									3.8	38	-36	-16

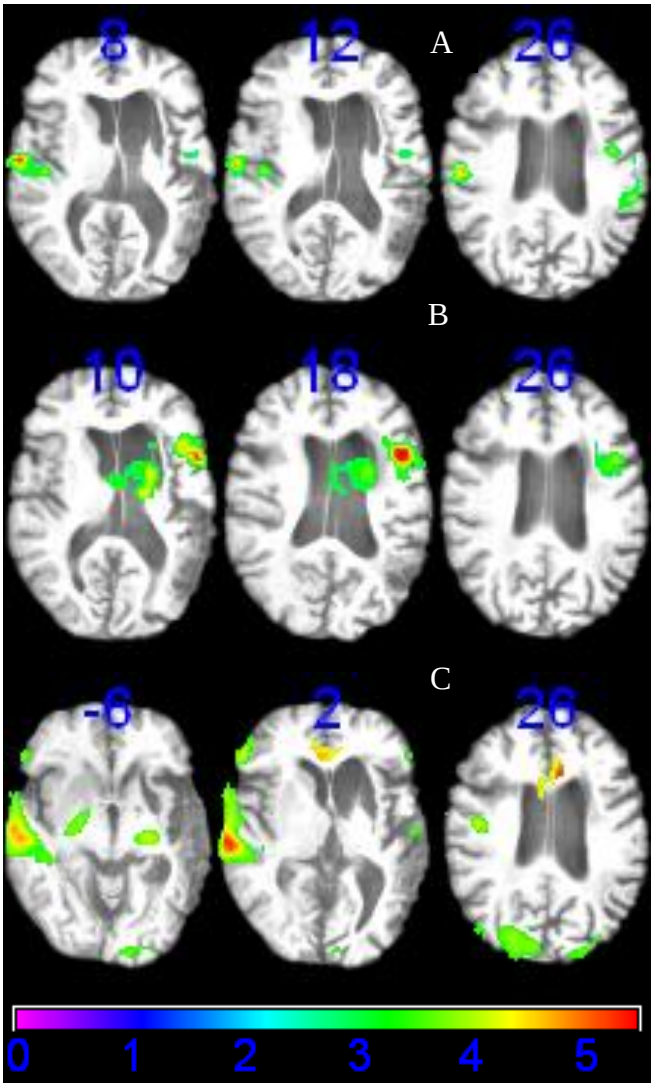


Figure 22: Activation maps for P8 for (a) lexical decision task, (b) semantic judgment task, and (c) picture naming task. Statistical maps are thresholded by using clusters determined by $Z > 3.5$ and a (corrected) cluster significance threshold of $P = 0.05$. Images are in radiological orientation with the right side of the brain to the left and the left side to the right.

6.2.3. Comparison between each patient and control groups' mean activation

This analysis was carried out to determine whether patients recruit the same brain regions as the normal control participants or whether they recruit novel brain regions to compensate for their structural deficits. The results of the direct comparison analysis revealed that some patients recruited the same regions as the normal control participants but to a greater extent, whereas others recruited novel regions that were not activated by the normal control participants.

Direct comparison analysis for the lexical decision task (word vs. fixation) did not reveal any significant difference in activation patterns between each patient and the control groups' mean activation. For the semantic judgment task, two patients (P1 and P2) had significantly greater activation than the control groups' mean activation. Both P1 and P2 activated contralesional frontal regions. P1 had significantly greater activation in the right inferior frontal gyrus and left superior frontal gyrus than the control group's mean activation. P2 had significantly greater activation in the right inferior frontal gyrus than the control groups' mean activation. For the picture naming task, all patients had significantly greater activation than the control groups' mean activation (see Table 17). Five patients (P1, P3, P4, P5 and P6) showed significantly greater activation in the left inferior frontal gyrus compared to that of the control groups' mean activation. Two patients (P7 and P8) showed increased activity in the cingulate gyrus.

Table 17: Activation coordinates for direct comparison between patients and control participants.

Region	Z	x	y	z
Semantic Judgment Task				
Participant 1				
Right inferior frontal gyrus, BA 44/45	3.6	34	14	26
Right occipital gyrus, BA 18	3.5	32	-80	8
Left postcentral gyrus, BA 3	3.5	-44	-16	48
Participant 2				
Right inferior frontal gyrus, BA 45	3.7	58	28	10
Left middle occipital gyrus, BA 19	3.5	-34	-86	10
Picture Naming Task				
Participant 1				
Left inferior frontal gyrus, BA 45	3.6	-42	40	2
Right frontal pole	3.5	24	42	-14
Participant 2				
Right Postcentral gyrus, BA 3	3.5	58	-16	24
Right superior temporal gyrus, BA 22	3.6	64	-26	-2
Participant 3				
Left inferior frontal gyrus, BA 44/45	3.8	-42	22	8
Left postcentral gyrus, BA 3	3.5	-46	-20	44
Left Heschl's gyrus, BA 41	3.5	-42	-30	18
Right postcentral gyrus, BA 3	3.5	44	14	32
Participant 4				
Left inferior frontal gyrus, BA 44/45	3.7	-48	6	20
Left precentral gyrus, BA 4	3.5	-58	4	14
Right middle occipital gyrus, BA 18	3.5	16	-88	30
Participant 5				
Left inferior frontal gyrus, BA 45	3.5	-46	40	-4
Left frontal pole	3.5	-16	62	-4

Table 17 (continued)

Participant 6				
Left inferior frontal gyrus, BA 44/45	3.6	-44	20	10
Right precentral gyrus, BA 4	3.81	48	-6	42
Participant 7				
Right inferior frontal gyrus, BA 44/45	3.2	44	24	8
Left anterior cingulate gyrus, BA 24	3.8	-10	28	24
Participant 8				
Left superior frontal gyrus, BA 8	3.5	-28	56	-10
Left cingulate gyrus, BA 24	3.6	-8	40	6
Right superior temporal gyrus, BA 22	3.7	62	-24	-4

6.3. REGIONS OF INTEREST ANALYSIS

Regions of interest analysis (ROI) were carried out to determine the relationship between task difficulty and neural activation patterns. Mean BOLD signal intensities from four regions of interest were extracted for the three tasks. The four regions of interest included the left inferior frontal gyrus (LIFG), right inferior frontal gyrus (RIFG), left posterior perisylvian regions (LPPR), and right posterior perisylvian regions (RPPR). The results of this analysis revealed greater BOLD signal change for the picture naming task compared to that in the lexical decision task or the semantic judgment task. The results of the ROI analysis for normal control participants are presented first, followed by the results for participants with aphasia.

6.3.1. Normal control participants

ROI data for normal control participants are presented in Figure 23. Non-parametric one-way Friedman ANOVA was employed to study the effect of the mean percent BOLD signal change in each region and the effect of the mean percent BOLD signal change for each task. When the Friedman ANOVA was found to be significant ($p < 0.05$), this analysis was followed by pairwise comparisons using Wilcoxon signed rank test. For the normal control participants, significant differences in the mean percent BOLD signal change were found for both task ($\chi2=11.23$, $p<000.1$) and region ($\chi2=11.23$, $p<0.000$). The Wilcoxon signed rank test revealed significantly greater BOLD signal change for the picture naming task compared to the lexical decision task (Z=-3.44,

p=0.00) and significantly greater signal change for the picture naming task compared to the semantic judgment task (Z=-2.8, *p*=0.00). Thus, greater intensity of activation was found during a difficult task (picture naming) compared to an easy task (lexical decision/semantic judgment). While examining the mean BOLD signal change for each region, the Wilcoxon signed rank test indicated significantly greater signal change in the LIFG compared to that in the RIFG (Z=-3.6, *p*=0.0003). Further, significantly greater signal change was found in LPPR compared to that in the RIFG (Z=-2.9, *p*=0.002).

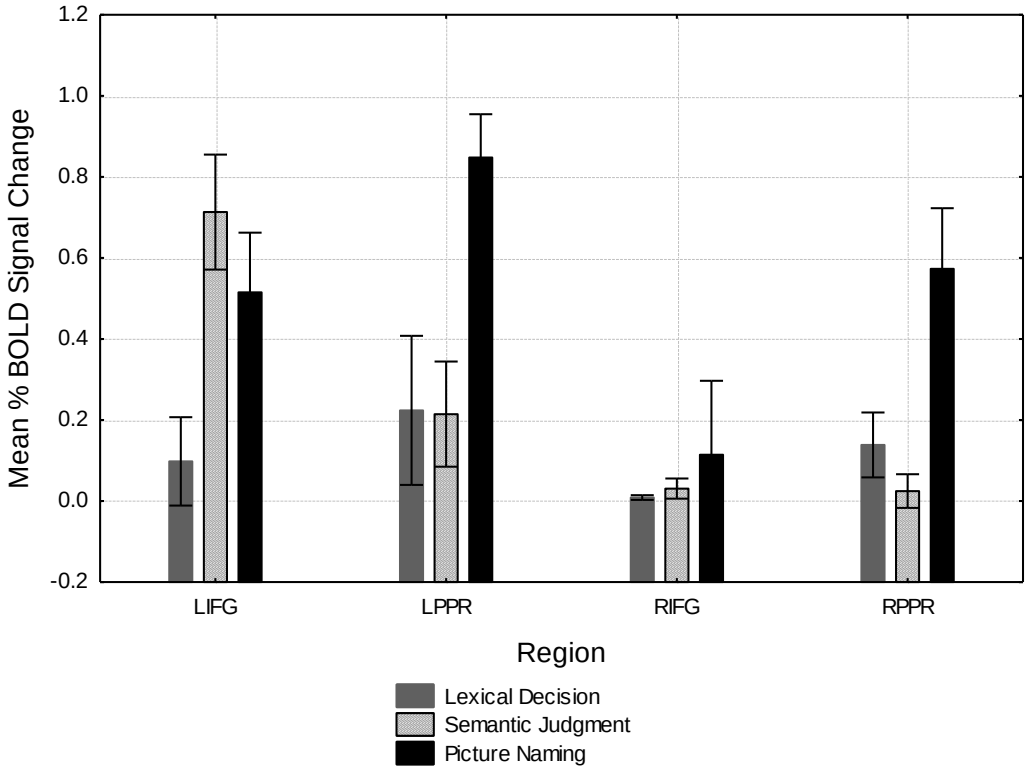


Figure 23: Mean percent signal change in the four ROIs for normal controls.

6.3.2. Participants with aphasia

ROI data for participants with aphasia are presented in Figures 24-27. Non-parametric one-way Friedman ANOVA was employed to study the effect of the mean percent BOLD signal change in each region and the effect of the mean percent BOLD signal change for each task. When the Friedman ANOVA was found to be significant ($p < 0.05$), this analysis was followed by pairwise comparisons using Wilcoxon signed rank test. For participants with aphasia, a significant difference in the mean percent BOLD signal change was found for task ($\chi 2=23.25$, $p<0.0001$), but no significant difference was found for BOLD signal change for region. The Wilcoxon signed rank test for each task revealed significantly greater BOLD signal change for the picture naming task compared to the lexical decision task (Z=-3.1, p=0.000) and significantly greater signal change for the picture naming task compared to the semantic judgment task (Z=-3.3, p=0.000).

To examine the relationship between lesion size and mean BOLD signal change in the different ROIs, a Spearman rank correlation analysis was carried out. For the picture naming task, there was a significant positive correlation between BOLD signal change in the RPPR and lesion volume (r=0.74, p=0.03) indicating that patients with large lesions had greater percent BOLD signal change in the RPPR than patients with small lesions. No other significant correlations were found.

For each task and region, a direct comparison between the patient group and the control group was made by using the Mann-Whitney U test. For task, significantly

greater BOLD signal change was found for picture naming in normal control participants compared to that in participants with aphasia (Z=-2.1, p=0.03). No significant difference was found between the two groups for the lexical decision task and the semantic judgment task. For region, significantly greater BOLD signal change was found in the LPPR in normal control participants compared to that in the patients (Z=-2.35, p=0.018). No significant difference was found between patients and normal controls for LIFG, RIFG and RPPR ROIs.

