Neuropsychological and functional magnetic resonance imaging investigations of anterior temporal lobe language function in patients with epilepsy. A pilot study.

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ABSTRACT

The anterior temporal lobe (ATL) sustains a degree of damage during surgery for temporal lobe epilepsy (TLE), and although classical language models implicate the ATL in language function, and naming difficulties are commonly reported by TLE patients post-surgically, the role of the ATL in language is not well understood. The present study aimed to examine the role of the ATL in language function, and methods for evaluating pre- and post-surgical language function of the ATL in patients with epilepsy using two approaches. The first study employed neuropsychological testing of pre-and post-surgical TLE patients on 3 conventional tests of language function, the Boston Naming Test (BNT), Controlled Oral Word Association Test (COWAT) and Animal Fluency, and one novel test: The Category Specific Names Test (CSNT). The CSNT was selected in an attempt to compensate for the problems of heterogeneous items, and the low ceiling in the BNT. Results of the CSNT had not been previously validated with TLE patients, and had not been routinely used in Australia. The second study looked at ATL activation in healthy controls and TLE patients using two new functional magnetic resonance imaging (fMRI) tasks. For the neuropsychological study, Bayesian analysis showed that the BNT was effective in differentiating left from right TLE in a sample of 42 patients with intractable epilepsy (LR+ = 8.37). The COWAT, Animal Fluency and the CSNT were not effective in differentiating left from right TLE. Very small likelihood ratios indicated only modest changes from pre-test odds. For the fMRI component of the study, although the two new fMRI tasks (Famous Faces naming, and Sentence Reading) resulted in the expected activation of language areas in group averaged data, they did not elicit consistent ATL activation across individuals, and subsequently did not meet the

criteria recommended for fMRI protocol development recommended by Schwartz, Devinsky, Doyle and Perrine. (1997). Their inclusion in an fMRI protocol was not supported.

Findings of the present study have important implications for pre-surgical evaluation of ATL language function in patients with epilepsy. Preliminary evidence was not found to support the use of the CSNT in patients with epilepsy. Results suggest that the BNT alone should be used for detecting naming impairment in patients with left-sided epilepsy. Benefits of using Bayesian analysis to examine the clinical applicability of research results, rather than conventional Null Hypothesis Significance Testing (parameter statistical) techniques are discussed.

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"I, Nancy Salton, declare that the Doctor of Psychology (Clinical Neuropsychology) thesis entitled Neuropsychological and Functional Magnetic Resonance Imaging Investigations of Anterior Temporal Lobe Language Function in Patients with Epilepsy. A Pilot Study is no more than 40,000 words in length including quotes and exclusive of tables, figures, appendices, bibliography, references and footnotes. This thesis contains no material that has been submitted previously, in whole or in part, for the award of any other academic degree or diploma. Except where otherwise indicated, this thesis is my own work".

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CHAPTER 1

Neuropsychological and Functional Magnetic Resonance Imaging Investigations of Anterior Temporal Lobe Language Function in Patients with Epilepsy. A Pilot Study.

General Introduction

Anterior temporal lobe epilepsy surgery is performed in patients with intractable temporal lobe epilepsy (TLE). Following surgery it is common for these patients to experience transient, and occasionally more chronic, language difficulties (Saykin et al,1992). As surgical entry to the temporal lobe is gained via the Anterior Temporal Lobe (ATL) which subsequently sustains a certain degree of damage, the role of this region in language function and methods for evaluating pre- and post-surgical language function of the ATL are the focus of the present study (Saykin et al, 1992). Pre-surgical evaluation aims to reduce the risk of post-surgical language difficulties by using neuropsychological assessment to characterize cognitive functioning, identify difficulties and concerns, and to provide support in terms of strategies and recommendations. A pre-surgical evaluation typically includes neuropsychological assessment to establish baseline functioning of cognitive functioning, mood and personality, electroencephalogram (EEG), magnetic resonance imaging (MRI), positron emission tomography (PET), single photon emission computed tomography (SPECT), and occasionally other methods, such as Wada, grids, cortical stimulation, and functional magnetic resonance imaging (fMRI). Neurosurgical, neurological and neuropsychological reviews are conducted after surgery to identify any post-surgical changes in functioning including seizure status, ongoing

needs for medications, and any changes in memory, language, mood, or other areas of cognition.

Functional imaging studies have identified higher levels of ATL activation in language tasks in patients with early onset TLE (Devinsky, Perrine, Llinas, & Luciano, 1993), and specifically during the retrieval of facial names (Reinkemeier, Markowitsch, Rauch, & Kessler, 1997; Seidenberg, et al., 2002; Tsukiura et al., 2002) and sentence reading (Bavelier et al., 1997). Similar results have also been identified in fronto-temporal dementia and cross-modal familiar person agnosia (Sperber & Hans, 2003) and also in a case involving left temporal infarct (Reinkemeier et al., 1997). It is evident from fMRI studies that the ATL region is potentially an important language area, particularly for some TLE patients who experience the most chronic confrontation naming difficulties identified post-operatively on neuropsychological assessment. The present research investigated the role of the ATL in language through two studies. The first employed neuropsychological testing of pre- and post-operative TLE patients on tests of language functioning (Chapter 2), while the second study looked at ATL activation in healthy controls and TLE patients using two new fMRI tasks (Chapter 3). This chapter will provide a broad overview of the literature relevant to this area, including epilepsy, language function, and the contribution of neuropsychological testing and fMRI to our understanding and treatment of intractable epilepsy.

