Abstract

Title of Thesis: A VOXEL-BASED APPROACH TO IDENTIFYING LESION SITES IN APHASIA: COMPREHENSION AND PRODUCTION DEFICITS IN SYNTAX, SEMANTICS AND PHONOLOGY

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The cortical regions of the brain traditionally associated with deficits of production and comprehension in language are Broca's and Wernicke's areas. Recent evidence suggests that other brain regions are involved and may be specific to linguistic areas of syntax, semantics and phonology. This paper describes the MRI results and language scores of 31 left hemisphere stroke patients with aphasia. Patients' lesions obtained from these MRI scans were reconstructed onto templates and entered into a voxel-based analysis program called Analysis of Brain lesion (ABLe) (Solomon, Raymont, Braun, Butman & Grafman, 2007) along with language scores. The results provided evidence for five key neuroanatomical regions of interest. These include the insula, the planum temporale, the operculum, the temporoparietal occipital (TPO) junction and the putamen. The results revealed common as well as unique areas of brain lesion for each of the behaviors.

A VOXEL-BASED APPROACH TO IDENTIFYING LESION SITES IN APHASIA: COMPREHENSION AND PRODUCTION DEFICITS IN SYNTAX, SEMANTICS AND PHONOLOGY

By

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Chapter 1: INTRODUCTION

Aphasia has been defined as "an acquired communication disorder caused by brain damage, characterized by an impairment of language modalities: speaking, listening, reading, and writing; it is not the result of a sensory deficit, a general intellectual deficit or a psychiatric disorder" (Chapey, 2001, p. 3). In the past, researchers, speech language pathologists, and other professionals have classified patients with aphasia into categories based their ability to perform behavioral tasks of production, comprehension and repetition. Paul Broca and Carl Wernicke were among the first to identify areas of the brain associated with specific types of deficits. Broca (1861) proposed that language is predominately processed by the left hemisphere in most individuals. He identified what is known today as "Broca's area," which is located in the inferior frontal gyrus and commonly thought to be involved in speech production. Carl Wernicke (1874) made advances in the field by delineating that the superior temporal cortex of the brain, now referred to as Wernicke's area, was primarily involved in auditory speech comprehension. Wernicke developed the model further to predict that if there was damage to the white matter tracts that connect Broca's area and Wernicke's area (the arcuate fasciculus), patients would have intact speech comprehension and production but a deficit in repetition would be detected. This was referred to as conduction aphasia and was first reported by Lichtheim (1885). However, these researchers were only able to examine the brains of aphasic patients post mortem, which posed some difficulty when looking at the relationship between the lesion and the associated behaviors. For example, it was not possible to determine which lesioned areas were associated with particular deficits, nor were they able to do further language testing on patients to determine if a common lesion in two people manifested in the same behavioral deficiency. This made it difficult to make conclusions regarding normal brain function (Rorden & Karnath, 2004).

Advances in technology that provide detailed images of the brain, such as Magnetic Resonance Imaging (MRI) and Computed Tomography (CT), have enabled researchers to identify areas of the brain that have been damaged in living patients making it possible to directly observe the speech and language behaviors associated with the lesion, while also performing additional speech-language testing. Studies using these new non-invasive techniques have found that the traditional views of the brain-language connection described by Broca and Wernicke are not always supported (i.e., Basso, Lecours, Moraschini, & Vanier, 1985; Mohr, 1976; Murdoch, 1988; Vignolo, Boccardi & Caverni, 1986). New approaches to studying brain-behavior relationships have proven to be invaluable in identifying lesions associated with certain deficits. Recent advances in neuroimaging have considerably improved the spatial and statistical accuracy of correlations between locations of brain lesions and aphasic behaviors (Bates *et al*., 2003; Dronkers, 2004; Dronkers, Wilkins, Van Valin, Redfern, & Jaeger, 2004).

The primary purpose of this thesis is to use a newly developed lesion-approach to examine 1) if aphasic individuals with syntactic, semantic or phonological deficits have specific left hemisphere lesions in common; 2) and if so, to identify the specific lesion sites associated with these deficits. In the following sections, various methods of lesion analysis are outlined. This is followed by a review of existing studies on the neural correlates of syntactic, semantic and phonological deficits. Based on this review as well as further neuroimaging studies, a hypothesis that the linguistic modalities of syntax, semantics and phonology are correlated with specific areas of lesion is made, and further directions of study are predicted.

Lesion analyses

Lesion analysis attempts to make correspondences between lesions and behavioral deficits. Past lesion studies have employed either one of two methods: lesion-defined analysis or behavior-defined analysis. The main difference between these two approaches is that the former approach begins with an area of lesion and attempts to determine resultant behavioral deficits while the latter starts with the behavioral deficit and attempts to identify a common site of lesion across different individuals with the same behavioral deficit. While these methods have been useful in offering information about the relationships between specific brain areas and certain behavioral functions, meaningful information is sometimes lost. This is secondary to the nature of these methods and can result in the oversight of critical areas of lesion or other behaviors involved in the deficit. A third approach, termed voxel-based lesion analysis, is the most recent advancement in lesion analysis and avoids problems faced by the previously mentioned methods. In this next section, the strengths and weaknesses of each of these three approaches will be discussed.

Lesion-defined analyses

In the lesion-defined approach, patients are grouped by a common area of injury and compared to a normally functioning comparison group in order to identify behaviors that correlate to the lesion in question. An example of the lesion-defined approach is a study conducted by Chao and Knight (1998) examining the dorsolateral prefrontal cortex and its role in inhibiting irrelevant inputs and controlling sustained attention. The authors studied patients with lesions confined to this specific area of the brain. They compared the performance of participants on specified behavior tasks to the performance of neurologically-intact volunteers in order to determine the impact of a lesion in the dorsolateral prefrontal cortex. It was determined that this region appears important for filtering distracting information and sustaining neural activity while patients are performing tasks using auditory working memory. Although the lesion-defined method can provide valuable information, it is rare to find lesions circumscribed to a single region of the brain. Hence patients with a variety of associated lesions are compared, therefore ignoring the influence of these associated lesions outside the particular region of interest. By nature, this method may overlook critical structures necessary for a behavior.

Behavior-defined approaches

The second approach is the behavior-defined approach, in which patients are grouped by a common behavioral deficit and the location of their lesions are compared. These comparisons are often made after the patients brain images have been reconstructed in a common stereotaxic space which serves as a common coordinate reference system such as the Talairach and Tournoux atlas (1988).[1] These reconstructions in Talairach space are then overlaid to find the common area of lesion. This common lesion can then be compared to lesions of patients without the behavioral deficit in question (Bates et al., 2003).

This behavior-defined technique that allows the investigation of behaviors and correlated lesion locations has become increasingly more popular. One such study was

[1]Talairach and Tournoux (1988) published an atlas of the human brain that established a coordinate system to identify a particular brain location relative to anatomical landmarks, a spatial transformation to match one brain to another, and a means of describing a standard brain with anatomical cytoarchitectonic labels.

conducted by Dronkers (1996) to assess lesion location of patients with apraxia of speech. Computerized reconstructions of the lesions of patients identified with apraxia were overlaid to determine the common area of infarct. The researchers were able to determine that 100% of the patients had an infarct in the precentral gyrus of the insula. However, since this is a common area of the brain affected by strokes, Dronkers overlaid patients who also had left hemisphere infarcts but no diagnosis of apraxia. In doing so, Dronkers was able to ensure that the area identified in the apraxic patients was not just an area of the cortex commonly damaged by a stroke but actually unique to the apraxic behavior. It was found that patients with left hemisphere infarcts negative for signs and symptoms of apraxia had similar areas affected by the stroke with the exception of the spared precentral gyrus of the insula.

The behavior-defined method provides an accurate means of identifying a common lesion location and ensures that the area of infarct is unique to the behavior in question. However, not all behaviors have been so clearly associated with lesions of specific areas of the brain using this method (Vanier & Caplan, 1990). A concern with this approach is determining behavioral cutoff scores to decide which patients are to be included in the group of deviant performers on the behavior in question; these cutoffs can limit information reflecting varying degrees of performance. Further, this method calls for the manual identification of the lesion site. This limitation could potentially introduce error and variability due to the subjectivity involved in manually identifying lesions.

Voxel-based approaches

The third and most recent method used to analyze the data obtained by new imaging techniques is on a voxel-by-voxel basis. A voxel is a unit of volume corresponding to the smallest element depicted in a three-dimensional reconstruction of a CT scan or MRI (Dark, 1997-2003). Voxels are typically 1-6 millimeter cubes. Using this measurement allows the researcher to identify very small distinct differences between lesions. Voxel-based analysis assesses each voxel and automatically divides the patients into two groups based on whether or not that voxel is included in the lesion. T-tests are then performed at each eligible voxel. Effect size is the alternative measurement to t-statistics in this method; the strength of the relationship between the two variables can be assessed based on the effect size. Bates et al. (2003) used this new voxel-based mapping system. This allowed lesions to be analyzed piece by piece, assessing one voxel at a time if necessary. The method referred to in the study is known as voxel-based lesion symptom mapping (VLSM). VLSM is based on computerized lesion reconstructions. These reconstructions are then compared to behavioral scores in order evaluate the effects of lesions on performance. VLSM can also identify similarities between statistical maps by calculating the correlations between t-scores on two behaviors, treating the voxels as subjects. This correlation reflects the overlap or lack thereof between behaviors and suggests that areas associated with performance on a particular behavior may or may not predict areas associated with the other behavior. This can also be used to compare VLSM maps with activation maps from functional imaging studies of normal subjects performing the same or similar tasks (Bates et al., 2003). As with the behavior-defined approach, manual lesion reconstruction is a possible limitation due to the risk of human error. This subjectivity can be reduced if lesions are traced by raters who are blind to the participant's deficits. The voxel-based approach is also limited by the task selected to isolate the behavior. For example, if the task involves multiple linguistic domains subtraction maps may be needed to isolate the behavior in question. The advantage of a voxel-based approach is that it does not require the researcher to choose either the lesion or the behavior approach, but instead uses continual behavioral and lesion information to create automated “t-maps” of behaviors and corresponding lesioned brain areas that are statistically significant. This eliminates the problems of neglecting significant structures in the brain, relying on a clinical diagnosis, and determining behavioral cutoff scores. It provides the researcher with a more comprehensive view of the behaviors and anatomy in question.

For example, Bates et al. (2003) examined one hundred and one stroke patients with aphasia using VLSM to identify common areas of lesion. Lesions were reconstructed by a neurologist who was blind to the diagnosis of each of the patients. These patients were assessed one year post onset on the behavioral sub-tests of fluency and auditory comprehension from the Western Aphasia Battery (WAB). Behavioral test scores were then compared for each group of patients based on whether they did or did not have a lesion affecting a particular voxel. This comparison generated t-maps for each voxel. Results yielded specific brain areas contributing to each behavioral deficit. For example, fluency was most affected by lesions in the insula and in the arcuate/superior longitudinal fasciculus in parietal white matter. Conversely, auditory comprehension was affected most by lesions in the middle temporal gyrus, with significant contributions also seen in the dorsolateral prefrontal cortex and parietal association cortex. Alternatives to t-statistics, as mentioned above, are possible such as measures of effect size; maps of effect size were very similar to t-maps shown in the study by Bates et al. (2003).

Novel uses of voxel-based analysis

The development of different methods to study the brain-language relationship has given researchers the ability to further understand the complex networking of the brain. There have been few studies completed using the voxel-based approach to confirm previous notions derived using lesion-based or behavioral-based analyses (Baldo, Schwartz, Wilkins & Dronkers, 2006; Bates et al., 2003; Saygin, Wilson, Dronkers & Bates, 2004; Wilson & Saygin, 2004). As noted earlier, the voxel-based method has been used to analyze lesions resulting in comprehension or production deficits as a whole (Bates et al., 2003; Dronkers et al., 2004; Dronkers, 2004). However, relatively little has been done to isolate the individual psycholinguistic components of language, (i.e. syntax, semantics, and phonology) and separately analyze comprehension and production of these psycholinguistic components in patients with aphasia. Isolating each linguistic component can be difficult due to the overlap across linguistic domains that occur in language. For example, in the sentence "kick the bucket" each of the three linguistic components are necessary to convey the information in this sentence. The syntax of the sentence is [verb phrase (Verb) [noun phrase (Determinate and noun)]] the majority of the sentence meaning is not determined by the syntax but by virtue of phonology and semantics. The phonology is the sounds that differentiate each word and the semantics is the overall meaning, which in this case is "to die." These individual parts are then further isolated in the brain into comprehension and production. A basic assumption is that language is organized by each of these components in several different areas of the brain. This can be assumed because brain damage does not always lead to an overall loss of language but is often characterized by patterns of impaired and spared performance. The way in which language is impaired depends on how it is organized in the brain. For example, a patient may present with isolated asyntactic comprehension in the absence of agrammatic production, or with anomia in the absence of semantic deficits, or the inability to repeat with intact semantic and syntactic production. Although these three aspects of language can manifest after brain damage as isolated deficits, based on the understanding of language there should be some cross over and interdependence between syntax, semantics and phonology. In this study it is hypothesized that unique brain structures will be lesioned for each of the three behavioral deficits, but it is also predicted that there will be some commonality between these three parts of language.

The present study examined the correlation between behavioral scores of comprehension and production in the areas of syntax, semantics, and phonology from well-known aphasia batteries and regions of the brain identified via voxel-based lesion mapping. The goal of the study was to use this method to determine the most accurate lesion location for each of these behaviors. This will aid in our understanding of the lesion locations causing linguistic deficits.

Lesion Studies on Syntactic Deficits

In English, syntax is the study of the rules that govern the way the words in a sentence are arranged. Sentences are the level of the language code at which the meanings of individual words are related to each other to express information about events and states in the world (Jackson, 1874). Sentences are interpreted on the basis of their organization and syntactic structure (Caplan, Hildebrandt & Makris, 1996). For example, if the organization of the sentence *The boy kissed Mary* is changed to *Mary kissed the boy*, there is a different meaning even though all of the words are the same. A syntactic comprehension deficit, often referred to as asyntactic comprehension, is evident when patients have difficulty understanding sentences in which syntactic structure must be used to determine meaning.

A deficit in syntactic production, often called agrammatic speech, is usually characterized by a lack of syntactic structure, word order errors, and speech consisting of predominantly content words. This can be seen during narratives and conversational speech or isolated during a picture description task.