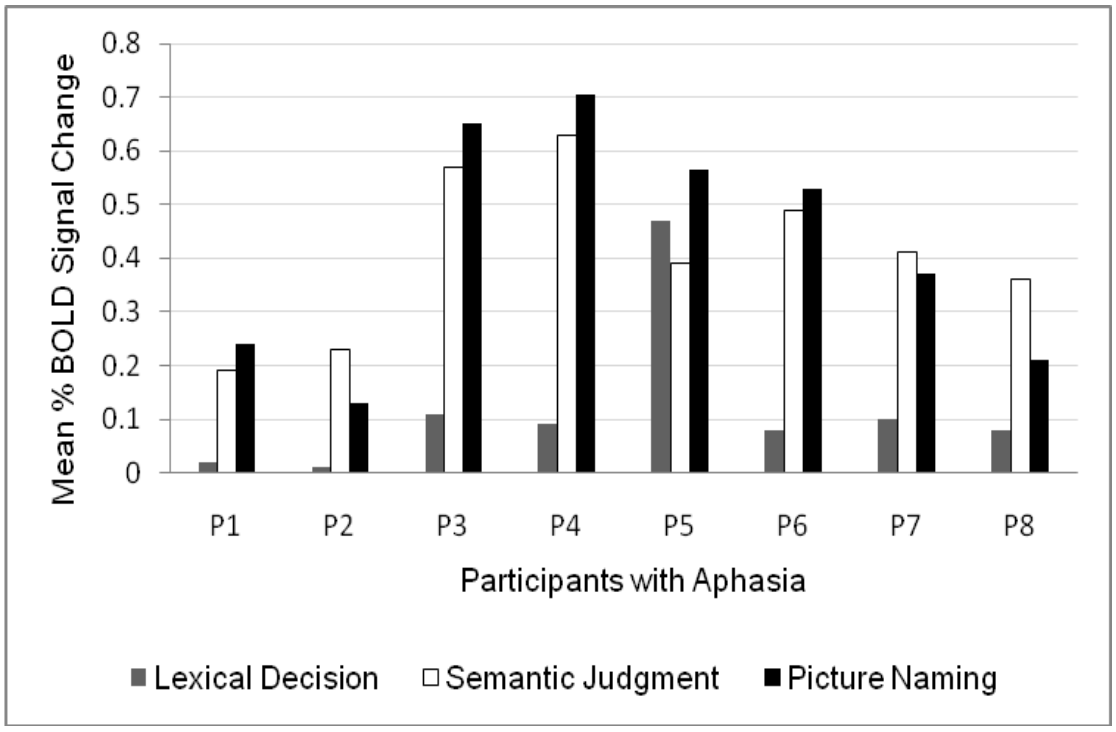


Figure 24: Mean percent BOLD signal change in the LIFG for participants with aphasia.

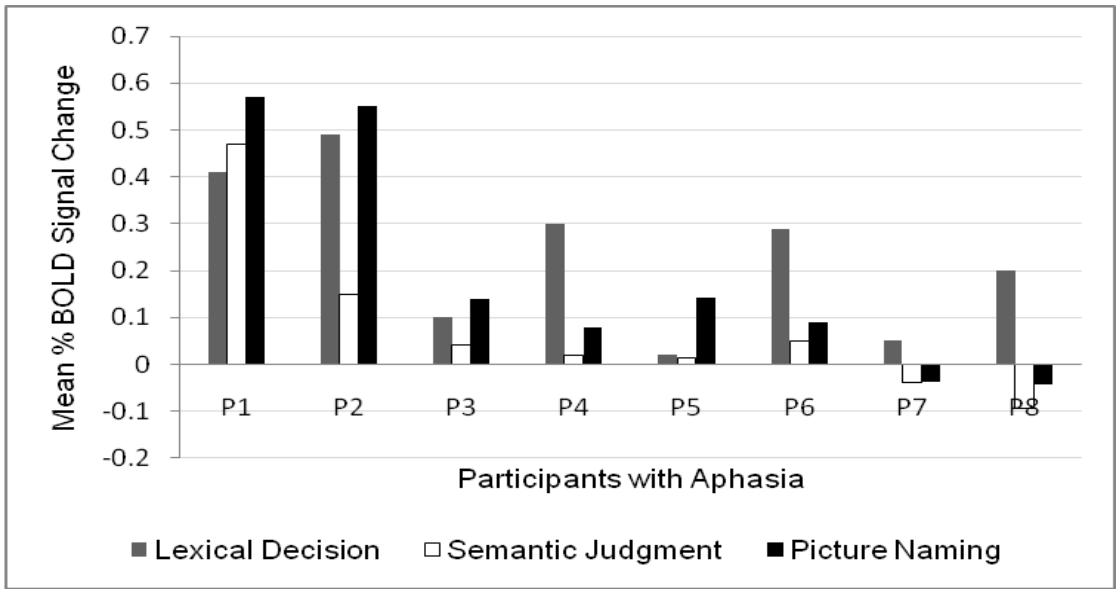


Figure 25: Mean percent BOLD signal change in the LPPR for participants with aphasia.

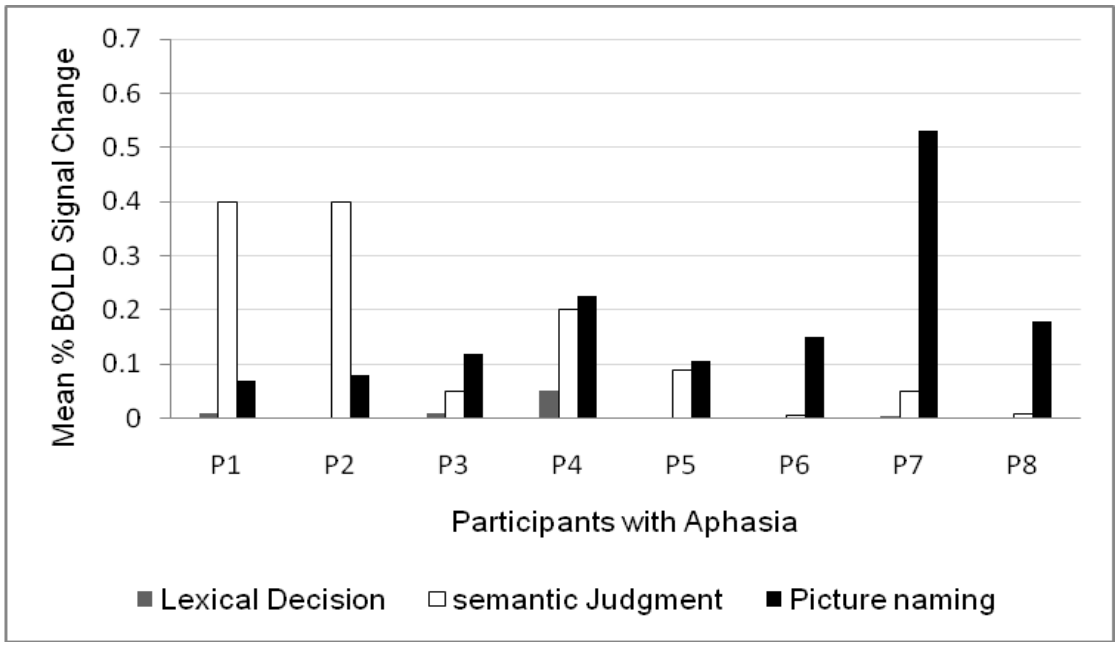


Figure 26: Mean percent BOLD signal change in the RIFG for participants with aphasia.

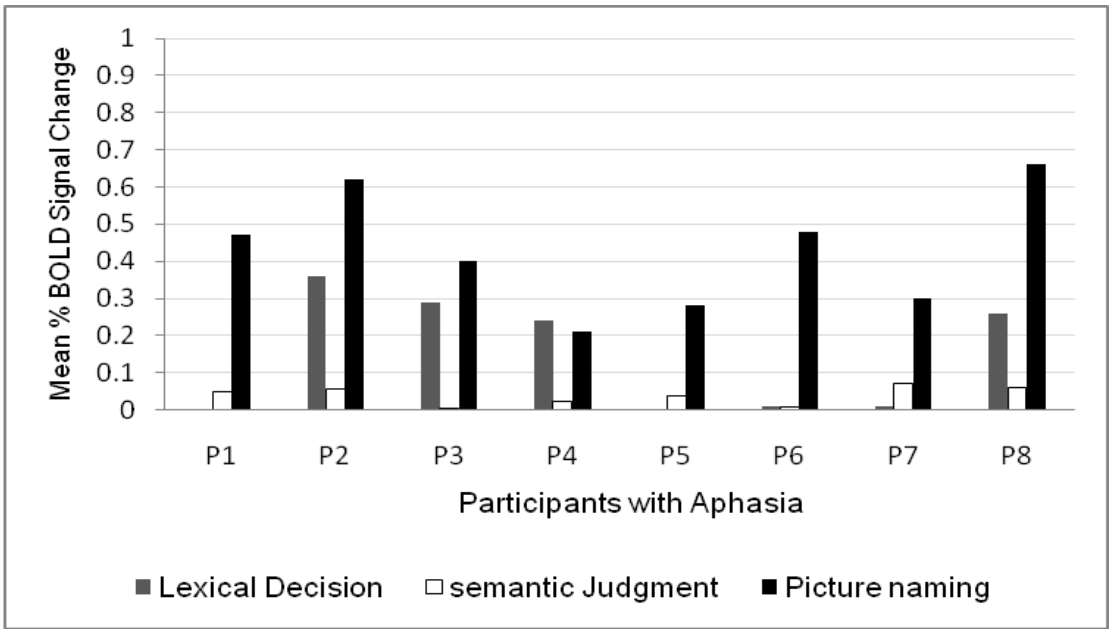


Figure 27: Mean percent BOLD signal change in the RPPR for participants with aphasia.

6.4. LATERALITY INDEX

The laterality index (LI) analysis was another measure utilized to determine the relationship between task difficulty and neural activation patterns. The results of the LI analysis for the normal control participants are presented first, followed by the results for patients.

6.4.1. Normal control participants

The results of the laterality index (LI) analysis for the normal control participants are presented in Figure 28. For the normal control participants, the mean laterality index for the lexical decision task was 0.46 ±0.65, 0.99±0.007 for the semantic judgment task

and 0.55±0.17 for the picture naming task. For the lexical decision task, one normal control participant (NC8) had negative laterality index. For all the other normal control participants, the LI was positive for all the three tasks. The effect of LI was analyzed by means of non-parametric one-way Friedman ANOVA. When the Friedman ANOVA was significant ($p < 0.05$), this analysis was followed by pairwise comparisons using Wilcoxon signed rank test. For the normal control participants, a significant difference was obtained for LI ($\chi 2=10.40$, $p<0.005$). The Wilcoxon signed rank test revealed that the semantic judgment task was significantly more left lateralized than the lexical decision task (Z=2.2, p=0.02) and the semantic judgment task was significantly more left lateralized than the picture naming task (Z=2.47, p=0.01).

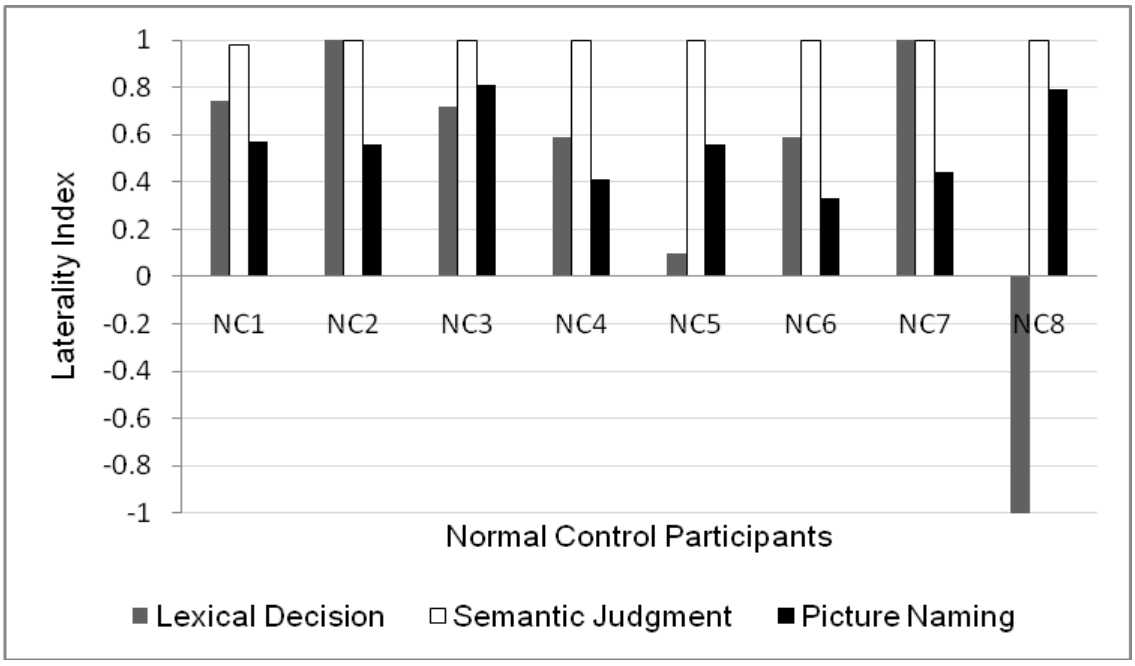


Figure 28: Laterality Index for normal control participants for the three tasks.

6.4.2. Participants with aphasia

The result of the laterality index (LI) analysis for participants with aphasia is presented in Figure 29. For participants with aphasia, the mean LI for the lexical decision task was 0.58±0.35, 0.93±0.07 for the semantic judgment task and 0.32±0.35 for the picture naming task. The effect of LI was analyzed by means of non-parametric one-way Friedman ANOVA. When the Friedman ANOVA was significant ($p < 0.05$), this analysis was followed by pairwise comparisons using Wilcoxon signed rank test. For participants with aphasia, a significant difference was obtained for task ($\chi 2=4.00$, $p<0.05$). Semantic judgment task was significantly more left lateralized than picture naming task ($Z=2.2$, $p=0.02$). For the picture naming task, two patients (P7 and P8) had negative laterality index indicating that picture naming task was right lateralized.

To understand the relationship between lesion size/volume and laterality index for each task, a Spearman rank correlation analysis was carried out. The results revealed a significant negative correlation between laterality index and lesion volume ($r=-0.55$, $p=0.002$) for picture naming task indicating that patients with larger lesion volumes were significantly more right lateralized than patients with smaller lesion volumes. The correlations between lexical decision and lesion volume and between semantic judgment and lesion volume were not significant.

There was no significant difference in the LI between normal control participants and participants with aphasia for the three tasks.