The literature on lesion localization for syntactic deficits is limited. It is thought that the posterior inferior frontal gyrus (Broca's area) is important for syntactic processing (Grodzinsky, 2000; Stromswold, Caplan, Alpert, & Rauch, 1996). However, other studies have described patients with syntactic disorders having lesions outside Broca's area (e.g., Caplan & Hildebrandt, 1988; Tramo, Baynes & Volpe, 1988; Wilson & Saygin, 2004). Wilson and Saygin (2004) used voxel-based lesion symptom mapping (VLSM) analysis and found that a posterior temporal region, comprising the posterior superior temporal gyrus, posterior superior temporal sulcus, and the posterior middle temporal gyrus, was most reliably associated with deficits in grammaticality judgment. However, they found that patients without deficits in these specific areas who generally had left frontal lesions also had severe syntactic impairments. Therefore, no particular cortical location could be associated with syntactic processing (Caplan et al., 1996; Caplan & Hildebrandt, 1988; Dick et al., 2001). Wilson and Saygin (2004) suggest that neural regions associated with syntactic processing are probably distributed throughout the perisylvian area.

The literature on deficits of agrammatic production is equally inconclusive. A study by Mohr et al. (1978) found that patients with a lesion restricted to Broca's area did not produce agrammatic speech; larger lesions of the frontal and parietal area and insula were required. Temporal and parietal lesions were seen in patients with relatively intact structural abilities in production but impaired production of function words (Kolk, Van Grunsven, & Keyser, 1985; Miceli, Mazzucchi, Menn & Goodglass., 1983; Nadeau & Rothi, 1992; Nespoulous et al., 1988).

In other words, more research is needed to identify lesions associated with asyntactic comprehension and agrammatic production. It would be particularly interesting to see if asyntactic comprehension and agrammatic production are the result of common lesions because of the ongoing debate about the centrality of syntactic deficits in aphasia and syntactic processing in normal individuals (Grodzinskly, 2000, Kean, 1995). The left hemisphere is consistently implicated in language deficits. However, it may be of interest to determine common lesions involved in syntax that are also seen in deficits of semantics and phonology.

Lesion Studies of Semantic Deficits

The semantic system, also known as the mental lexicon, consists of all relevant sensory, visual, and verbal information that provides meaning to a word (Shelton & Caramazza, 1999). Patients with semantic deficits often present with word finding difficulties or naming difficulties, which can manifest as semantic paraphasias. For example, a patient may identify a dog as a "cat" as a result of the similarities in semantic features (four legs, pet, mammal). Picture naming and picture identification are common means to assess the semantic system. Semantic production can be assessed using confrontational naming tasks, including naming of verbs, objects, proper nouns, or other measures such as category fluency. In contrast, semantic comprehension is commonly assessed using tasks of picture identification via pointing or picture matching. It has been questioned whether or not there are separate modality-specific semantic systems (visual-auditory-verbal; input-output) (Allport, 1985; Damasio, 1990; Paivio, 1971; Shallice, 1988; Warrington & Shallice, 1984). This position has been disputed and current neuroimaging results from a PET study comparing semantic processing of words and pictures supports the proposal of a common semantic system shared by verbal and visual inputs (Vandenberghe, Price, Wise, Josephs, & Frackowiak, 1996). Vandenberghe et al. (1996) found activation in overlapping brain regions during semantic processing tasks, specifically in the left superior occipital gyrus, middle and inferior temporal cortex, and the inferior frontal gyrus. Perani et al. (1999) isolated a specific activation in the inferior part of the left posterior inferior frontal gyrus and the left middle temporal gyrus when a lexical decision was performed on verbs compared to nouns.

Functional neuroimaging studies have established an association between semantic processing and the left inferior frontal cortex (Binder et al., 1997; Petersen, Fox, Posner, Mintun, & Raichle, 1988; Poldrack et al., 1999). However, frontal lesions do not typically result in pure semantic processing deficits (Noppeney, Phillips & Price, 2004). Demonet, Thierry and Cardebat (2005) hypothesized that semantic comprehension demonstrates consistent involvement of a more complex network, as seen in studies mentioned previously, involving the inferior temporal cortex, the middle and posterior temporal cortex (including the angular gyrus) and frontal association areas. The findings in lesion-based studies investigating semantic deficits have long been associated with

Wernicke's area (Hart & Gordon, 1990).Wernicke's area has been associated with deficits of word meaning (comprehension) (Lesser et al., 1986) and naming (production) (Ojemann, 1994). Lesion-based studies have suggested that the left frontal cortex is associated with processing verbs, whereas temporal cortex lesions more specifically affect object names (Demonet et al., 2005).

The inferior frontal cortex has been associated with motor programming and planning of speech articulation, which is an important component of single word object naming. The occipitotemporal area has also been implicated in impaired naming without comprehension deficits (Foundas, Daniels, & Vasterling, 1998; Hillis et al., 2006; Raymer et al., 1997).The involvement of both anterior and posterior regions of the brain demonstrates the complexity of the semantic system; therefore, it is not surprising that semantic deficits manifest in a variety of clinical symptoms. Deficits in semantics can be broad or as specific as an isolated naming impairment, which can include a variety of problems such as object naming, naming of proper nouns, verb naming and categorization deficits. These have all been associated with different areas of lesion as well as some overlapping areas. Baldo et al. (2006) found that semantic production in the form of category fluency deficits is associated with lesions in the more posterior cortex, including regions of the left temporal lobe and the post central gyrus. Tranel (2006) found that the left temporal pole is important for the retrieval of proper nouns, including people and places.

Thus far, few lesion-studies have investigated relationships among semantics, syntax and phonology. Further study is needed to understand the correlations between the complex network identified in current studies as the semantic system and the overlap of these areas across other linguistic modalities. For example, are these areas of the inferior frontal gyrus involved in semantic production similar across linguistic modalities or are there particular areas unique to semantic production?

Lesion Studies on Phonological Deficits

A phoneme is the smallest unit of sound that can change linguistic meaning. A deficit in phonologic comprehension usually implies difficulties perceiving speech sounds. A deficit in phonology production can manifest as phonemic paraphasias (i.e. a patient may label a table as a “fable”) or neologisms (a nonsense word used in place of the intended word i.e. “slardle” for knife). The patient is aware of the meaning associated with the word, but is unable to access the appropriate phonemes. Deficits in phonology may also be seen during repetition tasks, especially non-word repetition when no semantic cues are provided. There are some overlapping areas of the brain associated with semantics, syntax and phonology. Baldo et al. (2006) found that the parietal cortex, insula and the putamen were commonly lesioned in both deficits of phonologic as well as semantic fluency. According to Ojemann (1991), in reference to patients without lesions, stimulation mapping displayed activation in some of the same cortical sites during perception and production of speech, including the perisylvian cortex of the left inferior frontal, parietal, and superior temporal lobes. More specifically, the left superior temporal cortex appears to be involved in the processing of language-specific sounds (Demonet et al., 2005). Therefore, lesions in these specified locations could potentially result in deficits of both perception and production of phonology. Studies have also highlighted the involvement of the anterior part of the superior temporal gyrus and the superior temporal sulcus in the left hemisphere as the main neural substrates involved in the auditory representation of speech components. Lesions associated with the classical Wernicke's area have also been associated with phonological deficits, especially in the context of repetition tasks.

To summarize, lesions involved in deficits of phonology have been associated with frontal, temporal and parietal lesions. Some overlap has been seen in deficits of syntax, semantics and phonology but it is unclear whether these overlaps correspond to the same portion of the frontal, temporal or parietal lobes or if there are unique areas circumscribed to each domain. There have also been few studies done using dissociations to confirm if these areas are in fact localized to phonologic processing.

Research Questions and Hypotheses

The purpose of this study was to determine if specific brain regions could be identified that, when lesioned, impacted performance on language tasks of syntax, semantics and phonology. The following question was posed:

1. What areas of the brain are lesioned in patients with poor performance on specific language tasks of syntax, semantics and phonology?
    a. What areas are common among production deficits across all three linguistic domains and what regions are common among comprehension deficits across linguistic domains?
    b. What areas of the brain are commonly lesioned in different types of language deficits and what areas are unique to each linguistic deficit?

Based on a review of the current literature, the following hypotheses were formulated:

1. Syntax will manifest as a diffuse lesion involving both anterior and posterior brain regions. Semantics as a whole is anticipated to involve lesions in the temporal

region of the brain and should in general be attributed to more posterior lesions than both syntax and phonology, with some aspects of the inferior frontal gyrus seen in deficits of semantic production. Deficits in phonology can be assumed to involve lesions typically associated with Wernicke's area and the arcuate fasciculus since they have both been associated with deficits in repetition or in the area around Heschl's gyrus due to the nature of sound processing.

a. Common regions for production across language components would be in the area of the left frontal lobe and possibly include parts of the insula and precentral gyrus. Common areas for comprehension across modalities would likely include areas located in the posterior portion of the brain, localized to areas in the left temporal and parietal lobes. These areas are suspected to be involved across linguistic processes to at least some degree in all measures involving production or comprehension.
b. The areas of the brain lesioned in patients with poor performance on syntax, semantics and phonology will include some unique structures for each individual language component but it is proposed that there will be some commonality between structures. This is secondary to the nature of language and the interdependence between linguistic domains. The frontal operculum is expected to be damaged in each of the three linguistic domains; however, it is purposed that the same area within the operculum will not be damaged in deficits of syntax, semantics and phonology (Bookheimer, 2002).

Chapter 2: METHODS

Data Source

Data from an existing database at the National Institutes of Deafness and Communication Disorders (NIDCD) were analyzed for this study. This database consists of the language test scores of 31 patients with aphasia. All patients had sustained left hemisphere lesions and were diagnosed and tested by a speech language pathologist and neurologist at the NIDCD. The database also contains structural MRI scans for each patient. All patient information was coded via subject number. Patient names and MRI scans were password protected for confidentiality.

Particular subtests were chosen by the speech language pathologist to obtain a comprehensive profile of each patient's speech and language deficits. Behavioral scores are included from the *Western Aphasia Battery* (WAB) (Kertesz, 1982). According to their language profile on the WAB, fifteen participants were classified as having Anomic aphasia, four were categorized as having Conduction aphasia, three with Broca's, one with Global aphasia, two with transcortical motor, one with Wernicke's aphasia, one with Broca's aphasia and apraxia of speech and four participants scored within normal limits. These four patients who scored within normal limits on the WAB demonstrated deficits on the more specific subtests of the *Psycholinguistic Assessment of Language* (PAL) and *Psycholinguistic assessments of Language Processing in Aphasia (*PALPA.). The aphasia classifications indicated by the WAB are the classic aphasia categories and are determined based on which language skills are relatively more impaired than others. The classification of anomic aphasia implies significant word retrieval problems with relatively spared comprehension and fluency, whereas conduction aphasia is classified based on impaired repetition with generally fluent speech and spared auditory comprehension. In patients with transcortical motor aphasia, repetition is intact relative to very limited verbal output. Broca's aphasia, as discussed earlier, is the most classic form of non-fluent aphasia with relatively intact auditory comprehension and non-fluent speech rate. In contrast, Wernicke's aphasia presents with fluent speech and limited auditory comprehension. Finally, global aphasia is the most severe of the aphasias characterized by both impaired linguistic comprehension and expression.

Language Tests

Behavioral scores from the *Psycholinguistic Assessment of Language* (PAL) (Caplan, unpublished) and the *Psycholinguistic assessments of Language Processing in Aphasia* (PALPA) (Kay, Lesser, & Coltheart, 1992) were available in the database for all the patients. These tests are designed to be used by speech language pathologists and cognitive neuropsychologists to assess language processing skills in people with aphasia. Other behavioral tests including, but not limited to, the Apraxia Battery for Adults (Dabul, 2000) and a verb naming test (Berndt & Mitchum, 1997), were administered to a few of the individuals. For this study, based on the research questions and the test scores available, a subset of the available test scores were selected as measures of production and comprehension for phonology, syntax and semantics. An important factor in subtest selection for this study was the relative unambiguity with which performance on that subtest reflected the psycholinguistic skill in question. For example, a single word repetition subtest was selected as a measure of phonological production skills rather than a picture description task, since the latter also involves a significant amount of semantic and syntactic processing. The following tests were selected:

1. Production of syntax. The Picture Description subtest of the PAL was used as a measure of syntactic production. Participants were required to produce a sentence to describe the picture presented. The verb was provided to the subjects and there were arrows pointing to the items in the picture that needed to be included in the sentence. This subtest attempts to elicit several types of sentences, including passive, active, dative, dative-passive, and relative clauses. Although we recognize that performance on this task does recruit semantic and phonological processes in addition to syntax, it can be argued that this test primarily assesses production of syntax because of the criteria for scoring. For example, if a person produces an active sentence with the correct phonology and semantics for a passive target, then he/she does not get a score. Hence, intact syntactic production is crucial for a high score on this test.

2. Comprehension of syntax. The *Sentence-Picture Matching* subtest of the PALPA was used to assess participant's syntactic comprehension. The subtest uses pictures to test comprehension of spoken sentences. This test assesses the comprehension of four main types of sentences: reversible and non-reversible (in both the active and passive voice) and gapped and converse relations. For each sentence that is heard there is a choice of three pictures, one correct and two distractors. The majority of sentences use a restricted set of six animate referents. Participants are pre-tested on their ability to recognize these referents. As with syntactic production, this subtest also requires the participant to access multiple linguistic domains including the semantic and phonological systems to interpret the sounds that are heard and assign lexical meaning to these words. In spite of the access to semantics and

phonology, this measure isolates syntactic comprehension by using distractor pictures which require participants to syntactically parse the sentence in order to understand the meaning of the sentence, including word order and grammatical structure.

3. Production of semantics. The *Picture Naming* subtest of the PALPA was used as a measure of semantic output. This subtest requires participants to provide names of pictures (black and white line drawings). In order to understand the picture or object, the viewer needs to access the "visual object recognition system" which stores features of the item. Recognition of an object or picture will have occurred when the viewer has succeeded in matching up the visual features of the viewed stimulus with the details of one of the structural descriptions in the visual object recognition system (Kay et al., 1992). It can then proceed to the semantic system where the appropriate representation of the item will be accessed. Finally, the phonological output lexicon is accessed, where the corresponding spoken form of words are selected to produce speech (Kay et al., 1992). Although picture naming involves some aspects of the phonological system, it is commonly used to assess lexical production in aphasiology (Foundas et al., 1998; Hillis et al., 2006; Ojemann, 1994; Raymer et al., 1997; Schnur, Schwartz, Brecher, & Hodgson, 2006).

4. Comprehension of semantics. The *Spoken Word-Picture Matching* subtest of the PALPA assesses semantic comprehension, requiring patients to interpret the meaning of pictures. This test uses four distractor pictures: a close semantic distractor, a more distant semantic distractor, a visually similar distractor and an unrelated distractor. The test administrator states the word and the participant must choose the correct picture from the five pictures displayed. This test requires access to

the phonological input and semantic system but it does not require the subject to produce the name of the item.