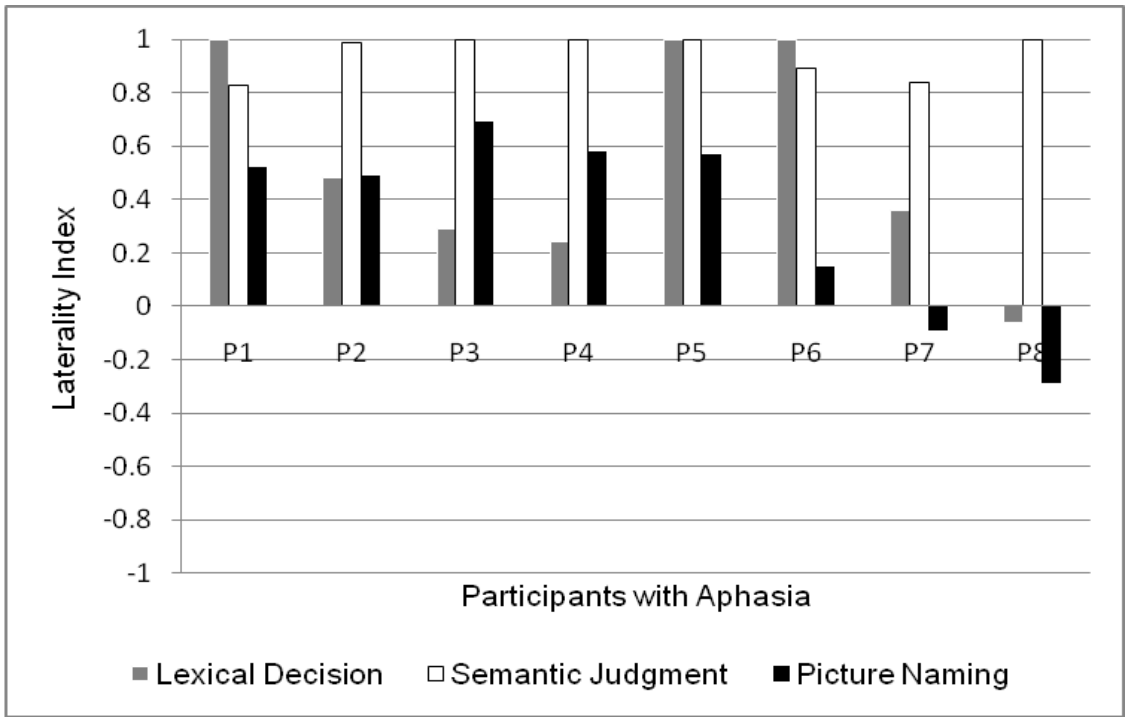


Figure 29: Laterality Index for participants with aphasia for the three tasks.

CHAPTER 7: DISCUSSION

The purpose of this study was to examine the neural correlates of language functions in eight chronic stroke participants with aphasia with different lesion sites (anterior, posterior, and antero-posterior) and lesion sizes. To this end, we utilized three tasks that have been successfully demonstrated to activate specific neuroanatomical networks in normal and brain-injured individuals. The overall results of the study suggest that in both patients and control participants, similar regions within the left and right hemisphere were activated when they performed certain specific tasks. Further, there was an interaction between lesion site/size and task difficulty in participants with aphasia.

This chapter begins with a discussion on the degree of support that was found for each of the proposed hypotheses in Chapter 4. This is followed by a discussion of the role of right hemisphere in language reorganization in post stroke aphasia. Next, the limitations of the present study are discussed. Finally, some suggestions for future investigations are listed. The prediction of differential neural activation patterns for correct versus incorrect responses could not be investigated due to high accuracy for all the three tasks. Only correct responses were included in the analysis.

7.1. NEURAL ACTIVATION PATTERNS FOR NORMAL CONTROL PARTICIPANTS.

This research question was addressed by using three different kinds of analyses: whole brain analysis, regions of interest analysis, and laterality index analysis. The results of the whole brain analysis will be discussed first, followed by the regions of

interest analysis, and finally the laterality index analysis.

The results of the whole brain analysis revealed differences in neural activation patterns for the three tasks. In general, more regions were activated during the picture naming task compared to that activated during the semantic judgment task or the lexical decision task. The results of the lexical decision task will be discussed first, followed by the semantic judgment task, and finally the picture naming task.

For the lexical decision task, it was predicted that normal control participants would activate the left posterior brain structures for word decision vs. non-word decision. The results partially support this prediction. Most normal control participants (NC1, NC2, NC3, NC4, NC6 and NC7) activated posterior and/or anterior regions for word decision vs. non-word decision. Activations were observed in the left angular gyrus (NC1 and NC3), left supramarginal gyrus (NC1, NC3 and NC4), left fusiform gyrus (NC4), left occipital cortex (NC2 and NC4), left middle temporal gyrus (NC3), and left inferior frontal and precentral gyrus (NC6) for word decisions vs. non-word decisions. This increased activity observed in the left angular gyrus, left supramarginal gyrus, and left fusiform gyrus during word decision compared to non-word decision is in agreement with previous fMRI literature examining orthographic and visual word form representations (e.g., Fiebach et al., 2002; Ischebeck et al., 2004; Katz et al., 2005). In addition to the left hemisphere activation, some normal control participants also activated the right supramarginal gyrus (NC4 and NC6) and the right angular gyrus (NC1and NC3) for word decision vs. non-word decision. Normal controls were not expected to activate the right

posterior regions. Nevertheless, this result suggests the involvement of right-hemisphere mechanisms in lexical decision task. Such mechanisms need not be related to language processing in the strict sense in that lexical decision also draws upon perceptual and visuospatial skills, which may recruit right posterior cortical processes. It should be noted that other researchers have also reported increased activity in the right supramarginal gyrus, right angular gyrus, and/or right fusiform gyrus during the lexical decision task (Indefrey & Cutler, 2004; Specht et al., 2008; Specht & Reul, 2003).

For three normal control participants (NC5, NC7 and NC8), the direct contrast between word decision vs. non-word decision did not reach statistical significance. It should be noted that all the non-words used in the present study were non-pronounceable non-words that maximized the phonological distinction between words and non-words. Nevertheless, the activation levels for the three participants failed to reach significance. One possible explanation could be that the three participants utilized similar phonological processing mechanism for processing both words and non-words resulting in no observable difference between the neural activation patterns. Alternatively, the task requirements for lexical decision are such that word responses require ('yes') responses and non-word responses require ('no') responses. These different response types may add additional variance to the data and obscure potential differences in neural activation patterns for words and non-words (Binder et al., 2003). It should be noted that previous studies have yielded conflicting results regarding differences in activation patterns between words and non-words, with some studies demonstrating no significant

differences (e.g., Binder et al., 2000), and other studies demonstrating differences (e.g., Rissman, Eliassen, & Blumstein, 2003).

The results from the other two tasks largely support the predictions put forth in Chapter 4. For the semantic judgment task, it was predicted that normal control participants would activate the left inferior frontal gyrus (LIFG). As predicted, robust activation was observed in the LIFG for all normal control participants for the contrast semantic judgment vs. size judgment. In addition, activation was also present in the left superior/middle temporal gyrus for some participants (NC2, NC6, NC7 and NC8). Activation of the temporal lobe has been associated with lexical–semantic processing (e.g., Pugh et al., 1996). An involvement of the posterior temporal regions in lexical–semantic processing is also suggested by clinical studies. It has been demonstrated that patients with Wernicke's aphasia are unable to semantically categorize words (e.g., Zurif, Caramazza, Myerson, & Galvin, 1974) or to explicitly judge words on the basis of semantic information (e.g., Goodglass & Baker, 1976), leading to the conclusion that controlled lexical–semantic processes are deficient in these patients (Milberg, Blumstein, & Dworetzky, 1987). The activations observed in the left inferior frontal gyrus and left middle temporal gyrus during semantic judgment concur with the results of previous studies that have examined the neural correlates of semantic processing (e.g., Kapur et al., 1994; Thompson-Schill et al., 1998; Wagner et al., 2001).

For the picture naming task, it was hypothesized that normal controls would activate a broad bilateral network (more left than right lateralized), including the left

inferior frontal gyrus, bilateral superior/middle temporal gyrus, left precentral gyrus, left postcentral gyrus, left supramarginal gyrus, and bilateral occipital cortex. The results support this prediction. All normal control participants activated bilateral superior temporal gyrus and occipital cortex. Some participants also activated the left middle/inferior temporal lobe (NC1, NC2, NC3 and NC6), left inferior frontal gyrus (NC1, NC3, NC4, NC6 and NC7), left precentral gyrus (NC7), left supramarginal gyrus (NC1 and NC8), and right supramarginal gyrus (NC8).

This bilateral recruitment is likely explained by task difficulty and cognitive demands associated with naming a picture. The patterns of activation observed within the control group for this task reflected multiple cognitive processes recruited during the completion of this task. For example, the left temporal lobe activated in the present data has been implicated during studies of lexical semantic processing and phonological processing. Further, the left inferior frontal gyrus was consistently recruited for processing related to lexical retrieval. The right temporal lobe activation might indicate additional resources required for the process of integrating phonological input. The results of the picture naming task are in line with other studies that have examined the neural correlates of picture naming (e.g., Binder et al., 1997; Indefrey & Levelt, 2004; Ramsey et al., 2001).

In summary, the results of the whole brain analysis revealed that semantic judgment and picture naming activated regions that are traditionally associated with semantic and phonological processing. However, the results indicate that the lexical

decision task could be performed with multiple sets of sufficient networks that did not necessarily include the left posterior perisylvian regions. In fact, the most striking feature of the contrast examining word vs. non-word across the eight participants is the high degree of inter-participant variability. It may be the case that the control condition designed to minimize segmental phonological processing was not a "tight" comparison resulting in no difference in activation between words and non-words for some participants. One solution to this problem would be to use pronounceable non-words. Although this is outside the scope of this study, it would be appropriate for future investigation.

In addition to investigating the patterns of cortical activation during the three tasks, the present study also sought to determine whether cortical activations would be modulated by the level of task difficulty, i.e., greater effort/activation would be demonstrated for the picture naming data. Both behavioral and imaging results support the expectation that activation is modulated by task difficulty. The results of the reaction time data in normal control participants indicate that lexical decision was faster than semantic judgment and picture naming. Further, making semantic judgments was faster than naming a picture. This finding is consistent with the Ellis and Young Model. According to the model, picture naming is a complex process and involves five different components, namely (1) visual perceptual processing, (2) visual recognition, (3) semantic processing, and (4) phonological planning and retrieval, and (5) speech initiation and articulation, whereas semantic judgment involves three components and lexical decision

task involves two components. Thus, longer reaction times during picture naming task could be attributed to increased processing demands due to higher level phonological and semantic processing.

Consistent with the whole brain analysis, the ROI analysis demonstrated greater BOLD signal change in the bilateral posterior perisylvian regions for the picture naming task compared to the semantic judgment task or the lexical decision task (see Figure 23) This finding is in agreement with other studies that have found a link between task difficulty and BOLD signal change (Chee et al., 2000, Carpenter et al., 1999; Fridriksson & Morrow, 2005). The laterality index analysis also indicated that activation patterns varied as a function of task difficulty. Picture naming was less left lateralized than lexical decision or semantic judgment.

7.2. NEURAL ACTIVATION PATTERNS FOR PARTICIPANTS WITH APHASIA.

This question was addressed by using three different kinds of analyses: whole brain analysis, regions of interest analysis, and laterality index analysis. The results of the whole brain analysis will be presented first, followed by the regions of interest analysis, and finally the laterality index analysis.

The results of the whole brain analysis revealed an interaction between lesion site, lesion size and task difference. For the lexical decision task, participants with aphasia were expected to activate the anterior perisylvian regions or the posterior perisylvian regions with contralesional activation for participants with antero-posterior lesions. The

direct contrast between words and non-words failed to reach statistical significance in all participants with aphasia. Activation for the contrast word compared to fixation was significant for all participants with aphasia. Consistent with the hypothesis, for participants with anterior lesions (P1 and P2), activation was observed in the left inferior parietal lobe and the occipital region. For participants with posterior lesions (P3, P4 and P5) involving the temporal and/or parietal regions, activation was observed in the spared perilesional tissue in the left temporo-parietal cortex (fusiform gyrus, supramarginal gyrus, and middle temporal gyrus) and in the ipsilesional occipital and frontal regions. For participants with antero-posterior lesions (P6, P7 and P8), activation was observed in the spared perilesional regions within the frontal, temporal, and/or parietal regions.

Activation was also observed in the right supramarginal gyrus (P2, P4 and P8), right angular gyrus (P3), and right planum temporale (P7). This increased activity observed in P2, P3, P4, P7, and P8 was very similar to that observed in the normal control participants. Therefore, this increased activity cannot be attributed to compensatory activity of utilizing the right posterior cortex to support orthographic-visual word form processing after the loss of orthographic-visual form within the left posterior perisylvian regions. Finally, it is worth noting that there was relatively large variability in activation patterns across the patients. Visual inspection of the lexical decision data did not reveal any difference in activation patterns based on lesion size.