5. Production of phonology. The *Repetition of Non-words* subtest of the PALPA was used to assess production of phonology. This measure requires patients to repeat made-up words, which does not require the access of the syntactic or semantic systems. According to Kay et al. (1992) this occurs via the acoustic-to-phonological conversion route, bypassing the lexical systems.

6. Comprehension of phonology. The *Word and Non-word Minimal Pairs* subtest was used to measure comprehension of phonology. The words were all monosyllabic with a consonant vowel consonant (CVC) structure. The participants were required to listen to two words or non-words and determine if they had the same or different phonological structure. Word pairs are minutely different according to voice, manner or place of articulation. For example, "pot and pot" would be the same structure, whereas "tot and pot" would be different. The scores from these six subtests were analyzed and correlated with lesion locations.

The production and comprehension of language is complex and involves a network of processes. Although several subtests use more then one linguistic system and may be impacted by other systems such as selective attention and memory, the goal is to find unique and common areas of damage resulting in poor performance on these six tasks of comprehension and production in syntax, semantics and phonology. Although these six measures are not the same as the psycholinguistic aspects they will be referred to as syntax, semantics and phonology comprehension and production in order to remain consistent throughout the paper.

Neuroanatomical images

Structural MRI images were obtained from the archives of the NIDCD for the thirty-one chronic aphasic patients. These images were obtained from a GE 1.5 Tesla MRI scanner at the NIH. These images were available in electronic form that could be submitted for automated lesion analysis.

Software and methods for lesion analysis

The computer used for the study is a linux machine using ABLe 2.3 (Analysis of Brain Lesion) implemented in MEDx medical imaging software package (Solomon, Raymont, Braun, Butman & Grafman, 2007). ABLe characterizes brain lesions in magnetic resonance imaging (MRI) of the adult human brain by spatially normalizing the lesioned brain into Talairach space (refer to Footnote #1, p.4). An atlas, called the AAL (Anatomic Automatic Labeling), is also used in the ABLe program which allows anatomical labeling of functional brain mapping experiments (Tzourio-Mazoyer et al, 2002). The MRI images of the 31 participants were registered in ABLe 2.3 and lesioned brain areas were manually traced. These tracings were confirmed for accuracy by two neurologists, Dr. John Butman and Dr. Allen Braun of NIH, who were blind to any identifying subject information while confirming lesion tracings. Any discrepancies were discussed and finalized based on a consensus.

Following manual lesion tracing, language scores of individual patients for each of the language measures were entered into ABLe. This software automatically correlates language scores with lesions that are typically associated with these scores across patients. This is done on a voxel-by voxel basis for the entire brain of each patient. The resulting t-values depend on the extent of correlation between a particular language score and the occurrence of a lesion in a particular voxel (or cluster of voxels) across patients. That is, if patients with low scores on syntax production all have lesions in a particular voxel, then the t-value for that voxel is large (and so is the effect size). In this manner, t-values (as well as effect size and percentage of brains having a lesion in that area) were obtained for each brain region for each of the six psycholinguistic measures. The areas identified by the t-maps were based on common areas of lesion for at least 4 participants, with a minimum cluster size of 2 voxels[2] and a minimum t-value of 1.2. The resultant output of t-values is called a t-map.

As a second level of analysis, an enhancement of ABLe (Solomon, unpublished) was used to compare and contrast lesions across language measures. This program allowed the production of comparison maps between two language measures, including a map of common lesions, maps of lesions unique to one behavior, and maps that reveal common regions that have a larger area of voxel involvement (.5 or greater) in one behavior over the other. These maps were produced across linguistic domains and between production and comprehension within each linguistic domain. For example, syntax production and phonology production were compared to examine brain regions with common lesions, and lesions unique to each. This was done for all permutations and combinations of the six language measures.

As a third level of analysis, t-values of lesions associated with two language measures (while excluding the third measure) were also obtained. This method is referred to as masking. For example, maps including syntax and semantics and excluding phonology, syntax and phonology excluding semantics, semantics and phonology

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[2] The voxel sizes are 0.9375mm in the x and y directions (that is in-plane or within the slice) and 1.5mm in the z direction (slice thickness).

excluding syntax, syntax excluding semantics and phonology, semantics excluding syntax and phonology, and phonology excluding syntax and semantics.

A fourth level of analysis, to further confirm results of the t-maps a two group analysis was performed using ABLe 2.3, evaluating dissociations between language measures and within language measures. The preserve of a double dissociation was tested between three groups: syntactic comprehension vs. syntactic production, phonology comprehension vs. phonology production, and syntactic production vs. semantic production. These groups were formed based on the mean of the behavioral scores; participants above the mean in behavior 1 and below the mean in behavior 2 were included in group 1 and compared with patients who were below the mean in behavior 1 and above the mean in behavior 2. Groups consisted of a minimum of 2 participants and excluded patients with low or high scores on both behaviors. Although this is the most reliable dissociation (Shallice, 1988), it was unable to be performed for all the behaviors. Therefore single dissociations (comparing participants who performed well within a single behavior, for example syntactic production to those who performed poorly on that same measure) were also conducted within behaviors. A two group analysis was performed comparing high scoring participants to low scoring participants within each behavior. A threshold of four participants was used for the analysis. To differentiate consistently between high and low scores the mean and standard deviation (SD) of each behavior was calculated. Participants scoring .5 SD or greater than the mean were included in the high scoring group and those .5 SD or more below the mean were included in the low scoring groups. These results were used to confirm findings in the previously mentioned measures.

Chapter 3: RESULTS AND DISCUSSION

Analysis of brain lesions revealed several regions of interest. For the purpose of reference, some of these relevant regions are identified in Figure 1.

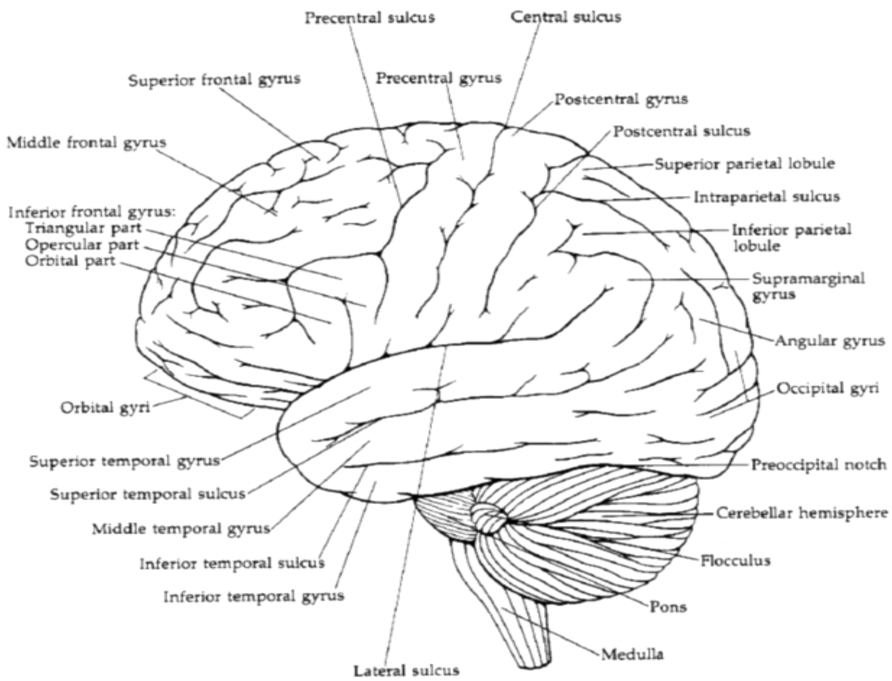


Figure 1. Figure showing relevant brain regions that are mentioned in the results section.

In this study, the data were interpreted based on the general categories of production and comprehension and the individual linguistic components of syntax, semantics and phonology. Several methods of data analysis were employed, which have been described earlier. The following section details the results from the individual t-maps and gives a general identification of brain areas associated with each behavior. Then a two group analysis was utilized to confirm findings from the t-maps. There were several areas of overlap identified between the individual t-maps. For this reason, masking was done for each measure of production. Results of the masking maps reveal areas unique to each behavior and common areas of overlap within each brain region. A caveat to this study was the small number of participants with low scores on semantic and phonologic measures of comprehension. Therefore, measures of comprehension were not included in the masks and t-maps describing comprehension should be interpreted with caution. The results of the present study are interpreted in reference to previous lesion studies and brain imaging evidence.

3.1. T-Maps for each behavior

T-maps were created for each behavior and results produced t-values for each lesioned brain area corresponding to the six behaviors. It also provided an effect size and the percentage of the lesion that each brain area comprised. A large effect is thought to be greater than .8, a medium effect is roughly less than .8 but greater than .5 and a small effect is less than .5 (Cohen, 1988). The effect size implies the relevance of the specific lesioned brain area in comparison with other lesioned structures. There were several areas of overlap between the different behaviors secondary to the nature of the t-maps.

3.1.1. Lesion Analysis for syntactic production

The results for the syntactic production map revealed a list of twenty left hemisphere structures. The percentage of involvement of each structure, t-values and effect size are included in Table 1. As shown in Table 1, the regions maximally associated with syntactic production scores are the rolandic operculum, post-central gyrus, inferior parietal lobe, supramarginal gyrus, and superior temporal gyrus. All three areas of the frontal operculum are involved, with the greatest association in the triangularis and opercularis. These results reveal a diffuse area of lesion involving portions of the frontal, temporal, and parietal lobes in the cortex and the subcortical putamen.

Table 1. Left hemisphere lesions that correlated with syntactic production scores. The neuroanatomical regions are listed by lobe, and then in decreasing order of contribution. The listed areas include only those lesioned in at least four patients, had a cluster size of at least two voxels and a t-value of at least 1.2

% of lesion	**Structure**	**t-value**	**Effect size (Cohen's d)**
8.27	Rolandic Operculum	3.51	1.33 ***
2.97	Precentral Gyrus	2.21	0.84 ***
7.11	Inferior Frontal Triangularis	1.99	0.76 **
2.13	Inferior Frontal Opercularis	1.89	0.72 **
10.12	Middle Frontal	1.88	0.77 **
2.09	Inferior Frontal Orbitalis	1.55	0.69 **
0.19	Middle Frontal Orbital	1.54	0.68 **
1.94	Superior Frontal	1.40	0.66 **
1.94	Insula	2.25	0.90 ***
11.18	Supramarginal Gyrus	3.51	1.33 ***
7.69	Inferior Parietal	3.20	1.21 ***
17.70	Postcentral Gyrus	3.18	1.20 ***
0.30	Angular Gyrus	1.78	0.74 **
0.24	Putamen	1.23	0.63 **
11.26	Superior Temporal	4.31	1.65 ***
1.31	Heschl's Gyrus	2.64	1.01 ***
0.24	Temporal Pole	2.06	0.83 ***
0.54	Middle Temporal	1.54	0.68 **
0.06	Middle Occipital	1.31	0.63 **

*small effect, ** medium effect, ***large effect

It was hypothesized that deficits of syntactic production would include a more diffuse area of the left hemisphere including the frontal as well as the temporal and parietal lobes. This is because syntactic production involves the processing and production of both semantic and phonologic information. Bavelier, Corina, Jezzard, Padmanabhan and Clark (1997) identified diffuse areas of the brain including both Broca's and Wernicke's area involved in sentence production during a sentence-reading study. As shown in Table 1, the findings are consistent with this prediction of diffuse involvement. As stated previously, the inferior frontal gyrus was lesioned in all three areas of the frontal operculum including the opercularis, triangularis and orbitalis. However, most significantly in the opercularis and triangularis, these findings are consistent with current research that found the opercularis to be a critical structure in syntax (Bookheimer, 2002). These findings are further confirmed on maps examining syntax minus phonology and semantics. These maps are interpreted and discussed in the following sections.

Findings of the superior temporal gyrus and supramarginal gyrus incorporating a significant portion of the syntactic production lesion are consistent with recent literature correlating syntactic processing and the supramarginal gyrus as well as the superior temporal gyrus (Caplan & Waters, 2002; Friederici, Steinhauer, & Frisch, 1999). Together with the angular gyrus, the supramarginal gyrus is a somatosensory association area receiving inputs from the auditory and visual systems. This may explain why lesions in these areas correspond to deficits in sentence construction prompted by visual images.

3.1.2. Lesion Analysis for syntactic comprehension

The t-map for syntactic comprehension revealed a smaller area of involvement than syntactic production and includes eleven structures in the left hemisphere. The percentage of involvement of each structure, t-values and effect size are included in Table 2. As shown in Table 2, the maximum involvement was seen in the triangularis of the inferior frontal gyrus, insula, angular gyrus and the superior and middle temporal gyri. The largest percentage of the lesion was circumscribed to the superior and middle temporal gyri. The frontal operculum was limited to involvement of the triangularis and orbitalis with the largest portion of the lesion reported in the triangularis.

Table 2. Left hemisphere lesions that correlated with syntactic comprehension scores. The neuroanatomical regions are listed by lobe, and then in decreasing order of contribution. The listed areas include only those lesioned in at least four patients, had a cluster size of at least two voxels and a t-value of at least 1.2

% of lesion	Structure	t-value	Effect size (Cohen's d)
6.76	Inferior Frontal Triangularis	1.45	0.54**
.28	Rolandic Opercularis	1.43	0.54**
1.97	Inferior Frontal Orbitalis	1.32	0.50**
20.00	Insula	1.43	0.54**
0.85	SupraMarginal Gyrus	1.35	0.54**
9.58	Angular Gyrus	1.32	0.53**
1.97	Inferior Parietal	1.23	0.50**
21.69	Superior Temporal	1.43	0.56**
27.32	Middle Temporal	1.33	0.53**
0.28	Temporal Pole	1.30	0.50**
0.56	Middle Occipital	1.23	0.50**

*small effect, ** medium effect, ***large effect

The findings of the superior and middle temporal gyri as predominant portions of the lesion are consistent with results reported in studies identifying deficits of comprehension and include the traditional Wernicke's area thought to be involved in language processing. The involvement of the angular gyrus is likely because of word processing involved in syntactic comprehension which is consistent with findings from Bavelier et al. (1997). In the inferior frontal gyrus, lesions of the triangularis and orbitalis were observed and no involvement in the opercularis was identified. This finding is inconsistent with the current view from neuroimaging studies that syntax is localized to the opercularis in the inferior frontal gyrus (Bookheimer, 2002). The insula, supramarginal gyrus, superior and middle temporal lobes and the temporal pole were also identified. These findings including the frontal, parietal and temporal lobes represent a diffuse area of the brain which as stated previously has been associated with syntactic processing.