For the semantic judgment task, activations in the patient group were detected in the same regions as the normal control participants. Consistent with the hypothesis,

patient with anterior lesions (P1 and P2) recruited perilesional frontal [pars triangularis (BA 45) and middle frontal gyrus], ipsilesional temporal (superior and middle temporal gyrus), and right inferior frontal gyrus. Patients with posterior lesions (P3, P4 and P5) recruited the left inferior frontal gyrus (BA 44/45). Patients with antero-posterior lesions (P6, P7 and P8) also recruited the left inferior frontal gyrus (BA 44/45). It should be noted that the inferior frontal gyrus (pars opercularis and pars triangularis) was spared in all participants with antero-posterior lesions. It is also noteworthy that patients without lesions involving the left inferior frontal gyrus activated the same neural regions as the normal control participants. The enhanced activation observed in the right inferior frontal gyrus for P1 and P2 may be indicative of right hemisphere reorganization for response selection during the semantic judgment task. P1's and P2's lesions involved parts of the Broca's area (pars opercularis). Research studies indicate that the left inferior frontal gyrus was found to be both necessary and sufficient to disrupt selection of competing semantic information during verb generation (e.g., Thompson- Schill et al., 1997, 1998). Similar to the results of the lexical decision task, visual inspection of the semantic judgment task did not reveal any difference in activation patterns based on lesion size.

The results of the picture naming task were very similar to that observed in the normal control participants. However, visual inspection of the data revealed differences in activation patterns based on lesion size. In general, bilateral activation was observed for all patients irrespective of the lesion site (anterior lesion, posterior lesion, and antero-posterior lesion). Patients with anterior lesions (P1 and P2) activated the left

superior/middle temporal gyri similar to that observed in the normal control participants, whereas patients with posterior lesions (P3, P4 P5) activated perilesional temporal and/or parietal regions and ipsilesional frontal regions. Patients with antero-posterior lesions showed activity in the spared tissue in the left hemisphere. All participants with aphasia irrespective of the site/size of lesion showed increased activity in either the right frontal (P7) or right temporal/parietal regions (P1, P2, P3, P4, P5, P6, and P8) for picture naming.

It should be noted that two participants with large antero-posterior lesions (P7 and P8) did not show any activity in the spared tissue in the left posterior regions during the picture naming task. However, these patients showed clear activation in the right frontal and/or temporal regions. One possible reason as suggested by Bonakdarpour et al. (2007) could be attributed to altered hemodynamic response in patient with occlusive stroke leading to an insufficient signal to noise ratio. Fridriksson et al. (2006) also found negative BOLD signal change in the left hemisphere and attributed this to localized rise in oxygen consumption without the usual increase in rCBF. Further, the results of Bonakdarpour et al. (2007) suggest that it is important to model the hemodynamic response function (HRF) after the patient's own hemodynamic curve during fMRI experiments to get reliable activation patterns because an underestimation of or complete lack of detection of activation may result when a canonical HRF is used for data analysis. Thus, the lack of activity observed in P7 and P8 might be attributed to altered hemodynamic response leading to insufficient signal to noise ratio. Because traditional

canonical HRF and not the patient's own HRF were used for data analysis, the interpretation of this data is limited. Alternatively, this could also be attributed to lesion size. Both P7 and P8 have large lesions compared to the other participants. The data of Heiss et al. (1997) indicate a link between large lesions and right hemisphere activation. According to the authors, large lesions encompassing the fronto-temporo-parietal regions are associated with poor recovery of language functions and reorganization to the right hemisphere.

It is clear from the results of the whole brain analysis that task difference modulates neural activation patterns. Further support for this premise comes from the results of the behavioral data. Reaction time data indicate that the lexical decision task was faster than the semantic judgment task and the picture naming task. Further, making semantic judgments was faster than naming a picture.

The ROI analysis provided further support to the premise that activation patterns are task, lesion site, and lesion size depended. As expected, increased percent BOLD signal change was found for the picture naming task compared to that observed for the lexical decision task or the semantic judgment task. In participants with aphasia, no significant difference was observed for region. Nevertheless, inspection of the individual participant data revealed that all patients except P8 showed greater BOLD signal change in the left hemisphere ROIs compared to the right hemisphere ROIs for the lexical decision task. This increased BOLD signal change in the right hemisphere ROIs for P8 might be related to lesion size, although there was no correlation between lesion volume

and ROIs for both the tasks. All patients showed greater BOLD signal change in the left hemisphere ROIs compared to the right hemisphere ROIs for the semantic judgment task. Lesion size correlated with the magnitude of signal change in the right posterior perisylvian regions (RPPR) for the picture naming task. Patient with larger lesions had greater signal change in the RPPR compared to patients with smaller lesions.

P1, P3, P4, P5, and P6 showed greater BOLD signal change in left inferior frontal gyrus (LIFG) for the picture naming task compared to the semantic judgment or the lexical decision tasks. The BOLD signal change for the patients was similar to the normal control participants in all regions except the left posterior perisylvian regions (LPPR). This could be attributed to lesion site. The greatest lesion overlap among the patients was in the left posterior regions, thereby leading to reduced activity in this region. Nevertheless, all patients with the exception of P7 and P8 showed some perilesional BOLD signal change in the left posterior perisylvian regions during tasks that recruit the posterior regions (lexical decision task and picture naming). Perilesional BOLD signal was also observed in the left frontal cortex for P1 and P2 during the semantic judgment task. Previous neuroimaging studies have emphasized that good recovery of language function in aphasia is associated with perilesional activity (Cao et al., 1999; Perani et al., 2003; Postman-Caucheteux, 2010; Warburton et al., 1996). The data from the three tasks support the premise that perilesional activity in chronic participants with aphasia is important for neural recovery.

Finally, the results of the laterality index analysis are in line with the results of the whole brain analysis and the ROI analysis. As predicted, semantic judgment task showed greater left lateralization than picture naming task and lexical decision task showed greater left lateralization that picture naming. During the lexical decision task, one patient with antero-posterior lesion (P8) showed negative laterality index. This might be attributed to lesion size, although there was no correlation between lesion volume and laterality index for the lexical decision task. General processing delays cannot explain this difference since reaction times were similar across all patients for the lexical decision task (see Figure 13). It is possible that increased recruitment of the right hemisphere regions for P8 could be attributed to task processing requirements. As mentioned previously, it is clear from the results of the normal control participants that the lexical decision task could be performed by multiple neural regions that are not traditionally involved in phonological processing.

During the picture naming task, patients showed less left lateralization and two patients with antero-posterior lesions (P7 and P8) showed predominant right lateralization indicating that patients with large lesions in the left hemisphere recruit increased right hemisphere regions to successfully complete the task. This explanation is further supported by correlation analysis between laterality index and lesion volume, which indicated that as lesion size increased the laterality index changed from positive to negative. While the present finding supports the hypothesis that picture naming would be

less left lateralized than semantic judgment or lexical decision, it does not support the hypothesis that lexical decision would be more left lateralized than semantic judgment. It is still not clear why the lexical decision task was less left lateralized than the semantic judgment task. One possibility is that the lexical decision task carries lower lateralization than the meaning judgment task due to a semantic component involved in the semantic judgment task. Previous studies have demonstrated greater left lateralization for tasks requiring semantic processing (e.g., Binder et al., 1995, Wise et al., 1991).

In summary, the results of the whole brain analysis, the ROI analysis and the LI analysis indicate that the incorporation of right hemisphere activity into the language network may be more prominent in case of a large lesion in the left hemisphere. Interesting, lesion size did not play a role in determining the activation patterns for the lexical decision task and the semantic judgment task. In contrast, for the picture naming task lesion size did play a role in determining the patterns of activation. One interesting finding was that all patients were able to perform all the three tasks with relatively high accuracy. It appears likely that the ability to perform the three tasks with high accuracy was possible for the patients because critical brain tissue in the left pars triangularis of Broca's region was spared. For example, Thompson-Schill et al. (1998) also observed that among aphasic patients with lesions that included the LIFG, there was a direct correlation between extent of lesion within the LIFG and selection-related errors on a task requiring the subject to generate a verb for a written noun. Alternatively, high performance accuracy could be related to the nature of the stimuli used in the experiment.

For example, both P7 (mean accuracy 81.6%) and P8 (mean accuracy 75.67%) had fairly high accuracy on the picture naming task despite having significant word retrieval deficits as revealed by the BNT (Please see Table 5 for test scores). All the stimuli in the present study were high frequency nouns, whereas the stimuli in the BNT included both high frequency and low frequency nouns.

7.3. DIRECT COMPARISON BETWEEN PATIENTS AND NORMAL CONTROL PARTICIPANTS

Direct comparison between each patient and the control groups' mean activation was performed to determine whether patients would recruit more right hemisphere regions than the normal control participants or whether patients would recruit novel regions to compensate for their structural deficit. It was predicted that patients with anterior and posterior lesions would recruit more contralesional right hemisphere regions and patients with antero-posterior lesions would recruit more novel regions (regions traditionally not activated by language tasks) to successfully complete the tasks. The results of this analysis partially support the hypothesis.

Direct comparison for the lexical decision task (word vs. fixation) did not reach statistical significance. For the semantic judgment task, direct comparison analysis revealed that only patients with anterior lesions (P1 and P2) showed greater overall activity in the right inferior frontal gyrus compared to the normal controls (see Table 17). Increased activity observed in the right inferior frontal gyrus may indicate a compensatory function due to a lesion affecting part of the left inferior frontal gyrus, a

region that is crucial for making semantic selection/judgment. Increased activity in the contralesional (right) hemisphere has usually been linked to a less favorable outcome in most studies and seems to be related to large lesions (Heiss et al., 1997), error processing (Postman-Caucheteux et al., 2010) or recovery level (Cao et al., 1999; Heiss & Thiel, 2006; Dombovy, 2009; Winhuisen et al., 2007). The observed right frontal activation for P1 and P2 cannot be attributed to error related processing or recovery level as only correct responses were included in the analysis and both patients had achieved high levels of recovery (please see Table 5 for standardized language test scores).

In an attempt to reconcile this finding with those from previous studies, we closely examined the activation patterns in each study on a case-by-case basis to determine if the right inferior frontal gyrus activity was associated with good recovery. Indeed, two out of the nine patients in Winhuisen et al.'s (2007) study showed persistent RIFG activation after repetitive TMS, which also was associated with good recovery. Further, several treatment studies also implicate the role of right frontal regions in language recovery (Crosson et al., 2005, 2007b, 2009). Since the left frontal cortex is critical for normal performance of semantic judgment, the present finding implies that activity in right frontal cortex likely represents an efficient compensatory strategy when part of the left inferior frontal gyrus is damaged.

For the picture naming task, the direct comparison between each patient's activation to that of the mean control groups' activation (see Table 17) revealed several interesting findings. First, greater mean cortical activation was observed in the left

inferior frontal gyrus, pars triangularis for patients P1, P3, P4, P5, and P6 compared to the normal controls. The left pars triangularis was spared in all patients suggesting that the anterior part of Broca's area may be the strategic center for developing a new, functionally reorganized, linguistic network able to control most aspects of language. Additionally, there is growing recent evidence which supports the idea that Broca's area and, more generally, the LIFG, plays an important role in unification processes (Hagoort, 2005), able to organize not only linguistic functions but also hierarchically structured behaviors (Koechlin & Jubault, 2006).

Second, there was no significant difference in activity in the right frontal or the right temporal regions between each patient and the mean control groups' data with the exception of P2, P7, and P8 (see Table 17). This lack of difference in right hemisphere activation suggests that well recovered patients utilize neural regions similar to that utilized by normal control participants. In contrast, analysis of the three patients with large left hemisphere lesions (see Table 3) showed increased right frontal activity for P7 and right temporal activity for P2 and P8. This finding is in line with that of Blasi et al. (2002) and Cao et al. (1999) who found right hemisphere activation in chronic aphasic patients with large left hemisphere lesions many years after stroke onset suggesting that right hemisphere along with left hemisphere supports language recovery in chronic stage.

Third, increased activity in the anterior cingulate cortex was observed for two patients with large lesions (P7 and P8). The anterior cingulate cortex has been recruited by tasks that engage selective attention, response selection, monitoring of conflicting

responses, error detection, and initiation of action (Barch et al., 2000; Botvinick et al., 1999; Carter et al., 1998; Fu et al., 2002; Kiehl, Liddle, & Hopfinger, 2000; MacDonald et al., 2000). To name a picture, the intended word must be selected from a competing set of other words. This may induce a degree of response conflict and place a demand on response selection, leading to activation of the anterior cingulate cortex. Both P7 and P8 have relatively greater difficulty in retrieving words compared to the other patients as revealed by the standardized aphasia tests [(BNT scores for both patients were 13/60) (Please see Table 5 for test scores)]. This would increase the likelihood of response conflict and the demands on response selection prior to overt articulation. Thus, the recruitment of this area during successful picture naming is most probably secondary to increased attentional demands. Reaction time data provide further support for this argument as both patients had longer reaction times compared to the other patients (See Figure 13).

In summary, the results indicate that most patients recruited undamaged regions within the left hemisphere and contralesional regions within the right hemisphere to compensate for their structural deficits. Two patients with anterior lesions (P1 and P2) recruited the contralesional region (right inferior frontal gyrus) during the semantic judgment task. Two patients with large lesions (P7 and P8) recruited regions (cingulate gyrus) that are not traditionally recruited during the picture naming task.

7.4. ROLE OF RIGHT HEMISPHERE IN FUNCTIONAL REORGANIZATION

In recent neuroimaging studies, some claims have been made regarding the relative importance of perilesional, ipsilesional and contralesional involvement in recovery of various aspects of language function. The findings of the present study indicate a role for both homologous contralesional cortex and perilesional and ipsilesional regions as efficient mechanisms for supporting language functions in well recovered chronic stroke patients. Further, the results acknowledge that factors such as individual differences in site and size of lesion, and severity of aphasia, as well as task difficulty are all likely to influence individual responses.