3.1.3. Lesion Analysis for semantic production

The t-map created to identify areas involved in semantic production included more posterior regions than those associated with syntactic production. Eighteen structures were identified. The percentage of involvement of each structure, t-values and effect size are included in Table 3. As shown in Table 3, the regions maximally associated with semantic production are the precentral gyrus, postcentral gyrus, supramarginal gyrus, angular gyrus, and the superior and middle temporal gyri. All three areas of the frontal operculum were included; however, the orbitalis was most significantly associated with semantic production. The majority of the lesion was reported in more posterior portions of the brain and except for the large involvement of the precentral gyrus and rolandic operculum, in the frontal lobe.

Table 3. Left hemisphere lesions that correlated with semantic production scores. The neuroanatomical regions are listed by lobe, and then in decreasing order of contribution. The listed areas include only those lesioned in at least four patients, had a cluster size of at least two voxels and a t-value of at least 1.2

% of lesion	Structure	t-value	Effect size (Cohen's d)
10.16	Precentral Gyrus	2.03	0.86***
9.76	Rolandic Operculum	1.79	0.73**
0.70	Middle Frontal	1.64	0.77**
2.11	Inferior Frontal Orbitalis	1.64	0.77**
2.26	Superior Frontal	1.46	0.74**
0.10	Inferior Frontal Opercularis	1.31	0.49**
0.07	Inferior Frontal Triangularis	1.28	0.71**
2.66	Insula	1.78	0.76**
7.80	Supramarginal Gyrus	2.44	0.97***

% of lesion	Structure	t-value	Effect size (Cohen's d)
7.95	Postcentral Gyrus	2.02	0.86***
9.02	Angular Gyrus	2.02	0.86***
6.09	Inferior Parietal	1.85	0.82***
0.22	Superior Parietal	1.28	0.71**
10.63	Superior Temporal	2.64	1.03***
3.90	Middle Temporal	2.44	0.97***
0.87	Heschl's Gyrus	1.81	0.81***
0.70	Temporal Pole	1.48	0.74**
2.43	Middle Occipital	1.65	0.77**

*small effect, ** medium effect, ***large effect

According to a review of neuroimaging literature by Gernsbacher and Kaschak (2003), the areas of the brain generally involved in semantic processing of words, word form access, and production include the left inferior-frontal gyrus, adjacent supplementary and pre-motor areas, and posterior temporal regions. The t-map revealed large areas of lesion in the angular gyrus, the supramarginal gyrus, and superior temporal lobe, all of which have been identified as areas corresponding to word retrieval deficits and semantics (Duffau et al., 2005; Hart & Gordon, 1990; Vandenberghe et al., 1996). The lesioned areas of the precentral gyrus, inferior frontal lobe, and the rolandic operculum are typically associated with measures of production (Indefrey & Levelt, 2000). Further implications of lesions in the inferior frontal lobe will be discussed later, specifically the orbitalis.

3.1.4. Lesion Analysis for semantic comprehension

T-maps created for deficits of semantic comprehension reveal similar structures to that of the semantic production maps with the exception of the areas identified as unique to speech articulation. There were thirteen structures identified among participants with deficits in semantic comprehension. The percentage of involvement of each structure, t-values and effect size are included in Table 4. As shown in Table 4, regions maximally associated with semantic comprehension deficits include all three portions of the inferior frontal gyrus with the largest percentage reported in the triangularis, the insula, putamen, pallidum and the superior and middle portions of the temporal lobe.

Table 4. Left hemisphere lesions that correlated with semantic comprehension scores. The neuroanatomical regions are listed by lobe, and then in decreasing order of contribution. The listed areas include only those lesioned in at least four patients, had a cluster size of at least two voxels and a t-value of at least 1.2

% of lesion	Structure	t-value	Effect size (Cohen's d)
0.13	Inferior Frontal Opercularis	2.77	1.07***
2.20	Inferior Frontal Orbitalis	2.14	0.83***
5.51	Middle Frontal	2.14	1.08***
20.62	Inferior Frontal Triangularis	2.10	1.02***
5.51	Precentral Gyrus	1.77	0.75**
12.58	Insula	2.70	1.10***
4.02	Postcentral Gyrus	1.78	0.83***
2.72	Inferior Parietal	1.78	0.83***
0.32	Angular Gyrus	1.49	0.66**
13.29	Putamen	3.04	1.29***
0.58	Pallidum	2.11	1.07***
2.01	Middle Temporal	2.30	1.09***
0.26	Superior Temporal	2.09	0.85***

*small effect, ** medium effect, ***large effect

The results of the semantic maps are inconsistent with the long standing thoughts originally presented by Broca (1861) and Wernicke (1874) that comprehension is more posterior and production associated with generally more frontal involvement. This map reveals more frontal involvement than the semantic production map. This inconsistency is likely because of the small number of patients who had low scores on comprehension measures. The deeper structures of the pallidum and putamen, both located within the basal ganglia, were localized in this map. These structures were also observed in the t-map for phonologic comprehension. The putamen, but not the pallidum, was also involved in lesions of syntactic production. A literature review of subcortical aphasia found that isolated lesions of these areas usually result in milder linguistic deficits (Fabbro, Vorano, Fabbro, & Tavano, 2002). Therefore, based on the deficits observed they hypothesized that these subcortical structures are likely to be involved in the regulation of the phonemic, syntactic and lexical chunks processed in the cerebral cortex (Fabbro et al., 2002).

3.1.5. Lesion Analysis for phonological production

The t-maps for phonological production revealed eighteen structures common to those with deficits in repetition. The percentage of involvement of each structure, t-values and effect size are included in Table 5. As reported in Table 5, regions of maximal involvement in phonologic production deficits include the triangularis, rolandic operculum, insula, and supramarginal gyrus. A large percentage of the lesion also includes the inferior parietal lobe and superior temporal lobe.

Table 5. Left hemisphere lesions that correlated with phonological production scores. The neuroanatomical regions are listed by lobe, and then in decreasing order of contribution. The listed areas include only those lesioned in at least four patients, had a cluster size of at least two voxels and a t-value of at least 1.2

% of lesion	Structure	t-value	Effect size (Cohen's d)
21.38	Inferior Frontal Triangularis	2.61	0.98***
3.66	Rolandic Operculum	2.38	0.89***
0.88	Inferior Frontal Opercularis	1.90	0.71**
1.24	Precentral Gyrus	1.89	0.77**
6.78	Inferior Frontal Orbitalis	1.87	0.77**
2.12	Middle Frontal	1.58	0.70**
0.24	Superior Frontal	1.22	0.62**
12.17	Insula	2.05	0.81***
3.97	Supramarginal Gyrus	2.64	0.98***

% of lesion	Structure	t-value	Effect size (Cohen's d)
3.57	Postcentral Gyrus	1.97	0.77**
12.69	Inferior Parietal	1.88	0.77**
3.48	Angular Gyrus	1.56	0.69**
0.30	Superior Parietal	1.23	0.62**
1.06	Heschl's Gyrus	1.97	0.74**
8.21	Superior Temporal	1.97	0.74**
3.97	Temporal Pole	1.84	0.75**
0.18	Middle Temporal	1.22	0.50**
1.12	Middle Occipital	1.37	0.64**

*small effect, ** medium effect, ***large effect

Deficits in phonological production were based on a repetition task of non-real words, as described in the methods section. This involves connections from the posterior area of the brain, where sounds are heard and processed. It is thought that information travels through a white matter tract called the arcuate fasciculus to the frontal regions where the motor movements for speech are planned and carried out. The t-map results reveal lesions consistent with this hypothesis. Heschl's gyrus and the superior temporal lobe are involved in the auditory perception of the word. The angular gyrus is thought to act as a way station between the primary sensory modalities and the speech areas (Geschwind, 1965). The involvement of the inferior frontal gyrus associated with phonological production, specifically the triangularis, is discussed in detail in the next section. The t-map results are consistent with the hypothesized brain network involved in repetition.

3.1.6. Lesion Analysis for phonological comprehension

The t-maps revealed twenty areas common to at least four participants with relatively low phonological comprehension scores compared to other participants. The percentage of involvement of each structure, t-values and effect size are included in Table

6. As reported in Table 6, regions maximally associated with phonologic comprehension include the rolandic operculum, insula, postcentral gyrus, inferior parietal lobe, supramarginal gyrus, and Heschl's gyrus. The amygdala was also reported in the results and was not observed in maps of any previous measures.

Table 6. Left hemisphere lesions that correlated with phonological comprehension scores. The neuroanatomical regions are listed by lobe, and then in decreasing order of contribution. The listed areas include only those lesioned in at least four patients, had a cluster size of at least two voxels and a t-value of at least 1.2

% of lesion	Structure	t-value	Effect size (Cohen's d)
0.86	Rolandic Operculum	2.28	0.85***
9.15	Inferior Frontal Triangularis	1.75	0.67**
21.56	Middle Frontal	1.74	0.77 **
2.66	Inferior Frontal Orbitalis	1.70	0.70**
13.78	Superior Frontal	1.73	0.77**
0.54	Inferior Frontal Operculum	1.75	0.66**
3.19	Precentral Gyrus	1.40	0.71**
0.04	Supplementary Motor Area	1.21	0.67**
0.04	Superior Medial Frontal	1.21	0.67**
10.98	Insula	2.36	0.93***
4.84	Postcentral Gyrus	2.10	0.86***
0.97	Inferior Parietal	2.10	0.86***
0.11	Supramarginal Gyrus	2.10	0.86***
0.39	Heschl's Gyrus	2.28	0.85***
2.26	Superior Temporal	1.87	0.77**
4.02	Temporal Pole	1.56	0.73**
0.54	Middle Temporal	1.53	0.72**
6.57	Putamen	1.73	0.77**
0.39	Pallidum	1.40	0.71**
0.04	Amygdala	1.20	0.67**

*small effect, ** medium effect, ***large effect

The results of the phonological comprehension t-maps reveal regions that have also been reported in all of the previous t-maps, and will be described in the following section, including the insula and superior temporal lobe. A small portion of this lesion involved the amygdala which, as stated, was not noted in any of the previous maps. Poor function of the amygdala has been associated with deficits in memory and emotion (Phelps, 2004). Areas typically seen in deficits of production including the supplementary motor area, precentral gyrus, and the rolandic operculum were also noted in this map. This inconsistency is likely a result of the small number of participants with low scores in phonological comprehension.

3.17. Common regions across t-maps

A region of the brain reported consistently across all t-maps was the superior temporal gyrus, the posterior portion of which is also known as Wernicke's area. This area, as mentioned previously, has long been associated with linguistic processing. However, recent literature on the superior temporal gyrus has concluded that it may also be involved in speech and non-speech perception (Gazzaniga, Ivry, & Mangun, 2002) as well as in production (Hickok & Poeppel, 2001). Lesions of the insula were also a consistent finding among all t-maps. This region is reported to be larger in the left hemisphere than the right, which implicates its role in language (Flynn, Benson, & Ardila, 1999). The current study will describe unique areas of the insula involved in each language measure of production that were made apparent in the masked maps. The pre-central gyrus, also known as the primary motor strip, was seen as a common area of lesion for measures of production. A lesion of the primary motor strip in deficits of production is possible because of the motor movements of the articulators essential for speech production. A small portion of the middle occipital lobe was noted in all lesions excluding semantic and phonologic comprehension. The middle occipital lobe has been correlated with object recognition in neuroimaging studies (Price, Moore, Humphreys, Frackowiak & Friston, 1996). A lesion to this area may impact patient performance on language tasks including object identification or picture description. Also regions of the inferior frontal gyrus were common to all measures; involvement of the frontal operculum will be discussed in detail in the following sections.

3.2. Two group analysis of double and single dissociations

The results of the double dissociations confirmed the findings for all the t-map analyses, except for the syntactic comprehension vs. syntactic production map. The double dissociation for syntactic comprehension vs. syntactic production reported structures that were not indicated in the t-maps. The double dissociation for syntactic comprehension vs. syntactic production did, however, provide consistent results in the group of participants with intact syntactic comprehension and poor syntactic production. The contradiction was seen in measures of syntactic comprehension. Dissociated structures included the opercularis, which was not seen at all in the t-map but was the largest area of the inferior frontal gyrus in the double dissociation, the precentral gyrus and Heschl's gyrus. The result of the contradictory double dissociation is actually more consistent with current literature and findings noted in the masked maps than results reported in the t-maps. This may be a result of the limited number of low-scoring participants on measures of comprehension.

A single dissociation analysis for all behaviors was conducted for additional confirmation of the findings of the t-map analysis. Scores could not be determined for comprehension measures. This demonstrated the insufficiency of these scores and warranted caution when interpreting the comprehension measures. The production measures confirmed the general findings of the previously reported maps. Table 7 presents each brain area identified in the single dissociations.

Table 7. Two group analysis of single dissociations (high scores vs. low scores for each behavior) with a threshold of 4 participants. The numbers of parentheses indicate t-values reported.

Syntax production	**Semantic production**	**Phonology production**
Precentral gyrus(33.01), superior frontal (1.36), middle frontal (18.20), opercularis (1.35) triangularis (11.31), orbitalis (1.95), rolandic (3.43), insula (12.06), middle occipital (6.02), postcentral gyrus (16.88), superior parietal (.19), inferior parietal (37.60), supra marginal (41.16), angular (35.21), heschl (12), superior temporal (13.98), superior temporal pole (4.82), middle temporal (13.98)	Precentral gyrus (.6), triangularis (.36), orbitalis (1.67), rolandic (1.11), insula (.05), occipital middle(5.87), postcentral gyrus (5.55), inferior parietal (11.12), supra marginal (17.44), angular (36.4), Heschl's (1.78), superior temporal (11.5), middle temporal (13.48)	Precentral gyrus (5.67), superior frontal (.22), middle frontal(9.44), opercularis (2.79), triangularis (4.31), orbitalis (.36), rolandic (.2), insula (5.97), middle occipital (5.78), postcentral gyrus (11.87), superior parietal (.19), inferior parietal (24.81), supra marginal (5.57), angular (17.31), putamen(3.87), heschl (.89), superior temporal (4.01), superior temporal pole(5.68) middle temporal (7.83)

3.3. Masking Maps

Relationships between t-maps were created using a method of masking that allowed researchers to isolate brain areas unique to each linguistic modality. These maps were created only for production measures due to the high performance of most patients on the comprehension measures. Seven maps were created: all production, semantics and phonology minus syntax, syntax and phonology minus semantics, syntax and semantics minus phonology, phonology alone, semantics alone, and syntax alone. Details of these maps are described below.