Recent studies of motor and speech recovery have suggested that some of the activations (particularly in the hemisphere contralateral to the lesion) observed in poststroke recovery may not reflect activity that is important to the task, but rather 'maladaptive/suboptimal' activation that is unrelated to functional performance (Naeser et al. 2005). In fact, inhibition of right hemisphere areas with repetitive TMS can result in task improvement (Winhuisen, 2007). However, the results of this study appear to support that view that right hemisphere does play an important role in reorganization. Clearly, right hemisphere activations seen in our study were not suboptimal; rather, in these cases at least, the pattern of brain activation was task and lesion site dependent. Results from motor recovery also support the role of contralesional hemisphere for neural recovery. Nair et al. (2007) studied motor representation in well-recovered stroke patients using two tasks: unimanual index finger (abduction–adduction) and wrist movements

(flexion–extension) using their recovered and non-affected hand. Their results suggested that good recovery utilizes both ipsilesional and contralesional resources, although results differed for wrist and index finger movements. Wrist movements of the recovered arm resulted in significantly greater activation of the contralateral (lesional) and ipsilateral (contralesional) primary sensorimotor cortex (SM1), while recovered index finger movements recruited a larger motor network, including the contralateral SM1, Supplementary Motor Area (SMA) and cerebellum. This further supports our finding that task differences can lead to differences in recruitment of right and left hemisphere regions.

The use of three different tasks with different cognitive demands helped clarify the role of right hemisphere regions in aphasia recovery. Had our investigation utilized only one task (e.g., semantic judgment task); we may have concluded that the non lesioned tissue within the left hemisphere contributed to neural recovery in chronic stroke patients. However, to investigate function in other areas we included the lexical decision task and the picture naming task. For example, the picture naming task was designed to place greater processing demand bilaterally and by doing so was able to elicit activation in the right superior/middle temporal gyrus and/or right inferior frontal gyrus for both patients and control participants. Further, by utilizing the picture naming task we were not only able to clarify the role of task difficulty, but also the role of lesion size. The role of lesion size became apparent only during a cognitively demanding task. This suggests that it is important to consider the difficulty of the task while examining the contribution

of right hemisphere in aphasia recovery.

7.5. STUDY LIMITATIONS

As stated earlier, the literature is mixed with regards to the relationship between left and right-hemisphere activity and language performance in aphasia. The present study examined functional imaging and behavioral responses during three tasks in eight high functioning stroke patients and eight age and gender matched controls. The results of this study are preliminary and a larger sample with more circumscribed lesion distributions could shed much needed light into the relationship between lesion site/size and task difficulty. Second, the present study only examined the neural substrates involved in single word processing and retrieval. Research studies indicate differences in neural activation for single word processing and sentence level processing (e.g., Hickok & Poeppel, 2007). Therefore, different activation patterns might have emerged had we utilized sentence-level stimuli instead of word level stimuli. A third limitation of this study was that it did not examine the connectivity between areas of the language network, especially since damage from stroke is so variable and may include white matter lesions in certain subjects and not others, thus causing different behavioral deficits (Wise, 2003).

7.6. FUTURE DIRECTIONS

The study of language recovery in aphasia is complex and remains poorly understood. To further investigate the relationship between right-hemisphere activation and lesion site/size, studies including patients with similar behavioral deficits and

circumscribed lesion characteristics should be undertaken. Research studies should also include sentence level stimuli to investigate neural recovery from stroke as everyday communication is not limited to single word utterances. Furthermore, future studies should also examine the integrity of white matter pathways connecting areas of the language network to one another to further understand the reorganization of language functions after stroke. Techniques such as diffusion tensor imaging (DTI) can be implemented in conjunction with fMRI to examine the connectivity between functional areas of the language network. This will provide important information regarding recovery in aphasia and potentially aid in the development and implementation of rehabilitation techniques aiming to enhance recovery in patients with specific deficits and lesion characteristics.

Appendix 1: Medical History Information

Aphasia Research Laboratory
Department of Communication Sciences & Disorders
University of Texas at Austin, TX 78712
Phone: 471-2035; Fax: 471-2957

Personal History

Name: _____ Date: _____

Age_____ Sex: _____ Handedness: L. R. Birth date: _____

Address: _____

Phone number: Home _____Other: _____

Spouse/Significant other: _____

Native language: _____

Other languages spoken: _____

Highest Degree Attained:_____Occupation_____

Contact information:

Person to contact in case of emergency: _____

Phone number: _____

Medical History

Date of Stroke: _____

Hospitalization period: _____

Person/Agency who has your complete medical record:

_____

Any previous speech therapy received: Yes /No

Duration and nature of therapy:

_____

Do you have a history of any of the following?

Heart Problems	Yes	No	Parkinson's Disease	Yes	No
Arthritis	Yes	No	Pick's Disease	Yes	No
Alzheimer 's disease	Yes	No	Depression	Yes	No
Memory Problems	Yes	No	Tumor	Yes	No
Learning Disability	Yes	No	Seizures	Yes	No

Do you wear glasses? Y N. If yes corrected to normal? Y N

Do you have a hearing impairment? Y N.
If yes, are you using a hearing aid. Y N

Speech and Language Characteristics:
Briefly describe if any difficulties noted in the following areas:
Verbal expression:
_____
Auditory Comprehension:
_____
Gestural expression:
_____
Reading abilities
_____
Writing abilities:
_____

Appendix 2: Neurological History survey

Aphasia Research Laboratory
Department of Communication Sciences & Disorders
University of Texas at Austin, TX 78712
Phone: 471-2035; Fax: 471-2957

Last name: _____First Name: _____

Date of birth: _____Height: _____ Weight: _____

I. Have you or your family ever had?

	You			**Your family**		
	Yes	No	Don't Know	Yes	No	Don't Know
Stroke	Yes	No	Don't Know	Yes	No	Don't Know
Transient Ischemic Attack	Yes	No	Don't Know	Yes	No	Don't Know
Alzheimer's Disease	Yes	No	Don't Know	Yes	No	Don't Know
Parkinson's Disease	Yes	No	Don't Know	Yes	No	Don't Know
Huntington's Disease?	Yes	No	Don't Know	Yes	No	Don't Know
Epilepsy	Yes	No	Don't Know	Yes	No	Don't Know
Cerebral Palsy	Yes	No	Don't Know	Yes	No	Don't Know

If you answered YES to any of the questions, please enter the details here

II. Have you ever

	Check one		
	Yes	No	Don't Know
Been seen a neurologist or neurosurgeon?	Yes	No	Don't Know
Had a head injury involving unconsciousness?	Yes	No	Don't Know
Required overnight hospitalization for a head injury?	Yes	No	Don't Know
Had encephalitis or meningitis?	Yes	No	Don't Know
Had cancer other than skin caner diagnosed in the past three years?	Yes	No	Don't Know

Been resuscitated?	Yes	No	Don't Know
Had problem due to abuse of drugs or medication recently?	Yes	No	Don't Know
Been treated for drug abuse?	Yes	No	Don't Know
Had heart surgery?	Yes	No	Don't Know
Had heart attack?	Yes	No	Don't Know
Taken medications for mental or emotional problems in the past five years?	Yes	No	Don't Know
Received electroshock therapy?	Yes	No	Don't Know
Had seizures?	Yes	No	Don't Know
Had brain surgery?	Yes	No	Don't Know
Had undergone surgery to clear arteries to your brain?	Yes	No	Don't Know
Had any illness that caused permanent decrease in memory and cognition?	Yes	No	Don't Know
Been diagnosed as learning disabled?	Yes	No	Don't Know
Been placed in special classes at school because of learning problems?	Yes	No	Don't Know
Diagnosed as having brain tumor?	Yes	No	Don't Know
Had major surgery with general anesthesia?	Yes	No	Don't Know
If so, did you have any change in your memory, ability to talk or solve problems one week after the surgery?	Yes	No	Don't Know

If you have answered yes to any of the above, please provide details here

III. Please answer the following

Do you use home oxygen?	Yes	No	Don't Know
Do you have difficulty understanding conversations even with a hearing aid?	Yes	No	Don't Know
Do you have trouble reading or with your vision even if you are wearing glasses?	Yes	No	Don't Know
Are you able to read ordinary print with your left eye alone?	Yes	No	Don't Know
Are you able to read ordinary print with your right eye alone?	Yes	No	Don't Know
Do you experience any double vision?	Yes	No	Don't Know
Do you have any history of glaucoma?	Yes	No	Don't Know
Do you have a history of macular	Yes	No	Don't Know

degeneration?			
Are you color blind?	Yes	No	Don't Know
Do you have diabetes which requires insulin to control?	Yes	No	Don't Know
Do you have hypertension which is not well controlled?	Yes	No	Don't Know
Are you taking medications for mental or emotional problems?	Yes	No	Don't Know
Do you have any difficulty using your hands?	Yes	No	Don't Know
Do you hands shake when you hold them still?	Yes	No	Don't Know
Are you receiving kidney dialysis?	Yes	No	Don't Know
Do you have liver disease?	Yes	No	Don't Know
Do you have lupus?	Yes	No	Don't Know
Are you able to write your name?	Yes	No	Don't Know
How often do you drink wine, beer or alcoholic beverages?	Often	Occasionally	Rarely

Can you think of any other information which might be relevant?

Appendix 3: Subject safety screen

Aphasia Research Laboratory
Department of Communication Sciences & Disorders
University of Texas at Austin, TX 78712
Phone: 471-2035; Fax: 471-2957

Last name: _____First Name: _____

Date of birth: _____Height:_____Weight: _____

I. The following may be hazardous to your health or may interfere with the MRI study by producing artifacts:

1. Are you metal worker or have you worked with metal lathes?	Yes	No
If so, have you always worn metal protection?	Yes	No
Do you have:	Yes	No
1. Metal fragments in your eyes?	Yes	No
2. Cardiac pacemaker?	Yes	No
3. Aneurysm clip?	Yes	No
4. Any type of internal electrode: pacing wires, cochlear implants?	Yes	No
5. Swan-Gauz catheter?	Yes	No
6. Halo vest or metallic cervical fixation device?	Yes	No
7. Hearing aid?	Yes	No
8. Any type of intravascular coil, filter or stent?	Yes	No
9. Implanted drug injection device?	Yes	No
10. Any type of foreign body, shrapnel or bullet?	Yes	No
11. Heart valve prosthesis?	Yes	No
12. Penile prosthesis?	Yes	No
13. Any type of ear implant?	Yes	No
14. Any type of surgical clip or staple?	Yes	No
15. Vascular access port?	Yes	No
16. Intraventricular shunt?	Yes	No
17. Artificial limb or joint?	Yes	No
18. Dentures?	Yes	No
19. Diaphragm (in place)?	Yes	No
20. IUD?	Yes	No
21. Tattooed eyeliner?	Yes	No

22. Any type of electronic, mechanical or magnetic implant?	Yes	No
23. Any type of implant held in place by magnet?	Yes	No
24. Any implanted orthopedic items (pins, rods, screws, nails, clips, plates, wire etc)?	Yes	No
25. Neurostimulator?	Yes	No
26. Implanted cardiac defibrillator?	Yes	No
27. Any other implanted item: Please describe	Yes	No

II. Female subjects, please complete the following:

1. Are you pregnant or do you suspect that you are pregnant?	Yes	No
2. Are you breast feeding?	Yes	No
2. Are you taking oral contraceptives or receiving hormonal treatment?	Yes	No

III. Have you ever had a surgical procedure of any kind?

Yes	No

If yes, please list all prior surgeries and approximate dates

IV. Have you even been injured by any metallic body (e.g., bullet, BB, shrapnel??

Yes	No

If yes, please describe

V. Have you even had any injury to the eyes involving a metal object (e.g., metallic slivers, shavings, foreign body etc...).

Yes	No

If yes, please describe

Appendix 4: Mean reaction time (RT), Mean accuracy rate (ACC), and Standard Deviation for each normal control participant.

Participant	**Lexical Decision**				**Semantic Judgment**				**Picture Naming**	
	Word		**Non-Word**		**Semantic**		**Size**		**Picture**	
	RT	ACC	RT	ACC	RT	ACC	RT	ACC	RT	ACC
NC1	902.16 (*270.57*)	100	1030.11 (*207.67*)	96.4 *(18.5)*	1934.44 *(473.96)*	90.7 *(29)*	1673. 73 *(359.7)*	93.7 *(24.4*)	2207.53 *(408.57)*	98.33 *(13)*
NC2	800 (*141.01*)	100	900.45 (*151.34*)	100	2394.42 *(591.53)*	92.3 *(0.27)*	1614.10 *(448.4)*	100	2245.25 *(725.27)*	100
NC3	911.56 (*223.36*)	100	1030.43 *(142.78)*	98.3 *(13)*	1994.31 (*644.35*)	93.33 (*25*)	1388.69 *(488.3)*	95.5 *(20)*	2338.33 *(564.86)*	100
NC4	1143.01 (*217.02*)	100	1254.32 (*283.25*)	96.6 (*18.1*)	2026.6 *(424.96)*	91.49 *(28*)	1188.2 *(439.5)*	91.4 *(28)*	2311.84 *(518.38)*	98.33 *(13)*
NC5	1075.8 (*239.84*)	100	1063.47 (*217.37*)	98.3 *(13)*	2368.98 *(655.16)*	93.18 *(25)*	1715.9 *(375.01)*	93.6 *(24.7*)	2769 *(1308.8)*	100
NC6	762.68 (*222.99*)	98.3 (*13*)	773.54 (*205.85*)	93.3 *(25.1*)	1478.51 *(421.87)*	91.49 *(0.28)*	1095.9 *(291.6)*	91.4 *(28.2)*	2357.73 *(490.9)*	100
NC7	1046.33 (*286.16*)	98.2 (*13*)	975.31 (*211.16*)	96.6 *(18.1*)	2555.46 (*536.4*)	90.7 (*29*)	2299.13 (*719.33*)	93.7 *(24.7*)	2645.17 (*579.66)*	100
NC8	883.79 *(164.26)*	100	881.55 *(115.30)*	98.3 *(12.9)*	1745.92 *(587.19)*	90.91 *(29)*	1271.11 *(528.5)*	93.7 *(24.7)*	2544.15 *(676.09)*	100

Appendix 5: Mean reaction time (RT), Mean accuracy rate (ACC), and Standard Deviation for each participant with aphasia.

Participant	**Lexical Decision**				**Semantic Judgment**				**Picture Naming**	
	Word		**Non-Word**		**Semantic**		**Size**		**Picture**	
	RT	ACC	RT	ACC	RT	ACC	RT	ACC	RT	ACC
P1	778.3 (*209.2*)	100	933.4 (*220.1*)	96.6 (*18*)	2981.41 (*658.69*)	91.1 (*28.7*)	1643.1 (*525.1*)	91.6 (*27.9*)	2758.95 (*792.35*)	91.67 (*28*)
P2	949.3 (*181.7*)	100	881.3 (*128.9*)	96.6 (*18*)	3117.6 (*657.2*)	79.4 (*40*)	1958.8 (*647.9*)	89.3 (*31*)	2692.3 (*605.1*)	90 (*30*)
P3	960.6 (*1070*	100	1006.6 (*173.7*)	98.3 (*13*)	2516.3 (*723.6*)	91.49 (*28*)	1509 (*456.8*)	93.6 (*24.2*)	2681.86 (*607.24*)	98.33 (*13*)
P4	1078.2 (*247*)	100	1002.4 (*224.6*)	100	2527.8 (*600*)	82.22 (*39*)	1317 *(332.5*)	91.6 (*27*)	2887.88 (*835.08*)	86.67 (*34*)
P5	1090.5 (*303.5*)	96.4 (*18.5*)	1004.8 (*323.6*)	96.6 (*18*)	2658.58 (*793.1*)	81.58 (*39*)	1677.4 (*603.7*)	88.8 (*31.7*)	1972.49 (*620.29*)	91.67 (*28*)
P6	782.9 (*237*)	100	769.9 *(247.7)*	98.3 (*13*)	2090.59 (*724.4*)	91.3 (28.4)	1566.4 (*590.6*)	95.8 (*20.1*)	2498.69 (*755.81*)	98.33 (*13*)
P7	1023.5 (*186.2*)	96.7 (*17*)	1068.4 (*320.9*)	92.8 (*25*)	3005.61 (*767.8*)	80 (*40*)	1242.3 (*260.3*)	91.4 (*28*)	3740.18 (*819.75*)	81.67 (*39)*
P8	942.1 (*282.9*)	98.2 (*13.1*)	1057.8 (245.7)	96.6 (*18*)	2705.74 (*507.7*)	80 (*40*)	1251 (*355.9*)	91.8 (*27.6*)	3401.19 (*648.12*)	75.67 (*39*)

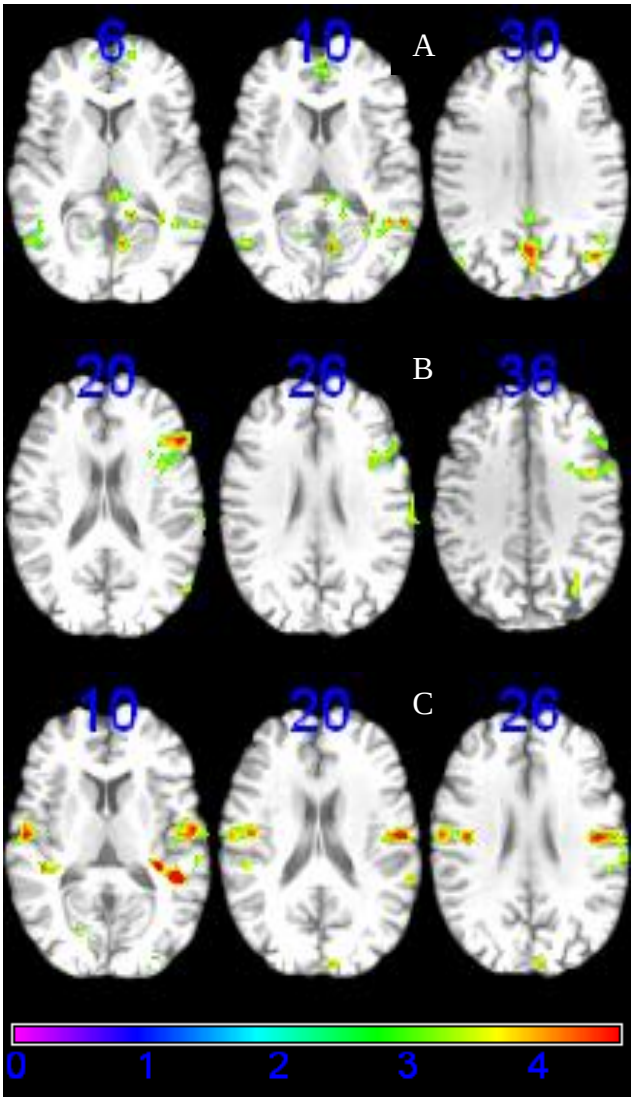
Appendix 6: Individual activation data for NC1

NC1's data show clear differences in activation patterns across the three tasks. In general, more regions were recruited during picture naming than during lexical decision or semantic judgment. As expected, for word decision vs. non-word decision activation was observed in left supramarginal gyrus, left frontal pole, and bilateral angular gyrus. For semantic judgment vs. size judgment, activation was observed in the left inferior frontal gyrus. For oral picture naming vs. scrambled picture viewing, activation was observed in the bilateral superior and inferior temporal gyrus, left inferior frontal gyrus, left postcentral gyrus, and bilateral occipital gyrus.

As expected, the reverse contrasts (control vs. experimental condition) mostly activated the occipital regions. Non-word decision vs. word decision activated the right precuneus and bilateral lateral occipital cortex. Size decision vs. semantic decision activated the right middle occipital cortex, right precuneus, and bilateral inferior parietal lobe. For scrambled picture viewing vs. picture naming, activation was observed in the left limbic lobe, left fusiform gyrus, and right angular gyrus.

Summary Table of Activation Coordinates for NC1

Region	Lexical Decision				Semantic Judgment				Picture Naming			
	Z	x	y	z	Z	x	y	z	Z	x	y	z
Left Frontal												
Inferior frontal gyrus, BA 44/45					4.7	-44	20	16	3.5	-44	20	20
Frontal pole	3.5	-14	60	-2								
Left Temporal												
Superior temporal gyrus, BA 22									4.7	-62	-18	-26
Inferior temporal gyrus, BA 20									3.6	-68	-8	6
Left Parietal												
Postcentral gyrus, BA 3									3.5	-66	-6	20
Supramarginal gyrus, BA 40	3.5	-56	-50	12								
Angular gyrus, BA 39	3.8	-38	-66	34								
Left occipital												
Occipital pole									3.7	-8	-92	24
Superior occipital cortex, BA 19	3.5	-42	-74	28	3.5	-44	-74	30				
Right Temporal												
Superior temporal gyrus, BA 22									4.8	66	-10	2
Inferior temporal gyrus, BA 20									4.6	54	-10	-28
Right Parietal												
Angular gyrus, BA 39	3.5	-52	-58	22								
Right Occipital												
Middle occipital gyrus, BA 18									4.01	-20	-94	12



Activation maps for NC1 for (a) lexical decision task, (b) semantic judgment task, and (c) picture naming task. Statistical maps are thresholded by using clusters determined by Z > 3.5 and a (corrected) cluster significance threshold of P = 0.05. Images are in radiological orientation with the right side of the brain to the left and the left side to the right.

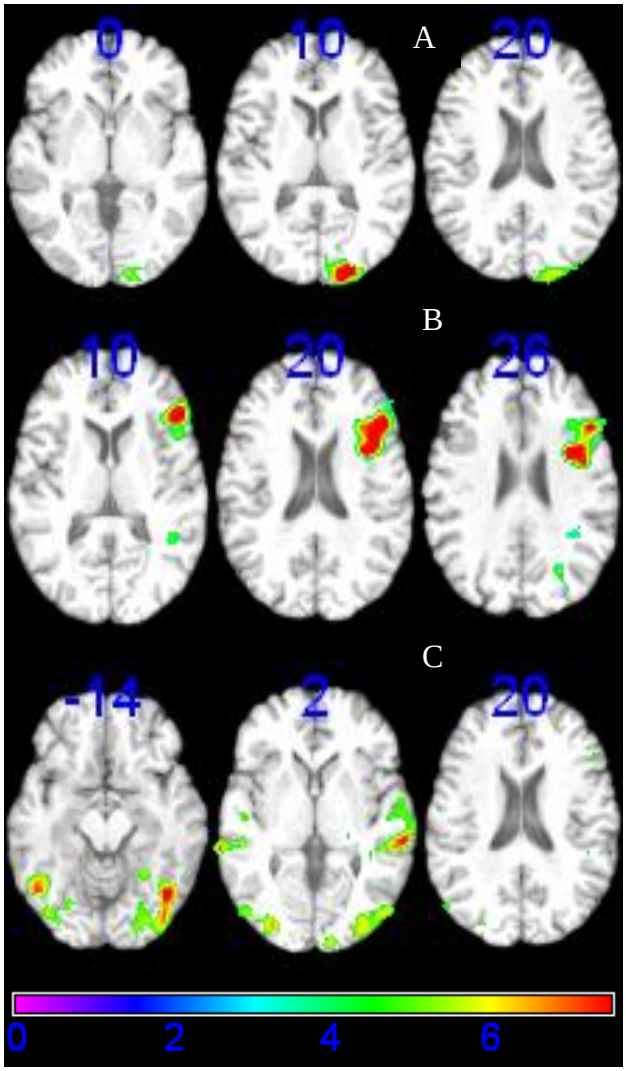
Appendix 7: Individual activation data for NC2

Activation was not observed in the left posterior regions for word decision vs. non-word decision. Instead, activation was observed in the left middle and inferior occipital gyrus. As predicted, activation was observed in the left inferior frontal gyrus and left middle temporal gyrus for the semantic judgment task vs. the size judgment task. For oral picture naming vs. scrambled picture viewing, activation was observed in the left superior and middle temporal gyrus, left lingual gyrus, right superior and middle temporal gyrus. However, activation was not observed in the left inferior frontal gyrus for the picture naming task

Activation did not reach significance for the contrasts non-word vs. word and size judgment vs. semantic judgment. Scrambled picture viewing compared to oral picture naming activated the left cingulate gyrus.

Summary Table of Activation Coordinates for NC2

Region	Lexical Decision				Semantic Judgment				Picture Naming			
	Z	**x**	**y**	**z**	**Z**	**x**	**y**	**z**	**Z**	**x**	**y**	**z**
Left Frontal												
Inferior frontal gyrus, BA 44/45					7.0	-40	10	22				
Left Temporal												
Superior temporal gyrus, BA 22									7.0	-50	-40	8
Middle temporal gyrus, BA 21					4.2	-52	-48	-4	7.2	-48	-46	-4
Left Occipital												
Middle occipital gyrus, BA 18	7.5	-18	-92	18					6.7	-26	-60	-4
Inferior occipital gyrus, BA 17	3.5	-16	-98	2								
Right Temporal												
Superior temporal gyrus, BA 22									4.3	56	0	-6
Middle temporal gyrus, BA 20									6.9	60	-40	-6



Activation maps for NC2 for (a) lexical decision task, (b) semantic judgment task, and (c) picture naming task. Statistical maps are thresholded by using clusters determined by Z > 3.5 and a (corrected) cluster significance threshold of P = 0.05. Images are in radiological orientation with the right side of the brain to the left and the left side to the right.