3.3.1. All Production tasks combined

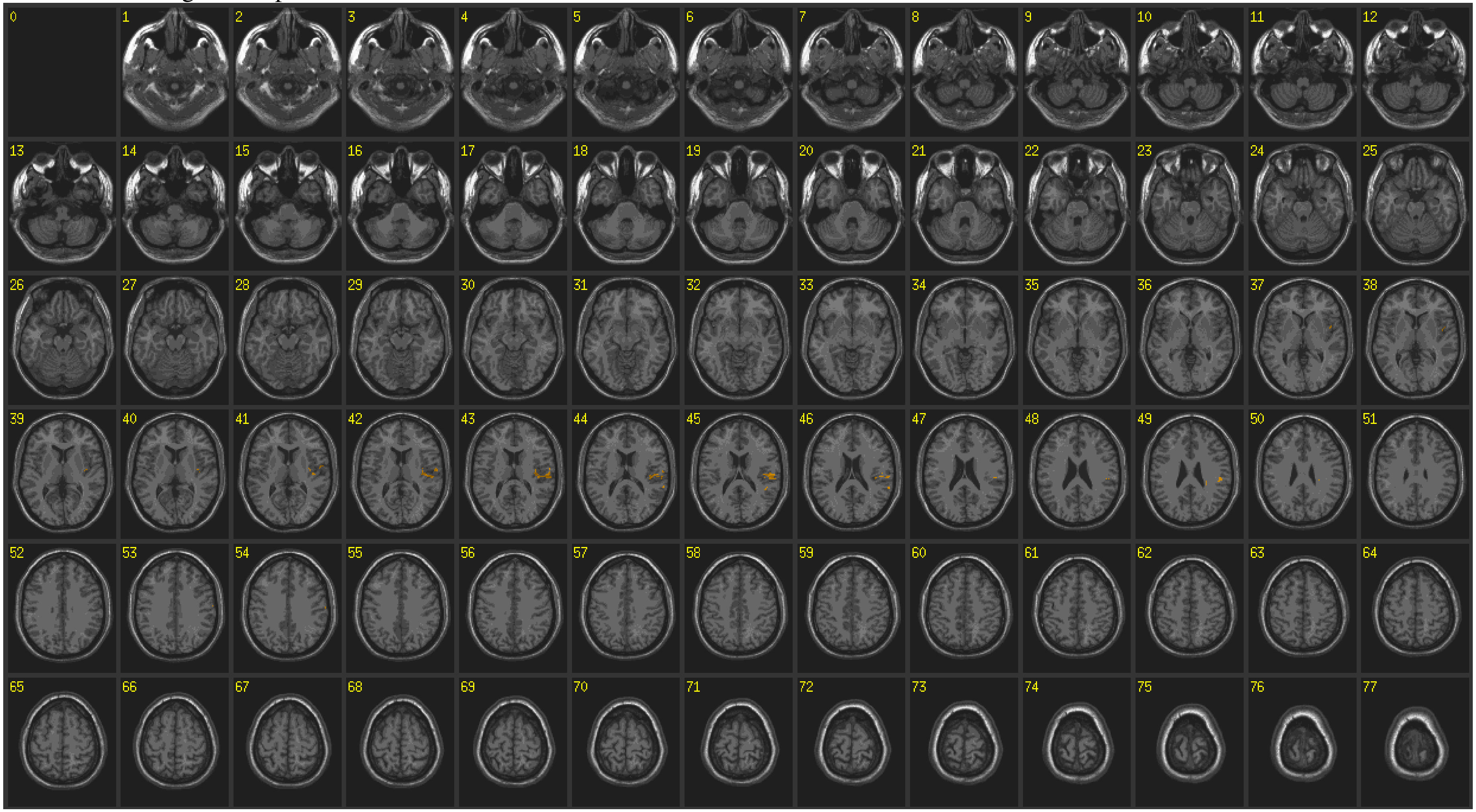
T-maps identifying deficits in the production of syntax, semantics and phonology were combined to determine common areas of lesion, as shown in Figure 2. According to the results, the planum temporale, located on the posterior and superior surface of the temporal lobe, was seen as a commonality in all of the production maps and, in contrast, was not observed in any maps involving language comprehension. The planum is thought to be part of Wernicke's area and involved in language comprehension and auditory processing (Meyer et al., 2005; Binder, Frost, Hammeke, Rao & Cox, 1996). The planum is reported to be asymmetrical in some people; a large postmortem study of 100 brains found that the planum is six times more likely to be larger in the left hemisphere than the right hemisphere (Geschwind & Levitsky, 1968). This fact has been of interest to researchers for many years. Asymmetry or lack thereof in the planum has also been associated with different disorders including dyslexia, autism, stuttering and schizophrenia (Chiarello, Lombardino, Kacinik, Otto & Leonard, 2006; Rojas, Camou, Reite & Rogers, 2005; Josse & Tzourio-Mazoyer, 2004; Foundas et al., 2004; Josse, Mazoyer, Crivello & Tzourio-Mazoyer, 2003; Eckert & Leonard, 2000; Shapleske, Rossell, Woodruff & David, 1999). However, the role of the planum in comprehension and production of language remains in question, although there is mounting evidence that supports the planum's role in language processing. Bushbaum et al. (2004) found the posterior planum, also referred to as the Sylvian-parietal temporal (Spt), to be active during both silent reading and speech perception and found support for the notion that this structure can be involved in ordinary speech production. This finding supports the fact that a lesion to the left temporoparietal region, such as those seen in the current study, can cause deficits in speech production, leaving speech perception relatively intact.

Recently, Hickok and Poeppel (2004) have suggested that the posterior planum temporale acts as an auditory-motor interface that transforms sound-based representations of speech in the auditory cortex to their articulatory counterparts in the frontal cortex. Several recent neuroimaging studies support the notion that the planum is involved in speech production (Herholz et al., 1996; Hickok et al., 2000; Price et al., 1996). These studies support our results that demonstrate involvement of the planum temporale in all production deficits. The lack of planum involvement in comprehension deficits in the present analysis may be a result of the limited number of participants with deficits in comprehension of semantics and phonology. Nonetheless, the planum temporale does appear to be a common lesioned area in participants with poor production scores across language categories.

The insula appeared to be the commonality across linguistic domains of production as well as comprehension, although as mentioned previously, generalization across measures of comprehension should be interpreted cautiously. The exact location of the deficits within the insula appears to be unique to the different linguistic categories. The areas common to all production deficits included the posterior insula. The posterior insula appeared to be common among lesions impacting both syntax and semantics. According to Flynn et al. (1999), the posterior insula is comprised of a “granular isocortical area which functionally is linked to somatomotor systems.” This link to the motor system supports the findings of the posterior insula in all production measures.

The final area common area to all production deficits included a small portion of the superior temporal gyrus. Interestingly, there was no common area of the frontal operculum involved in all production. However, unique areas were seen within each language category and will be discussed below.

Figure 2. All measures of production
Areas in orange correspond to the common area of lesion seen in these measures

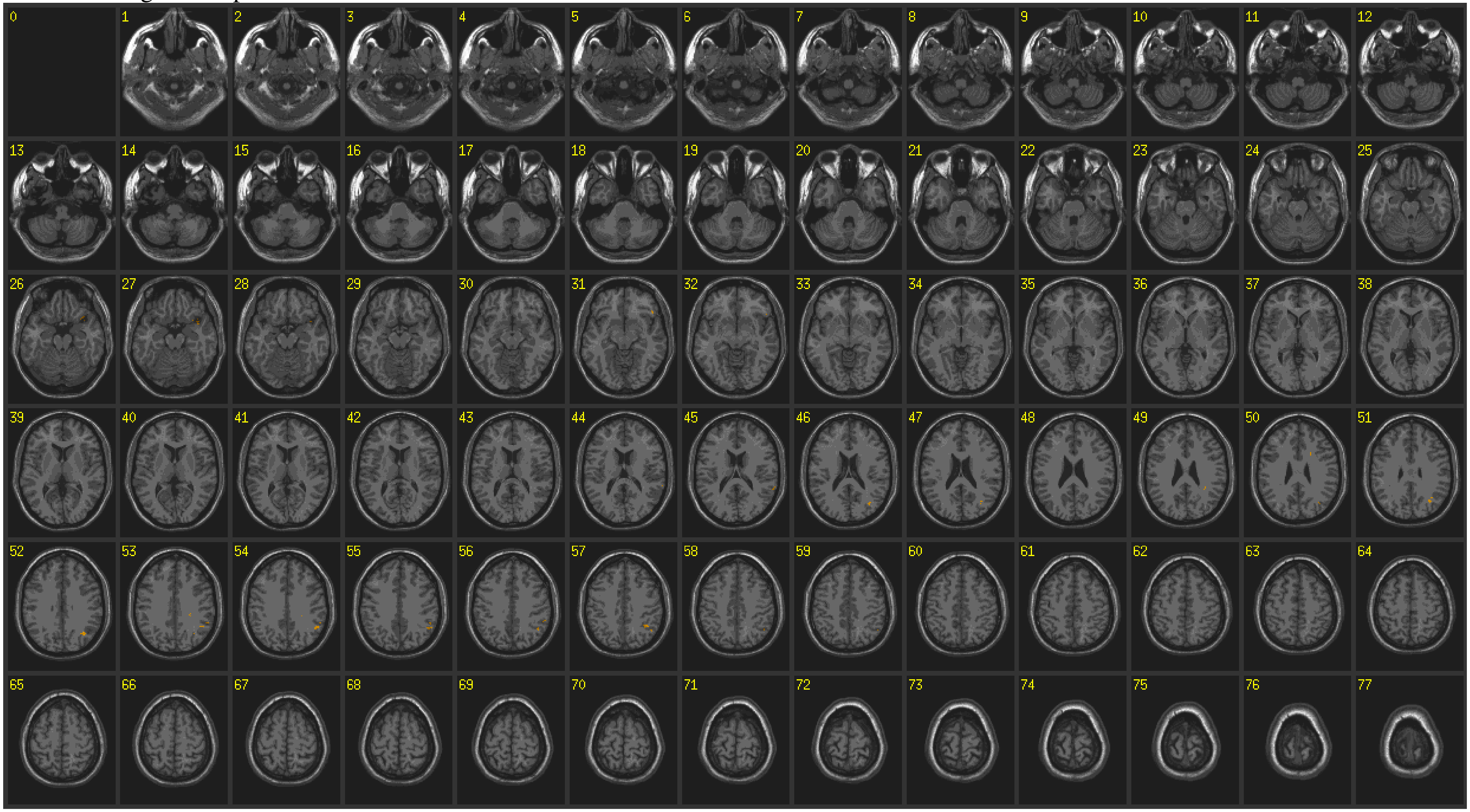


Areas of the planum temporal, insula, and small portion of the temporal lobe are common across measures of syntactic, semantic and phonologic production.

3.3.2. Semantics and phonology minus syntax

Brain maps of lesions involved in semantic and phonologic production were combined and brain areas involved in syntactic production deficits were subtracted out. The results are shown in Figure 3. As one might expect, the areas displayed were a small insignificant portions of the brain predominantly isolated to the parietal lobe and a small area of the temporal lobe. Martin (2003) reviewed the most recent neuroimaging literature and found that the left posterior temporal region is involved in linking semantic and phonological representations in word production, which may explain the posterior activation observed when analyzing semantics and phonology without syntax.

Figure 3. Semantic and phonologic production minus syntax
Areas in orange correspond to the common area of lesion seen in these measures

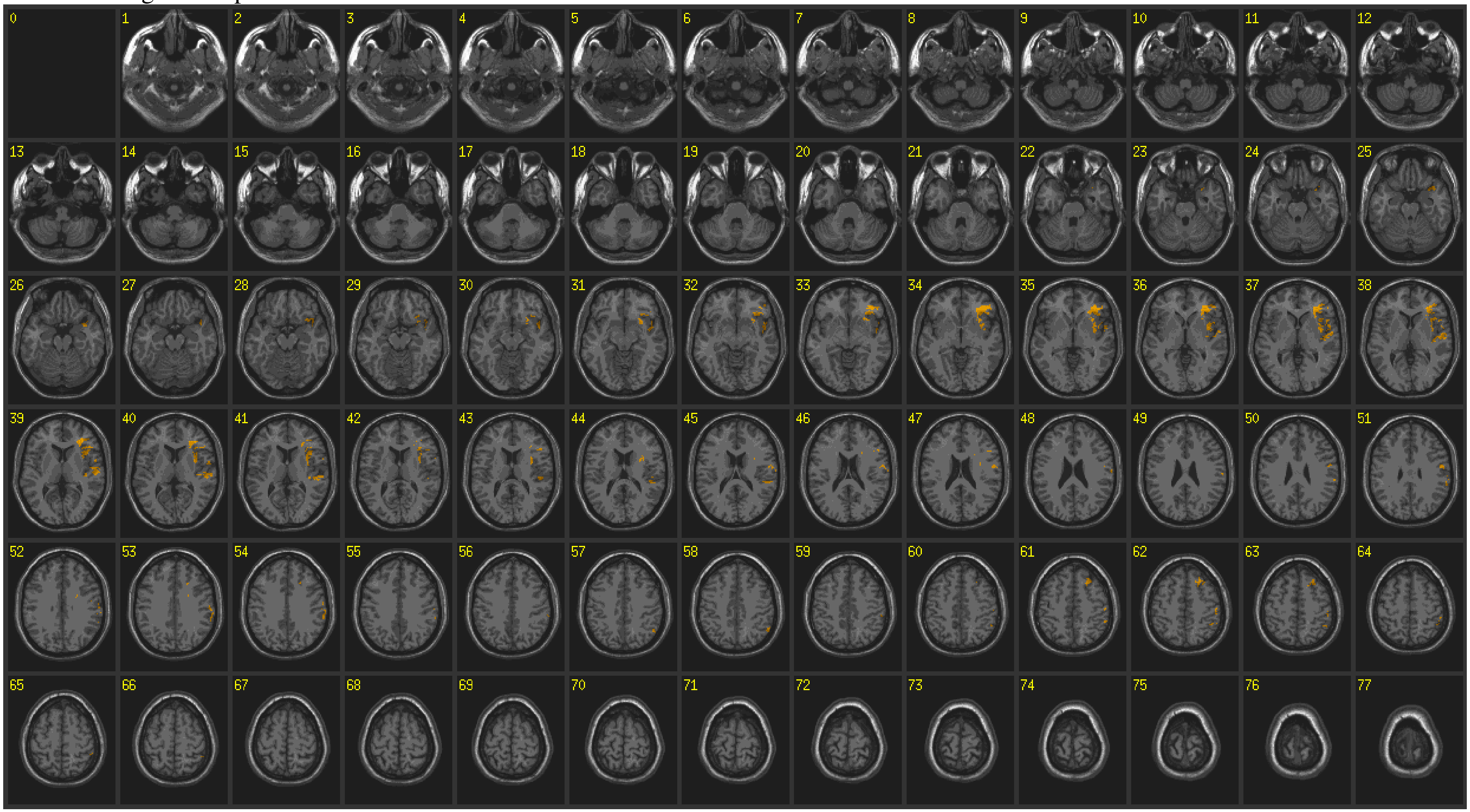


Only a small portion of the parietal lobe is common between semantics and phonology when syntax is subtracted (slices 44-57).

3.3.3. Syntax and phonology minus semantics

Maps of syntax and phonology production were combined and areas involved in semantic production were subtracted out, as shown in Figure 4. This map revealed a more anterior lesion. It incorporated a large portion of the anterior insula and the operculum, including the triangularis and opercularis and a small portion of the putamen. A small portion of the parietal cortex was also associated with these deficits. Results are consistent with findings that the opercularis and triangularis are active during syntactic and phonological processing (Bookheimer, 2002). The anterior insula has been associated with speech production in a number of recent functional neuroimaging studies (Fox et al., 2000, Wise, Greene, Buchel & Scott, 1999; Fiez & Petersen, 1998; Dronkers, 1996).

Figure 4. Syntactic and phonologic production minus semantics
Areas in orange correspond to the common area of lesion seen in these measures

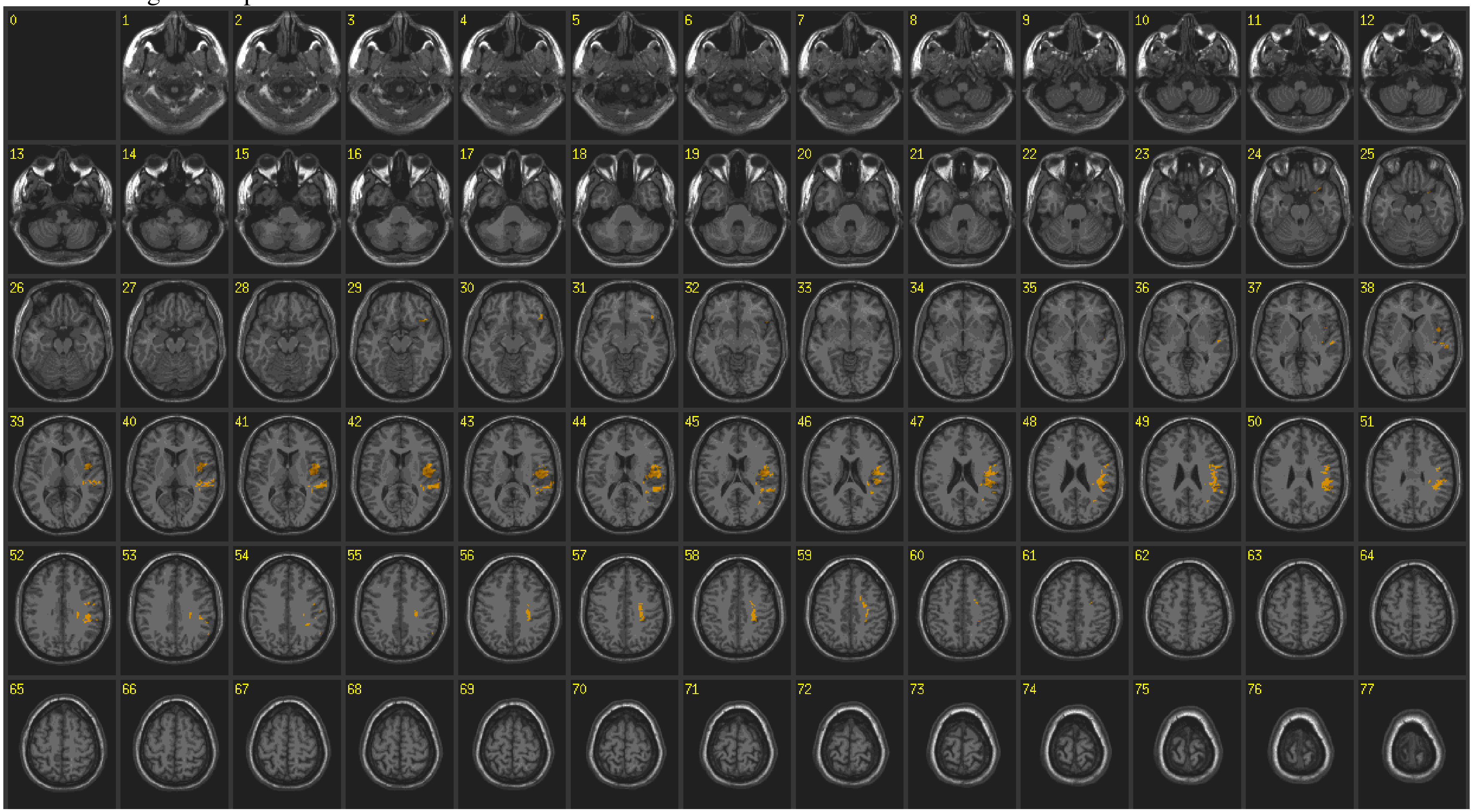


Areas common to syntactic and phonological deficits minus semantics are localized to a more anterior portion of the brain, including a large portion of the anterior insula and the operculum including the triangularis and opercularis and a small portion of the putamen.

3.3.4. Syntax and semantics minus phonology

A map that combined syntax and semantics and masked out phonology revealed predominately posterior lesion involvement, as shown in Figure 5. The map included the posterior insula, superior temporal and middle temporal lobe, supramarginal gyrus, portions of the parietal lobe, and superior longitudinal fasciculus. A small portion of anterior involvement was noted in the orbitalis, which has been associated with semantic processing (Bookheimer, 2002). The large quantity of temporal involvement reflects the inclusion of semantic measures.

Figure 4. Syntactic and semantic production minus phonology
Areas in orange correspond to the common area of lesion seen in these measures

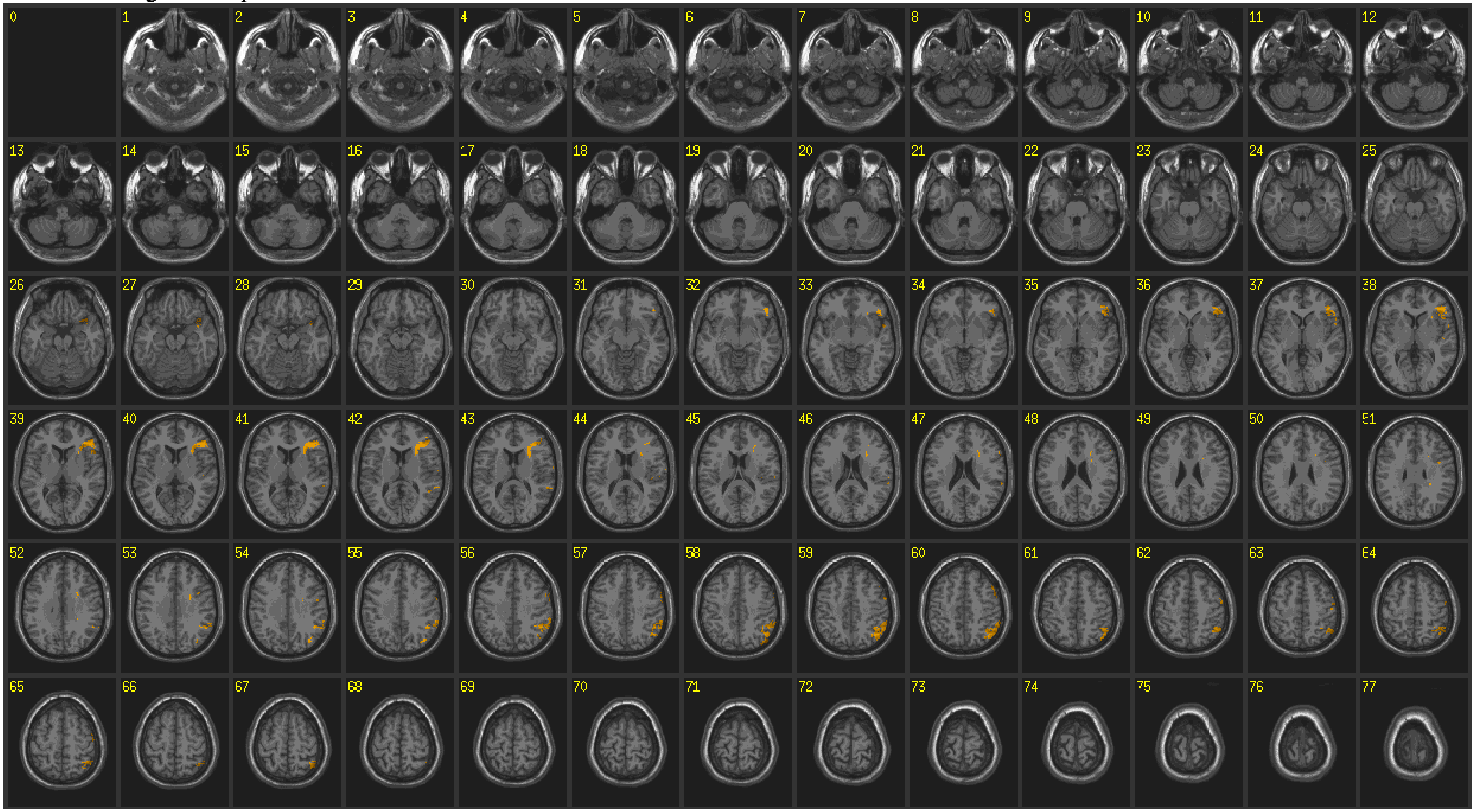


Regions common to syntax and semantics were generally located in the posterior aspects of the brain and included the posterior insula, superior temporal and middle temporal lobe, supramarginal gyrus, portions of the parietal lobe, superior longitudinal fasciculus and a small portion of the orbitalis.

3.3.5. Production of Phonology

Areas of lesioned brain identified in phonologic production deficits were combined and brain areas involved in production of syntax and semantics were subtracted from this map, as shown in Figure 6. Examination of the map revealed involvement of primarily the frontal and parietal lobes with very limited temporal association. This limited temporal involvement is noted because lesions of the temporal lobe are shared between semantics and phonology. Specifically, the opercularis and triangularis and some anterior insular involvement were seen in the frontal lobe and superior and middle parietal association in the more posterior aspect of the brain. According to a review of fifty-eight neuroimaging studies by Indefrey and Levelt (2000) that used a variety of tasks involving speech production, it was found that sub-lexical phonological coding (i.e. non-word repetition) was associated with regions of the left posterior inferior frontal gyrus and the left mid-superior temporal gyrus. The findings of limited temporal involvement in the current study are due in part to the subtraction of areas involved in semantics, which includes a large area of the temporal lobe. Several paradigms targeting phonological processing have demonstrated posterior inferior frontal gyrus activity in the region of the opercularis (Friederici, Optiz & Von Cramon, 2000; Zatorre, Meyer, Gjedde & Evans, 1996; Demonet, Chollet, Ramsay, Cardebat & Nespoulous, 1992). Interestingly, the opercularis and parietal lobe have also been noted to be active during imitative motor tasks (Iacaboni et al., 1999). Although the study did not target speech repetition, it is in fact an imitative motor task.

Figure 6. Phonological production minus syntax and semantics
Areas in orange correspond to the common area of lesion seen in these measures



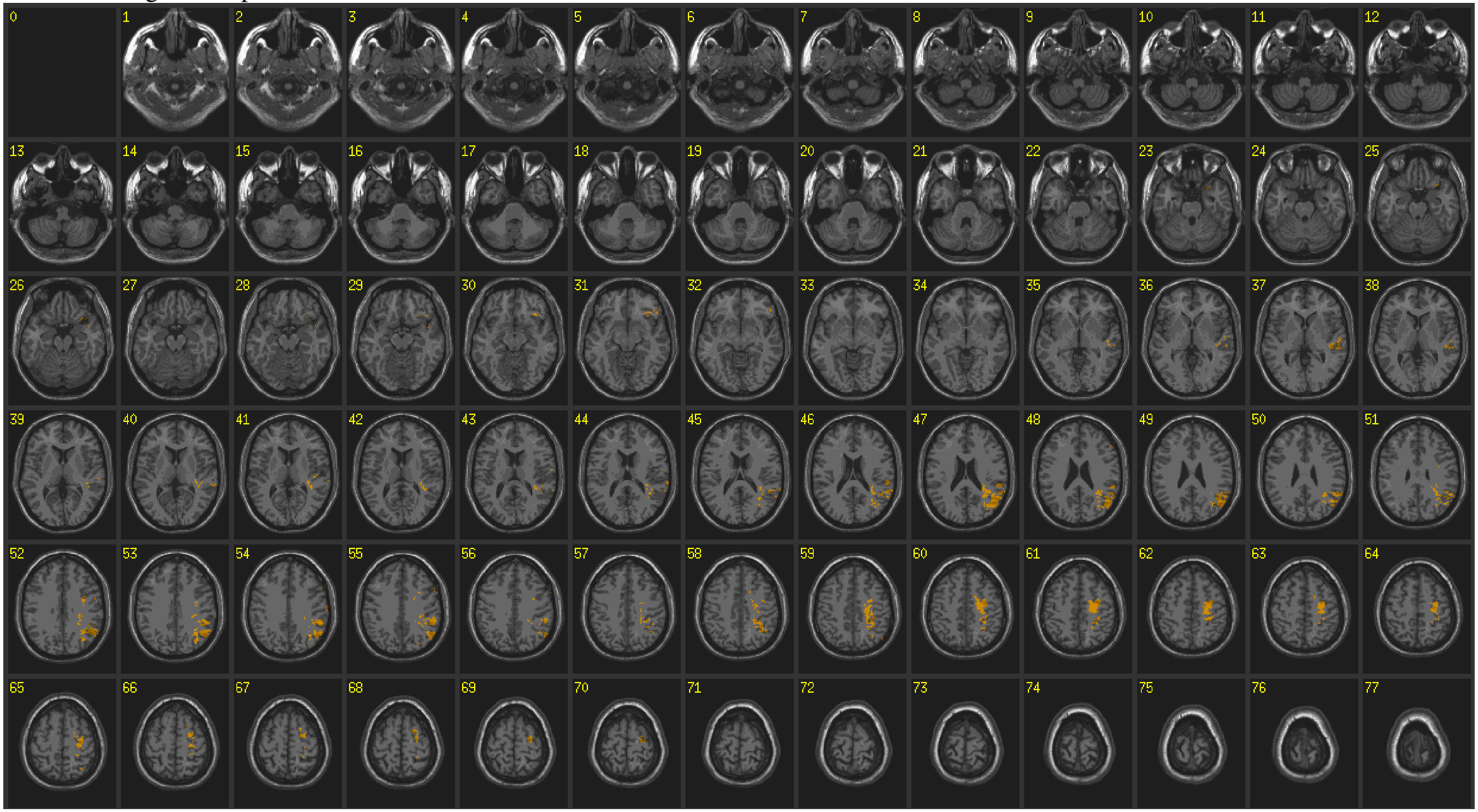
Regions associated with phonology alone consist of the frontal and parietal lobes including the opercularis, triangularis, anterior insular, and the superior and middle portions of the parietal lobe.