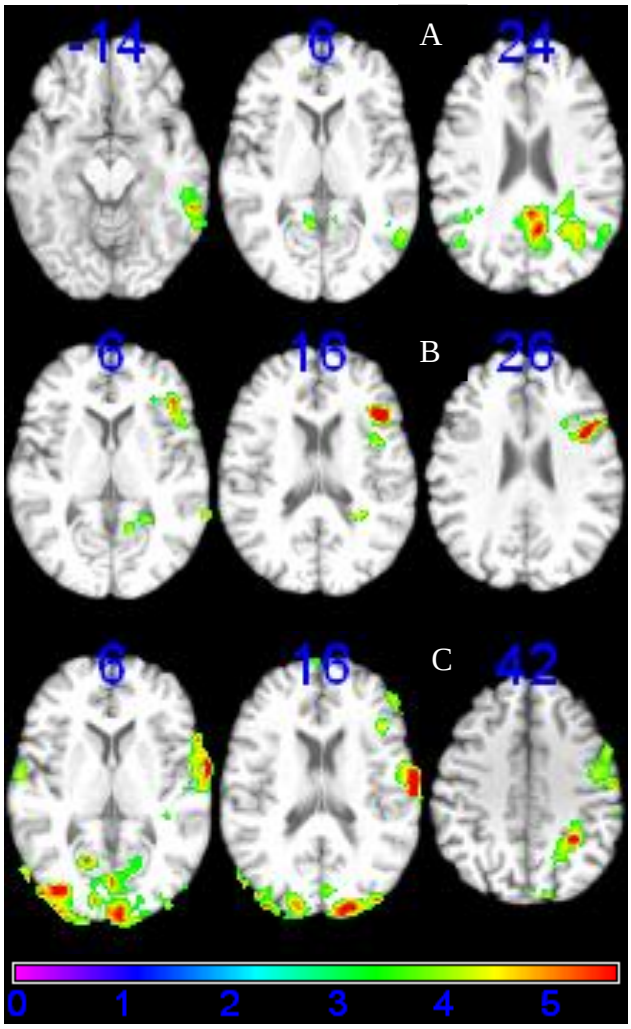
Appendix 8: Individual activation data for NC3

For NC3, activation was observed in the left supramarginal gyrus, left middle temporal gyrus, left middle frontal gyrus, and bilateral angular gyrus for word decision vs. non-word decision. For semantic judgment vs. size judgment, activation was observed in the left inferior frontal gyrus and left middle frontal gyrus. For oral picture naming vs. scrambled picture viewing, activation was observed in the bilateral inferior frontal gyrus, right middle frontal gyrus, right superior temporal gyrus, right lateral occipital cortex, and left inferior occipital cortex. More right hemisphere structures were recruited during the picture naming task compared to that recruited during the lexical decision task or the semantic judgment task.

As expected, the control conditions mostly activated the occipital regions. Activation did not reach significance for word decision vs. non-word decision. For size judgment vs. semantic judgment, activation was observed in the right middle temporal gyrus and bilateral lateral occipital cortex. Scrambled picture viewing compared to picture naming activated bilateral middle occipital gyrus and left precuneus.

Summary Table of Activation Coordinates for NC3

Region	Lexical Decision				Semantic Judgment				Picture Naming			
	Z	**x**	**y**	**z**	**Z**	**x**	**y**	**z**	**Z**	**x**	**y**	**z**
Left Frontal												
Inferior frontal gyrus, BA 44/45					6.0	-48	28	10	4.1	-44	28	14
Middle frontal gyrus, BA 46	3.5	-36	14	38	6.3	-40	6	38				
Left Temporal												
Superior temporal gyrus, BA 22									6.7	-51	-42	8
Middle temporal gyrus, BA 20	3.5	-60	-34	-16					6.2	-54	-40	-4
Left Parietal												
Supramarginal gyrus, BA 40	3.9	-52	-44	40								
Angular gyrus, BA 39	4.0	-40	-56	18								
Left Occipital												
Inferior occipital gyrus, BA 17									5.1	46	-80	-2
Right Temporal												
Superior temporal gyrus, BA 22									3.5	58	-18	-2
Right Parietal												
Angular gyrus, BA 39	3.5	-38	54	20								
Right Occipital												
Inferior occipital gyrus, BA 18									5.1	46	-80	-2



Activation maps for NC3 for (a) lexical decision task, (b) semantic judgment task, and (c) picture naming task. Statistical maps are thresholded by using clusters determined by Z > 3.5 and a (corrected) cluster significance threshold of P = 0.05. Images are in radiological orientation with the right side of the brain to the left and the left side to the right.

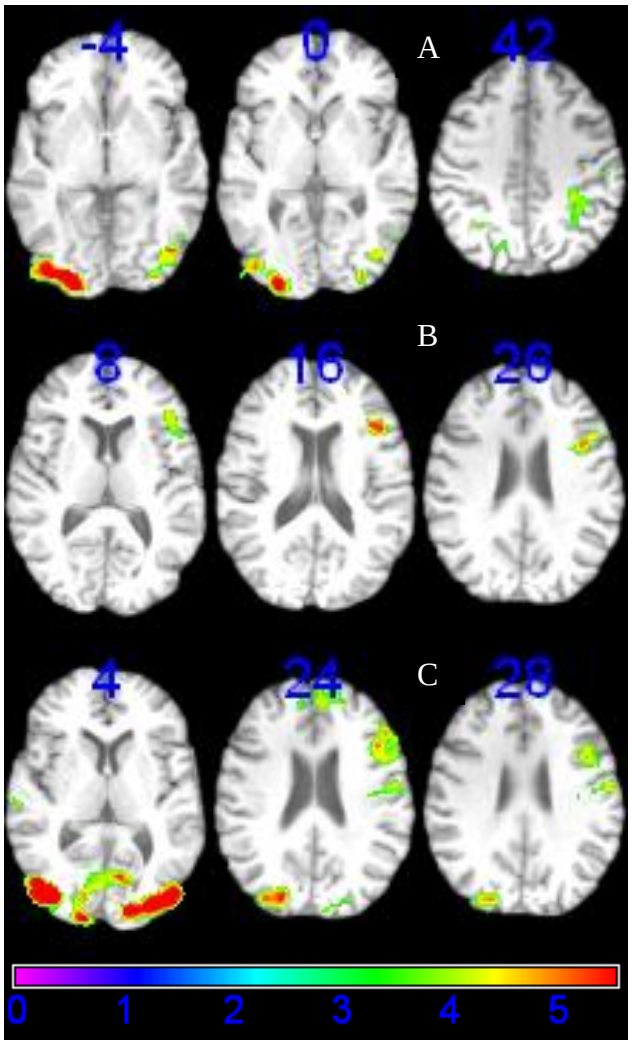
Appendix 9: Individual activation data for NC4

Similar to the other normal control participants, NC4 showed significant bilateral activation for the picture naming task. Activation was mostly left lateralized for the lexical decision task and the semantic judgment task. For word decision vs. non-word decision, activation was observed in the left fusiform gyrus, left inferior occipital gyrus, right middle occipital gyrus, and the left supramarginal gyrus. Activation was also observed in the right supramarginal gyrus. For semantic judgment vs. size judgment, activation was observed in the left inferior frontal gyrus and left precentral gyrus. For oral picture naming vs. scrambled picture viewing, activation was observed in the inferior and superior frontal gyrus, bilateral superior temporal gyrus, right middle temporal gyrus, and right lateral occipital gyrus. Activation was also observed in the right cingulate gyrus for the picture naming task.

Similar to the other control participants, NC4 showed significant activation in the visual cortex for the control conditions. For non-word decision vs. word decision, activation was observed in the left inferior occipital gyrus. Size judgment vs. semantic judgment activated the right Heschl's gyrus and bilateral middle occipital gyrus. Activation for scrambled picture viewing compared to oral picture naming did not reach statistical significance.

Summary Table of Activation Coordinates for NC4

Region	Lexical decision				Semantic Judgment				Picture Naming			
	Z	**x**	**y**	**z**	**Z**	**x**	**y**	**z**	**Z**	**x**	**y**	**z**
Left Frontal												
Inferior frontal gyrus, BA 44/45					6.1	-40	24	16	4.2	-42	40	8
Precentral gyrus, BA 3					5.4	-42	0	36				
Superior Frontal gyrus, BA 8									4.5	-2	18	56
Left Temporal												
Superior temporal gyrus, BA 22									3.5	-68	-26	8
Left Parietal												
Supramarginal gyrus, BA 40	3.6	-40	-44	38								
Fusiform gyrus, BA 37	6.1	-44	-60	-14								
Left Occipital												
Inferior occipital gyrus, BA 17	6.8	-38	-90	-10					4.5	40	-82	4
Right Temporal												
Superior temporal gyrus, BA 22									4.5	66	-18	4
Middle temporal gyrus, BA 21									4.1	50	-38	4
Right Parietal												
Supramarginal gyrus	4.0	36	-40	38								
Right Occipital												
Inferior occipital gyrus, BA 18	6.2	44	-78	-10								
Cingulate												
Right cingulate gyrus, BA 24									3.5	16	48	0



Activation maps for NC4 for (a) lexical decision task, (b) semantic judgment task, and (c) picture naming task. Statistical maps are thresholded by using clusters determined by Z > 3.5 and a (corrected) cluster significance threshold of P = 0.05. Images are in radiological orientation with the right side of the brain to the left and the left side to the right.

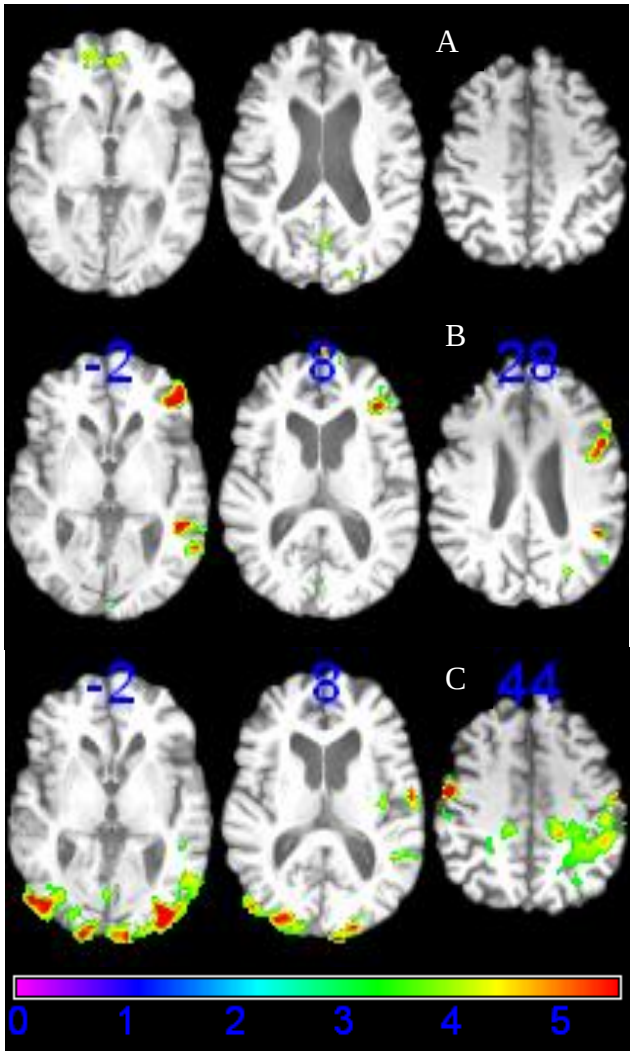
Appendix 10: Individual activation data for NC5

Activation did not reach significance for word decision vs. non-word decision. However, activation was significant for word decision vs. fixation. Activation was observed in the left middle occipital gyrus, left cingulate gyrus, and right medial frontal cortex. For semantic judgment vs. size judgment, activation was observed in the left inferior frontal gyrus and left precentral gyrus. For oral picture naming vs. scrambled picture viewing, activation was observed in the bilateral superior and middle occipital gyrus. Similar to NC2, NC5 did not show activation in the left inferior frontal gyrus for the picture naming task.

Activation did not reach significance for the control condition in the lexical decision task (non-word vs. word). Activation did not also reach significance for the contrast fixation vs. word. For size judgment vs. semantic judgment, activation was observed in right occipital fusiform gyrus and right inferior parietal lobe. For scrambled picture viewing vs. oral picture naming, activation was observed in the right angular gyrus and left lateral occipital gyrus.

Summary Table of Activation Coordinates for NC5

Region	Lexical decision				Semantic Judgment				Picture Naming			
	Z	**x**	**y**	**z**	**Z**	**x**	**y**	**z**	**Z**	**x**	**y**	**z**
Left Frontal												
Inferior frontal gyrus, BA 44/45					8.8	-48	26	14				
Precentral gyrus, BA 3					4.06	-48	2	14				
Left Temporal												
Superior temporal gyrus, BA 22									6.6	-54	-30	8
Left Occipital												
Middle occipital gyrus, BA 18	3.5	-18	-90	18					6.2	-30	-82	8
Left Cingulate												
Anterior cingulate, BA 24	3.5	-4	50	-4								
Right Frontal												
Medial frontal cortex, BA 10	3.5	14	54	-4								
Right Temporal												
Superior temporal gyrus, BA 22									6.1	58	-28	8
Right Occipital												
Middle occipital gyrus, BA 18									3.9	36	-74	8



Activation maps for NC5 for (a) lexical decision task, (b) semantic judgment task, and (c) picture naming task. Statistical maps are thresholded by using clusters determined by Z > 3.5 and a (corrected) cluster significance threshold of P = 0.05. Images are in radiological orientation with the right side of the brain to the left and the left side to the right.