3.3.6. Production of Semantics

A map was created to isolate semantic production; areas identified in syntax and phonology were excluded, as shown in Figure 7. Lesions involved in only semantic deficits revealed more posterior involvement including the temporal parietal lobe and the superior longitudinal fasciculus with a small amount of anterior insular association and a small portion of the posterior insula. A small portion of the operculum was also involved, specifically the orbitalis.

These findings are consistent with the current thought that both the temporal lobe and the inferior frontal gyrus are both critical parts of the semantic system involving storage and retrieval of semantic information (Noppeney et al., 2004; Fiez, 1997; Thompson-Schill, D'Esposito, Aquirre, & Farah, 1997). The orbitalis has also been associated with the semantic system. According to Bookheimer (2002), the anterior inferior frontal gyrus, specifically the junction between the pars triangularis and the pars orbitalis, has been consistently identified as playing a role in semantic processing. Bookheimer (2002) concludes that this region appears to be important for executive aspects of semantic processing that involve semantic working memory, directing semantic search, or drawing comparisons between semantic concepts in working memory.

Figure 7. Semantic production minus syntax and phonology
Areas in orange correspond to the common area of lesion seen in these measures

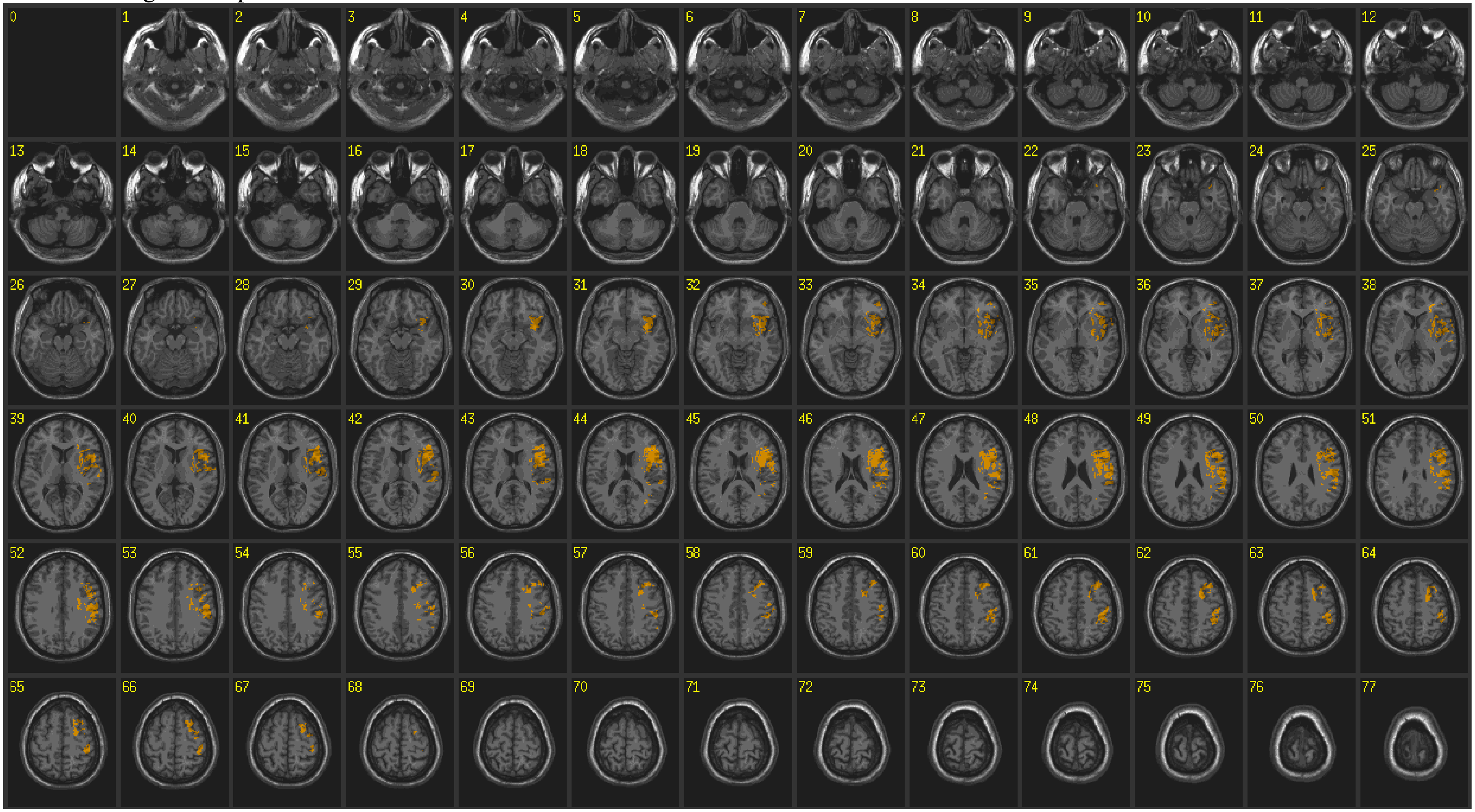


A more posterior portion of the brain was seen in deficits of semantics alone including the temporal parietal lobe and the superior longitudinal fasciculus with a small amount of the posterior insula and orbitalis.

3.3.7 Production of Syntax

Lesions contributing to syntactic production deficits were isolated, excluding areas involved in semantics and phonology, as shown in Figure 8. Results revealed common lesions of the putamen, anterior insula, portions of the parietal and temporal lobe and the operculum including the opercularis, orbitalis, and most significantly the triangularis. There was also some white matter involvement. In general, lesions contributing to syntactic deficits were more diffuse. Supporting the idea that syntactic production is not confined to one particular region of the brain but a network of structures. According to a review by Gernsbacher and Kaschak (2003), the processing of sentences involves Wernicke's area, superior and middle temporal regions, Broca's area, inferior frontal gyrus, middle and superior frontal regions and some right hemisphere involvement of the homologues areas. Several studies have also demonstrated evidence of basal ganglia involvement in syntactic processing (Friederici & Kotz, 2003; Kotz, Frisch, Von Cramon, & Frederici, 2003). The triangularis was the most significant part of the operculum that contributed to syntactic deficits, which is consistent with recent neuroimaging literature (Bookheimer, 2002).

Figure 8. Syntactic production minus semantics and phonology
Areas in orange correspond to the common area of lesion seen in these measures



A diffuse area of involvement was observed in regions of syntax alone including the putamen, anterior insula, portions of the parietal and temporal lobe and the operculum including the opercularis, orbitalis, and most significantly the triangularis.

Chapter 4: CONCLUSIONS AND DIRECTIONS FOR FUTURE RESEARCH

The purpose of this study was to identify brain lesions that contribute to deficits in syntax, semantics and phonology. The results provided evidence for five key neuroanatomical regions of interest. These include the insula, the planum temporale, the operculum, the temporoparietal occipital (TPO) junction, and the putamen. Our results revealed common as well as unique areas of brain lesion for each of the behaviors.

4.1 Insula

Analysis of brain lesions revealed the insula as a region of interest. For the purpose of reference, the insula is identified in Figure 9.

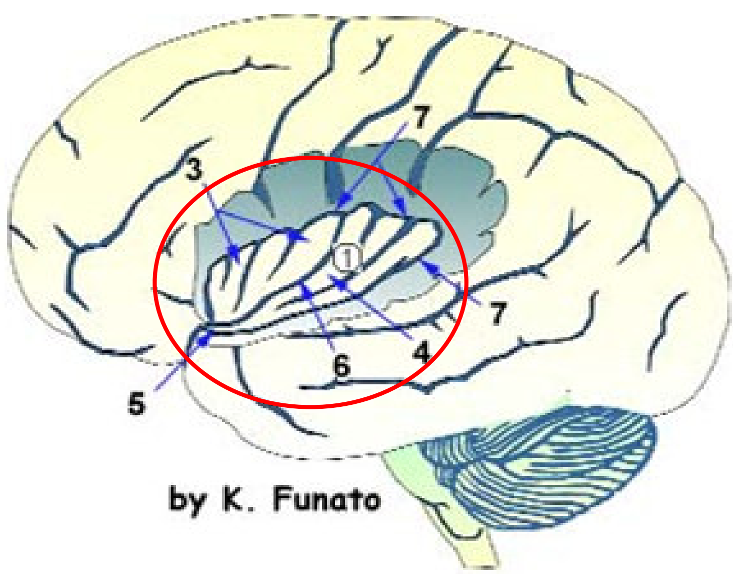


Figure 9. The frontal and temporal lobe are pulled back at the sylvian fissure to reveal the insula.

The insula was allocated as a diffuse area of involvement in both comprehension and production measures across linguistic modalities. However, the focus is on insular association with deficits of production as a result of the small subject number for comprehension measures. The insular region of the left hemisphere is larger than that of the right, which has led researchers to suggest its role in language (Flynn et al., 1999). The Mohr et al. (1978) study evaluated lesions of twenty directly observed cases, twenty years of autopsy records from the Massachusetts General Hospital, and published cases since 1820. They found that Broca's aphasia does not occur with cortical lesions confined to Broca's area alone. The results of this study revealed portions of the insula that were correlated with deficits in each linguistic modality. It was found that portions of the posterior insula adjacent to the planum temporale were commonly lesioned across all measures of production. The anterior insula was commonly lesioned in participants with deficits in syntax and phonological production, whereas masked maps of syntax and semantics revealed a more posterior portion of insular involvement. Syntax alone was associated with a large diffuse area of the insula involving both the posterior and anterior insula. The anterior insula has been reported in several studies to be associated with speech production deficits (Bates *et al*., 2003; Dronkers, 1996) and is thought to be involved in motor coordination of speech-related movements (Ackermann & Riecker, 2004). It has also been found that a lesion of the anterior insula was predictive of low mean length of utterance (MLU) and type token ratio (TTR) (Borovsky, Saygin, Bates, & Dronkers, 2007). These deficits are suggestive of deficiencies in syntactic production, which are consistent with the current findings. A study by Caplan, Alpert, Waters, and Olivieri (2000) attempted to isolate syntactic processing from articulation by having subjects repeat the word 'double' during the syntactic comprehension task; this yielded activation of the anterior part of Broca's area. Nestor et al. (2003) proposed that, based on the role of the insula in motor articulatory planning (independent of syntactic processing), this shift in activation suggests a transition in the left frontal/insular network from more anterior involvement in syntactic processing to a more posterior role for motor articulation. This hypothesis is consistent with the findings of a common posterior insular involvement in all production measures, possibly due to the role of articulation in all production measures, with an anterior association in syntactic processing.

The posterior insula was also involved in lesions associated with semantics alone. This corresponds to an overall posterior lesion seen in semantic deficits throughout the study. A study by Ojemann and Whitaker (1978) supports the findings of the current study of semantic deficits in the posterior insula. They produced transient anomia through electrical stimulation of the posterior insula. It has also been found that there are fewer cortical connections between the posterior insula and the frontal lobe than the anterior insula and the posterior insula appears to have more connectivity with the parietal lobe (Flynn et. al., 1999).

Deficits of phonology alone exhibited a more anterior lesion in the insula. Wise et al. (1999) have found that the anterior insular cortex contributes to phonological production during repetition tasks. This may explain why deficits in phonological production assessed using repetition tasks reveal common lesions of the anterior insula.

The exact function of the insula is still a highly debated question in our understanding of the brain and language. These findings are consistent with current research on the key role of the insula in speech production. Future research continuing to investigate the function of the anterior versus the posterior insula would be of considerable interest.

4.2 Planum temporale

Analysis of brain lesions revealed the planum temporale as a region of interest. For the purpose of reference, the planum temporale is identified in Figure 10.

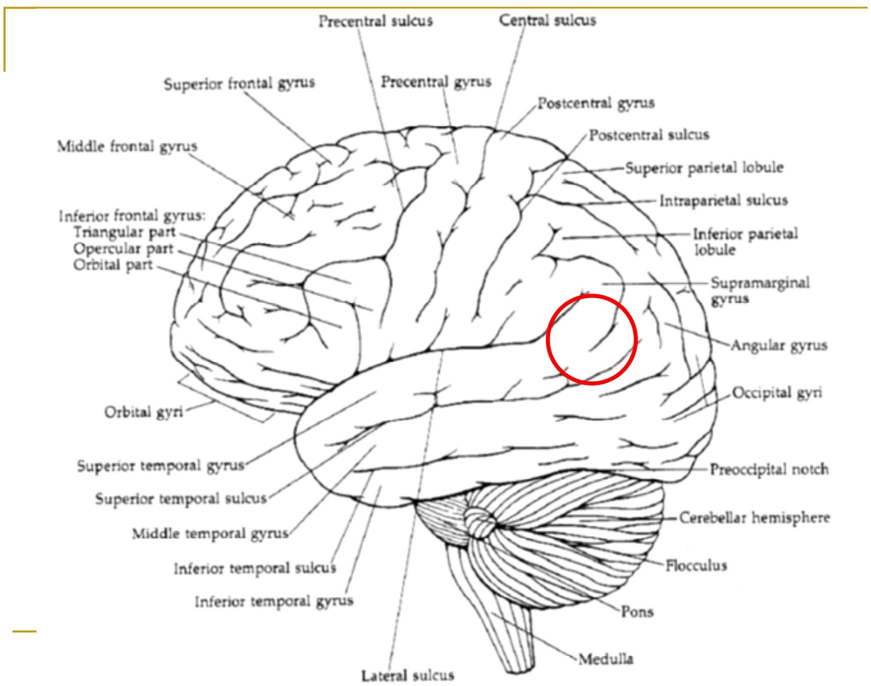


Figure 10. The planum was identified as a region of interest and is located in the posterior superior portion of the temporal lobe.

The second key region of interest was the planum temporale, which was a common area of lesion in all production deficits. As mentioned previously, the planum was originally thought to be apart of Wernicke's area but its exact function is still a topic of debate. The finding of planum involvement in production deficits has been supported by several current neuroimaging studies (Herholz et al., 1996; Hickok et al., 2000; Price et al., 1996). It is also interesting that the planum is asymmetrical in patients with other types of production deficits such as stuttering, autism, and dyslexia (Chiarello et al., 2006; Rojas et al., 2005; Foundas et al., 2004). This may imply that this area of the brain is a critical part of language production and a deficit in this area, be it congenital or acquired, significantly impacts the ability to generate language. It would be of interest to use fMRI to see the role of the planum during all aspects of language production in normal volunteers.