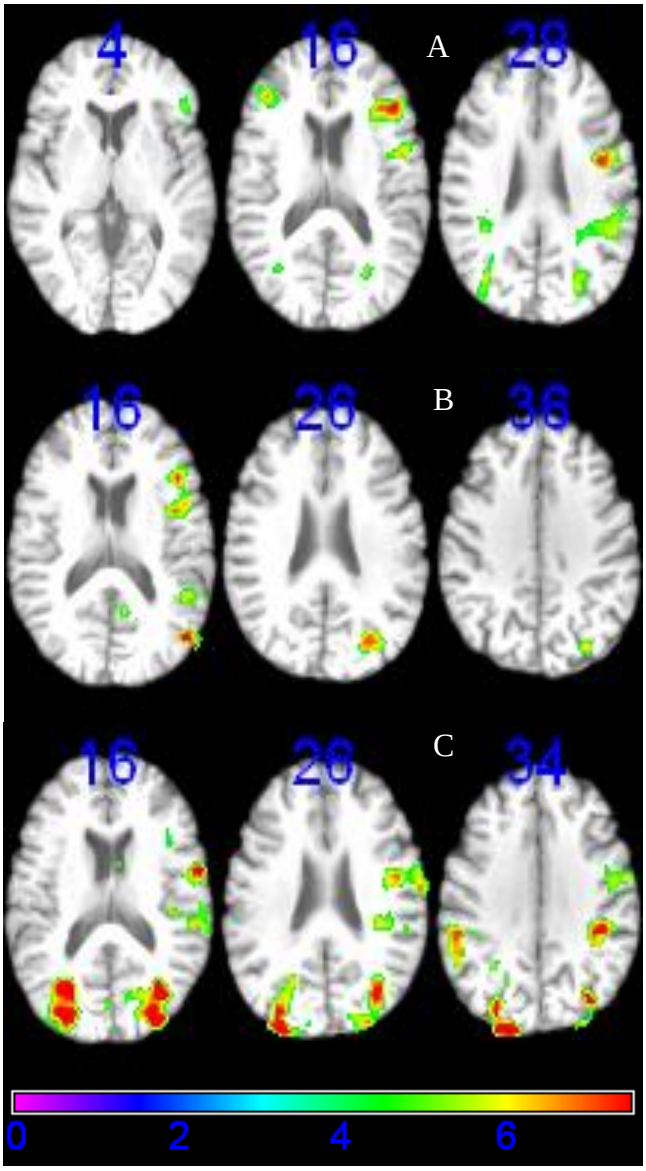
Appendix 11: Individual activation data for NC6

For NC6, activation was not observed in the left posterior regions for word decision vs. non-word decision. Instead, activation was observed in the right supramarginal gyrus. Activation was also observed in the left inferior frontal gyrus and left precentral gyrus. For the semantic judgment task vs. the size judgment task, activation was observed in the left inferior frontal gyrus, left superior temporal gyrus, and middle occipital gyrus. For oral picture naming vs. scrambled picture viewing, activation was observed in left inferior frontal gyrus, left middle temporal gyrus, right superior temporal gyrus, and bilateral middle occipital gyrus. More right hemisphere structures were recruited during the picture naming task compared to the lexical decision task or the semantic judgment task

For the control conditions, activation did not reach significance for the contrasts non-word vs. word and scrambled picture vs. picture. For size judgment vs. semantic judgment, activation was observed in the right middle occipital gyrus and bilateral lateral occipital gyrus.

Summary Table of Activation Coordinates for NC6

Region	Lexical Decision				Semantic Judgment				Picture Naming			
	Z	**x**	**y**	**z**	**Z**	**x**	**y**	**z**	**Z**	**x**	**y**	**z**
Left Frontal												
Inferior frontal gyrus, BA 44/45	6.7	-44	28	18	7.1	-46	30	8	4.5	-44	8	26
Precentral gyrus, BA 4	4.8	-50	2	18								
Left Temporal												
Superior temporal gyrus, BA 22					6.8	-54	-50	14				
Middle temporal gyrus, BA 20									7.55	-60	-32	-8
Left Occipital												
Middle occipital gyrus, BA 18					6.0	-48	-79	12	8.7	-50	-72	-8
Right Temporal												
Superior temporal gyrus, BA 22									7.8	56	-16	-8
Right Parietal												
Supramarginal gyrus, BA 40	3.6	42	-40	34								
Right Occipital												
Middle occipital gyrus, BA 18	3.7	43	-75	-10					7.6	40	-76	-8



Activation maps for NC6 for (a) lexical decision task, (b) semantic judgment task, and (c) picture naming task. Statistical maps are thresholded by using clusters determined by Z > 3.5 and a (corrected) cluster significance threshold of P = 0.05. Images are in radiological orientation with the right side of the brain to the left and the left side to the right.

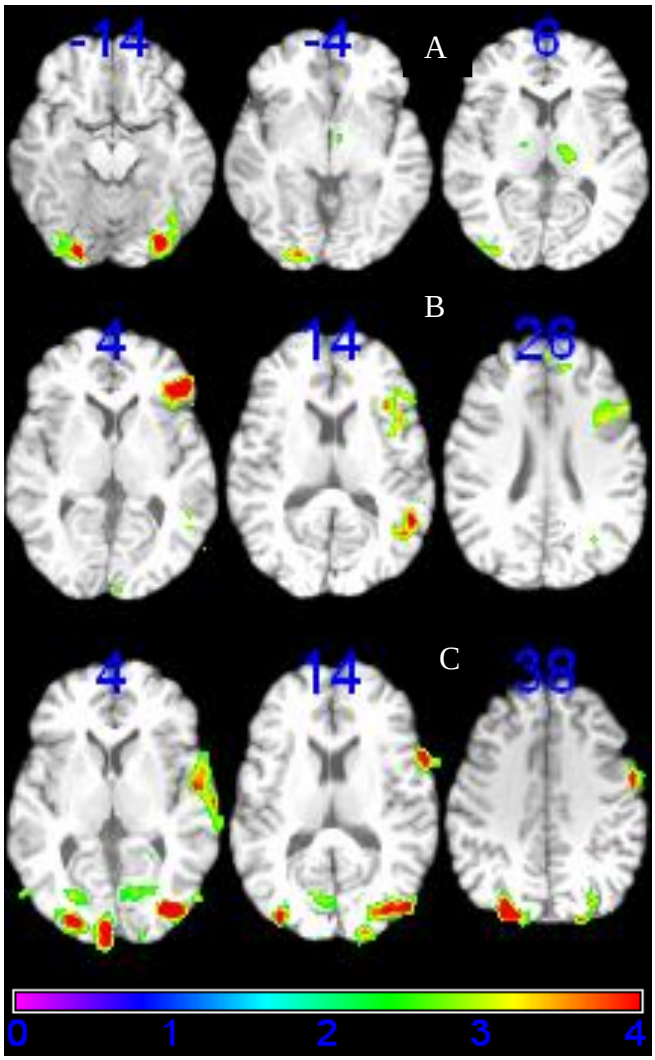
Appendix 12: Individual activation data for NC7

Similar to NC5, NC7's activation did not reach significance for word decision vs. non-word decision. For word decision vs. fixation, activation was observed in the left fusiform gyrus and right middle occipital gyrus. For semantic judgment vs. size judgment, activation was observed in the left inferior frontal gyrus, left superior temporal gyrus, and left angular gyrus. For oral picture naming vs. scrambled picture viewing, activation was observed in the left medial frontal gyrus, left superior frontal gyrus, bilateral precentral gyrus, and right superior temporal gyrus.

Results for the contrasts non-word vs. word and size judgment vs. semantic judgment did not reach statistical significance. Scrambled picture viewing compared to oral picture naming activated the left middle occipital gyrus and left angular gyrus.

Summary Table of Activation Coordinates for NC7

Region	Lexical Decision				Semantic Judgment				Picture Naming			
	Z	**x**	**y**	**z**	**Z**	**x**	**y**	**z**	**Z**	**x**	**y**	**z**
Left Frontal												
Inferior frontal gyrus, BA 44/45					3.6	-44	38	8	3.8	-16	30	58
Precentral gyrus, BA 4									3.7	-32	-8	58
Middle Frontal gyrus, BA 8									4.1	-12	2	58
Left Temporal												
Superior temporal gyrus, BA 22					3.5	-38	-34	8				
Left Parietal												
Angular gyrus, BA 39					3.9	-46	-56	34				
Fusiform gyrus, BA 37	3.8	-44	-52	-16								
Right Frontal												
Precentral gyrus, BA 4									3.6	58	-2	16
Right Temporal												
Superior temporal gyrus, BA 22									3.53	52	-2	-16
Right Occipital												
Middle occipital gyrus, BA 18	3.7	34	-90	4								



Activation maps for NC7 for (a) lexical decision task, (b) semantic judgment task, and (c) picture naming task. Statistical maps are thresholded by using clusters determined by Z > 3.5 and a (corrected) cluster significance threshold of P = 0.05. Images are in radiological orientation with the right side of the brain to the left and the left side to the right.

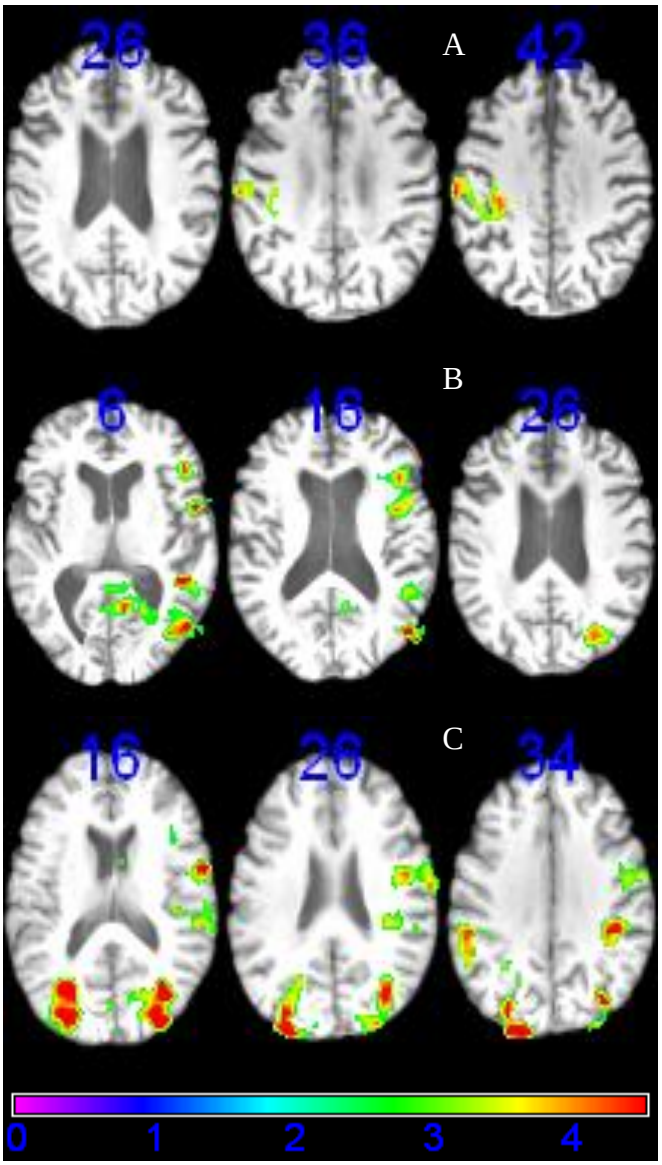
Appendix 13: Individual activation data for NC8

For NC8, activation did not reach significance for word decision vs. non-word decision. For word decision vs. fixation, activation was observed in the left middle occipital gyrus, right supramarginal gyrus, and bilateral precentral gyrus. For the contrast semantic judgment vs. size judgment, activation was observed in the left inferior frontal gyrus, left precentral gyrus, left middle temporal gyrus, and left supramarginal gyrus. Similar to all the other control participants, NC8 recruited bilateral language regions during picture naming. For oral picture naming vs. scrambled picture viewing, activation was observed in the right precentral gyrus, bilateral superior temporal gyrus, bilateral supramarginal gyrus, and bilateral middle occipital gyrus.

The activations observed for the control conditions for NC8 were also similar to that observed for all the other control participants. For non-word decision vs. fixation, activation was observed in the right angular gyrus and bilateral superior occipital gyrus. Activation did not reach statistical significance for size judgment vs. semantic judgment. Scrambled picture viewing vs. oral picture naming activated the right lateral occipital gyrus and left inferior temporal gyrus.

Summary Table of Activation Coordinates for NC8

Region	Lexical Decision				Semantic Judgment				Picture Naming			
	Z	**x**	**y**	**z**	**Z**	**x**	**y**	**z**	**Z**	**x**	**y**	**z**
Left Frontal												
Inferior frontal gyrus, BA 44/45					3.7	-46	24	16				
Precentral gyrus, BA 3	3.5	-40	-14	62	3.6	-48	2	16				
Left Temporal												
Superior temporal gyrus, BA 22									4.0	-52	-38	12
Middle temporal gyrus, BA 21					3.9	-46	44	6				
Left Parietal												
Supramarginal gyrus, BA 40					3.7	-50	-48	16	4.4	-58	-38	36
Left occipital												
Middle occipital gyrus, BA 18	3.7	-16	-94	-12					3.5	-34	-84	22
Right Frontal												
Precentral gyrus, BA 4	3.5	30	-20	62					3.9	56	-4	20
Right Temporal												
Superior temporal gyrus, BA 22									3.9	60	-28	16
Right Parietal												
Supramarginal gyrus, BA 40	3.8	38	-38	42					3.6	42	-42	42
Right Occipital												
Middle occipital gyrus, BA 18									3.5	32	-82	22



Activation maps for NC8 for (a) lexical decision task, (b) semantic judgment task, and (c) picture naming task. Statistical maps are thresholded by using clusters determined by Z > 3.5 and a (corrected) cluster significance threshold of P = 0.05. Images are in radiological orientation with the right side of the brain to the left and the left side to the right.

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