4.3 Operculum (Inferior Frontal Gyrus)

Analysis of brain lesions revealed the operculum as a region of interest. For the purpose of reference, the operculum is identified in Figure 11.

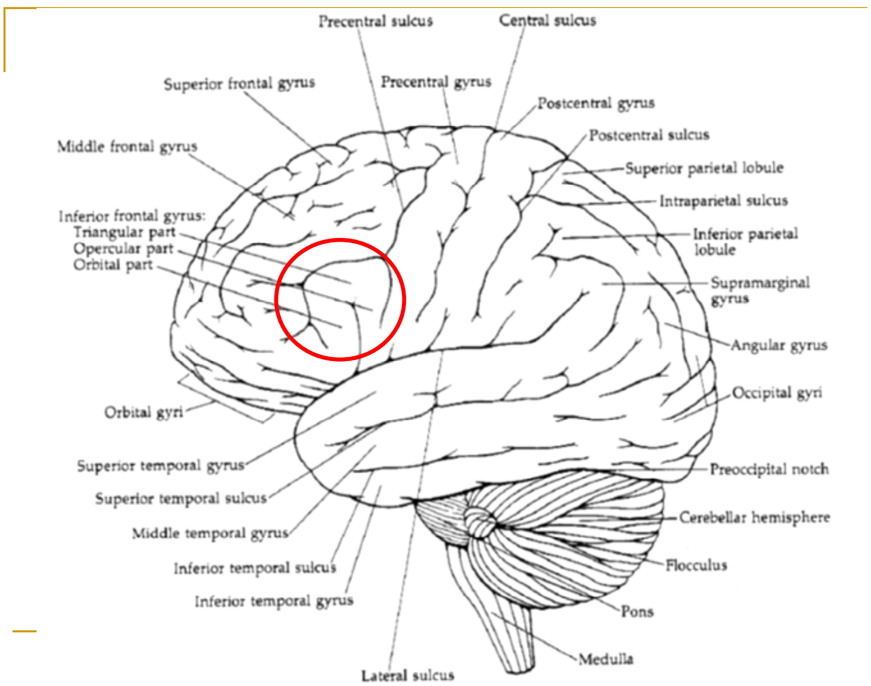


Figure 11. The operculum is divided into three sections the triangularis, opercularis and orbitalis. The operculum was identified as a key region of interest.

The individual areas of the operculum and their relationship to language deficits are the third key finding in this study. Lesions to this area have been known to produce a wide range of deficits, collectively known as Broca's aphasia. The results are consistent with recent fMRI research that has identified at least three separate regions of specialization within the inferior frontal gyrus separate from those predominantly involved in motor speech. These are syntax, semantics and phonology (Petersen et al., 1988). The results revealed that there was no common area of the operculum found in all the production measures and are consistent with Bookheimer (2002) that identified distinct portions of the operculum correlated with each linguistic domain.

The opercularis and some portions of the triangularis were associated with syntactic deficits. This finding is consistent with a study done by Friederici et al. (2000), who assessed the processing of sentences void of semantic information called "Jabberwocky" sentences, word strings containing only function words and non-words, in comparison to normal sentences. They found that Jabberwocky sentences and normal sentences both activated the temporal lobe, but the Jabberwocky sentences produced additional activation in Broadmann Area (BA) 44, also known as the pars opercularis. They suggest that this area is specific not simply for syntax, but for increased selective attention to syntactic structure. A study by Dapretto and Bookheimer (1999) contrasted syntactic and semantic aspects of sentence processing. They found that the superior portion of BA 45, also known as the triangularis, demonstrated increased activation for the syntactic condition alone. The aforementioned studies identified brain areas associated with syntactic processing, whereas the results of the current study were based on syntactic production deficits. These similar findings may be because the areas involved in semantic and phonologic production were subtracted out. These results may represent a more isolated syntactic processing deficit when other brain areas involved in production are removed from analysis.

A small portion of the operculum was associated with semantics alone, including a portion of the orbitalis and a small area of the triangularis. The orbitalis was also seen in the map that isolated syntax and semantics and masked out phonology. This is consistent with a literature review by Bookheimer (2002) that found BA 47 (also known as the orbitalis or anterior inferior frontal gyrus) to be involved in some aspects of semantic processing. According to the review, executive function elements of semantics appear to be localized to this area such as semantic working memory, directing semantic search or drawing comparisons between semantic concepts. If this is accurate, a lesion to this area of the brain could manifest as a deficit in picture naming secondary to a reduced capacity to direct the semantic search. Studies directly assessing deficits in word generation have also been linked to the orbitalis (Gurd et al., 2002; Martin, Haxby, Lalonde, Wiggs, & Ungerleider, 1995). These findings provide further evidence for the role of the orbitalis in semantic production.

Deficits in phonology production revealed associated lesions in a large portion of the operculum, specifically the triangularis and opercularis. Phonology and syntax minus semantics revealed a similar area of involvement; however, the lesion was more ventral. A deficit in phonology alone, in comparison, is associated with lesions that extend more dorsally than those seen in the common map of syntax and phonology and involves more of the triangularis. There have been several studies using non-words to study aspects of phonological processing (including syllable counting, rhyme judgment and silent reading) that have all found activity in the left inferior frontal gyrus (Herbster, Mintun, Nebes, & Becker, 1997; Poldrack et al., 1999; Pugh et al., 1996). The finding of opercularis and triangularis (BA44/45) involvement in phonology is consistent with several recent neuroimaging studies (Demonet et al., 1992; Paulesu et al., 1993; Zatorre et al., 1996). Poldrack et al. (1999) found greater activation in this area during the phonological processing of pseudo-words than real words. This higher activation in the posterior dorsal portion of the operculum was also seen to be more active during pseudo-word repetition versus verb generation (Warburton et al., 1996). These studies support our results and suggest that the triangularis and opercularis may contribute to phonological production deficits, specifically non-word repetition.

The inferior frontal gyrus has been associated with language production since the times of Broca. The association of distinct portions of the operculum with syntax semantics and phonology is a more recent development. The findings of this study confirm the current belief that syntax is generally associated with the opercularis, semantics with the orbitalis and phonology with the triangularis (Bookheimer, 2002). Although some overlap of the triangularis and opercularis are seen in deficits of phonology and syntax, the exact function of the inferior frontal gyrus within these specific linguistic modalities is still in question. Does this area act as a more executive control center or does it provide a more specific link to memory and attention or some other aspect of language production? Continued studies on the exact role of the inferior frontal gyrus in each aspect of syntax, semantics and phonology would be of considerable interest in future research.

4.4 Temproparietal occipital junction

Analysis of brain lesions revealed the TPO junction as a region of interest. For the purpose of reference, the TPO junction is identified in Figure 12.

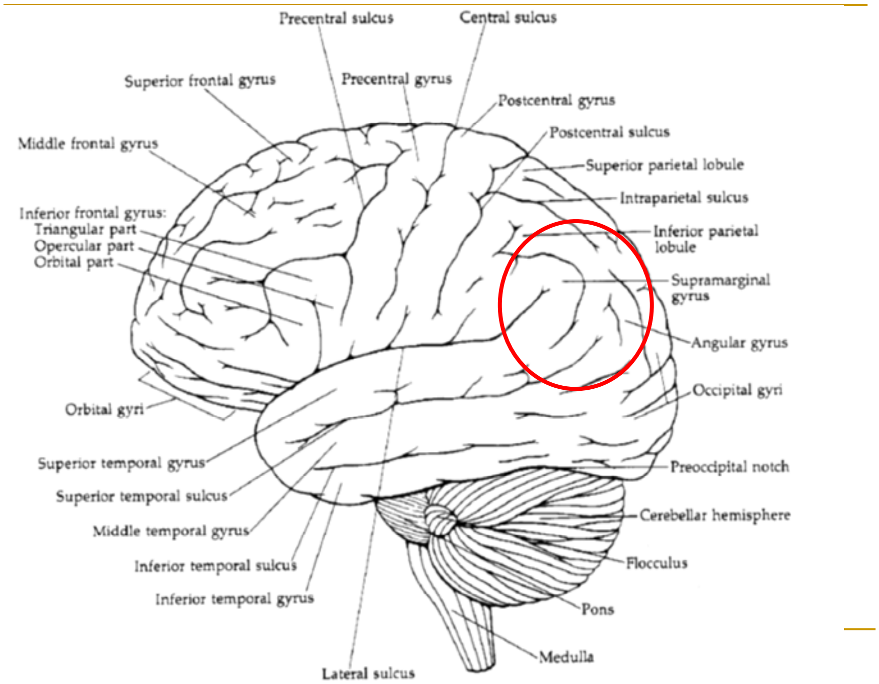


Figure 12. The TPO junction was identified as a region of interest. It includes the angular gyrus, supramarginal gyrus and the inferior parietal lobule.

The fourth key area of interest is the TPO junction, including the angular gyrus and supramarginal gyrus which were both implicated predominantly in lesions of semantic production. The angular gyrus is part of the inferior parietal lobule. It is an association area that acts as a way station between the primary sensory modalities and the speech areas (Geschwind, 1965). Geschwind (1965) also hypothesized that this area is involved in semantic processing, including the assimilation and creation of cross modal associations allowing for higher order associations. This increases the capacity for organization, labeling, and multiple categorization of sensory-motor and conceptual events, essentially extracting meaning from stimuli across sensory modalities. Object naming, which was used in the current study to assess semantic production, depends on these associations between sensory modalities and speech. This explains why a lesion to this area may contribute to a deficit in picture naming. The angular gyrus has been associated with anomia, which describes severe word-finding and confrontational-naming difficulty (Bennett & Hacker, 2006). This suggests that this region may play a role in lexical selection (associating the concept or object in the picture with the corresponding noun or verb). The angular gyrus has been associated with semantic production in other recent neuroimaging studies as well (Borovsky et al., 2007). Lesions of the TPO junction have been linked with transcortical sensory aphasia (poor comprehension with intact repetition) (Kertesz, Sheppard, & McKenzie, 1982). Intact repetition in this instance may explain why the TPO junction was not seen in lesions associated with deficits in phonology. Unlike semantics, deficits in phonology were associated with parietal lesions more dorsal to the TPO junction including the superior parietal lobule and the supramarginal gyrus.

4.5 Putamen

Analysis of brain lesions revealed the putamen as a region of interest. For the purpose of reference, the putamen is identified in Figure 13.

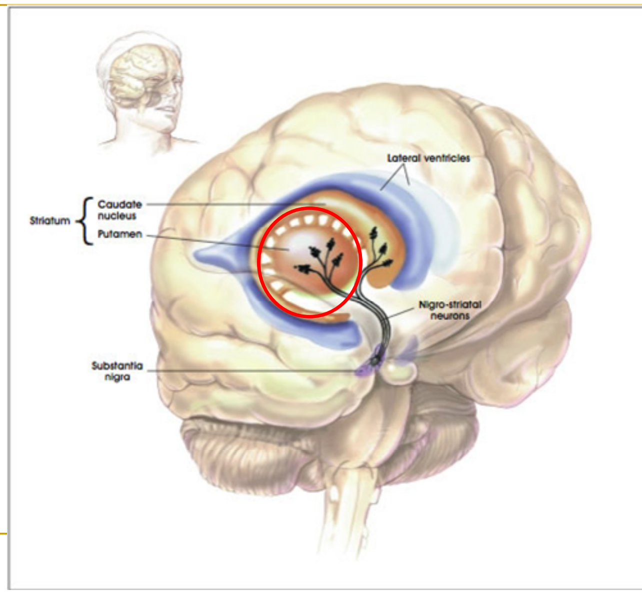


Figure 13. The putamen was the only subcortical structure identified as a key region of interest. It is a portion of the basal ganglia.

The final area that was of interest during our study was the putamen, which is a portion of the basal ganglia. The role of the putamen in language remains poorly understood. The current study found the putamen to be a common area of lesion between syntactic and phonologic production deficits. A portion of the putamen was also selectively associated with deficits in syntactic production measures alone. A study by Alexander, Naeser, and Palumbo (1987) reviewed 19 cases of aphasia and found that damage to the subcortical structures including the putamen resulted in speech production deficits and agrammatism. A study of bilateral damage to the putamen and part of the caudate nucleus revealed similar findings in the distinction of meaning conveyed by syntax (Pickett, Kuniholm, Protopapas, Friedman, & Lieberman, 1998). The putamen has also been associated with syntactic production in bilinguals (Golestani et al., 2006).

Lesions of the putamen have been associated with sparse language output and impaired articulation. Robles, Gatignol, Capelle, Mitchell & Duffau (2005) directly stimulated the putamen during surgery in patients with brain tumors and found that direct stimulation resulted in anarthria (loss of motor abilities that enable speech). This motor speech connection is consistent with the involvement of the putamen in lesions resulting in deficits in production. Greater activation in the putamen has been correlated with faster phonological processing (Tettamanti et al., 2005). A study using diffusion tensor imaging recently showed that the putamen is primarily connected to motor and pre-motor regions as well as posterior regions of the prefrontal cortex (Lehericy et al., 2004). These posterior regions of the frontal cortex have been associated with phonological processing and articulatory control (Poldrack et al., 1999). A study by Klein, Zatorre, Milner, Meyer & Evans (1994) found that this region was involved during overt word repetition in the second language compared to the first language in bilingual individuals, which further demonstrates the role of the putamen in phonology production as seen in the current study. The common link in all these studies is the involvement of the putamen in sequencing. Sequencing is necessary for syntactic construction, repetition, and faster phonological processing. The correlation of the putamen with sequencing, may account for lesions of this subcortical structure in patients with syntactic and phonologic deficits. Functions of deeper cortical structures and their role in language are an area of interest for future research.

Summary

The hypothesis was confirmed that deficits of production have common areas of lesion including the frontal lobe and the insula. When these lesions are correlated with impairments in syntax, semantics and phonology, other specific structures were identified. Syntax was impaired displaying diffuse lesions corresponding to frontal, temporal and parietal areas. Lesions correlated with semantics are generally involved in the more posterior aspect of the brain, including the TPO junction. Finally, deficits of phonology were associated with more anterior lesions which involved the frontal lobe. Phonological deficits were also associated with posterior lesions in a dorsal portion of the parietal lobe above the TPO junction.

This study begins to answer some of the questions that have been proposed in the hypothesis, it is understood that based on the nature of analyzing lesioned brains, not all areas that contribute to linguistic deficits in syntax, semantics and phonology can be identified. Areas typically recruited in “normal” language may be different from those “necessary” for that process. This study reveals what those “necessary” areas are (within the limits of the tasks used). Neuroimaging reveals what the typical areas are and can be compared to the current study to further our knowledge of the brain language relationship. The hope is to contribute to the understanding of specific brain areas that, when lesioned in the aphasic brain, selectively contribute to deficits in the linguistic domains of syntax, semantics and phonology.

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