Epilepsy

Epilepsy has been described by as a condition that involves recurrent seizures, which are defined as disorderly neuronal discharges (Gastaut, 1973). The prevalence of

epilepsy is reported to be 5 in 1000 children, and 4 to 7 in 1000 adults, with a higher prevalence in females than males (Hauser & Annegers, 1993). Seizures are classified as focal, or generalized, and each of these categories can be further subdivided (Engel, 2001). A focal seizure (also known as a partial seizure) occurs in a confined section of nerve cells, usually in one hemisphere of the brain. Focal seizures are further classified on the basis of the patient's level of consciousness during the seizure; they are identified as simple partial in patients who are conscious, and as complex partial in patients whose consciousness is impaired (Engel, 2001).

Generalized seizures involve a more widely distributed abnormal neuronal discharge, and are often preceded by prodromal (pre-attack) signs such as anxiety or mood changes (Engel, 2001). Sub-types of generalized seizures include tonic-clonic, tonic, atonic, clonic, myoclonic, or absence. A tonic-clonic seizure involves impaired consciousness, and short, alternating periods of heightened muscle tension, and muscle relaxation. Tonic seizures typically involve heightened muscle testing and flexing of arms, and relaxing and flexing of legs. In contrast, atonic seizures involve an abrupt loss of muscle tone. Clonic seizures are rare, but most common in children who have a fever. They are accompanied by a rapid loss of consciousness, loss of muscle tone, and spasms. Myoclonic seizures are identified in newborns and children, and involve rapid muscular contractions. Absence seizures are classified as typical, or atypical. Typical absence seizures involve unresponsiveness, and sometimes abnormal muscular movements of the face and eyelids. In contrast, atypical absence seizures involve a higher level of awareness, and do not exceed 10 seconds (Engel, 2001).

In approximately 20 % of people with epilepsy, seizures may be severe and intractable, in that they do not respond to anti-convulsant medication (Hauser & Annegers, 1993). Intractable epilepsy occurs most commonly in TLE, accounting for 70 % of intractable epilepsy diagnoses, with hippocampal sclerosis present in approximately 50 % of these patients (Wieser, 2004). The inability to control seizures pharmacologically places people with intractable seizure disorders at risk of brain damage due to persistent irregular brain activity, or traumatic brain injury that occurs secondarily to loss of consciousness, or even death (Saykin et al., 1992). Identification and removal of the epileptogenic focus is then considered as a treatment option. For patients with unilaterally localized temporal lobe seizures, the surgeon gains entry to the medial temporal lobe through the ATL and removes the affected area, most often the hippocampus and amygdala (Saykin et al., 1992). Following surgery, 64 per cent of patients who had undergone an anterior lobectomy were found to be seizure free (Wiebe, Blume, Girvin & Eliasziw, 2001), with higher rates observed when analyses were restricted to patients with Mesial Temporal Lobe Sclerosis (Lachhwani & Wyllie, 2006). Before and during TLE surgery, the surgery team attempts to identify and preserve language function of the dominant temporal lobe (Baxendale, 2002). This is achieved through neuropsychological testing, and imaging of the areas of the brain involved in language (Jing, Takigawa, & Benasich, 2002). Despite these efforts, it has been reported that 25 % of patients experience chronic naming difficulties following TLE surgery (Langfitt & Rausch, 1996).

Lateralization of Language Function.

The aim of any surgical intervention is to improve general health and quality of life. Preservation of language abilities is considered important because impairment in language could potentially reduce quality of life. Pre-surgical investigation of areas of the brain involved in language is imperative because surgery is often performed in the language dominant hemisphere (typically the left hemisphere), and potentially in close proximity to fundamental speech and language circuits (Baxendale, 2002). Patients who have surgery in their language-dominant hemisphere have been found to have a greater risk of naming and reading deficits (Baxendale, 2002). Furthermore, evaluation is important because a universal language map (for example, Brodman's areas) can not be applied due to individual differences in the representation of language abilities in the brain (McDermott, Watson, & Ojemann, 2005).

During the pre-surgical evaluation, it is important to determine language laterality, that is, the hemisphere that primarily controls language function. This may be achieved through neuropsychological assessment, Wada, grids and fMRI. Atypical language areas have been identified in some individuals that include right hemisphere involvement, and an overlapping of expressive and receptive regions (Berger, Ojemann, & Lettich, 1990). Furthermore, Snyder, Novelly, and Harris (1990) found the frequency of mixed language dominance (involvement of both hemispheres) to be considerably variable across research centers, with some studies reporting zero occurrences, and other studies reporting up to 60 %. It was proposed that the different methodologies used in localization of language are likely to account for a considerable proportion of this variance. Loring et al. (1990) suggested that pure right hemisphere dominance for

language may be as rare as approximately 2 % of the population, and state the importance of considering language lateralization as a continuous, rather than a dichotomous variable. This is supported by fMRI studies of language mentioned in Chapter 3.

Handedness is an important factor in determining language lateralization, with left-handed people showing a higher degree of right hemisphere involvement in language than right-handed patients (Risse, Gates, & Fangman, 1997). In their review of the literature, Risse et al. (1997) highlighted the variation seen across studies, with left-hemisphere language dominance reported anywhere between 63 to 96 % in right-handed patients, and between 38 to 70 % in left-handed patients. On the basis of this variability between studies, it follows that different methodological approaches and statistical analyses may result in different classifications of language dominance.

Hermann et al. (1999) found no relationship between surgical approach and naming difficulties in a sample of patients with TLE. They did, however, find an association between the extent of cortical resection and naming difficulties, suggesting that conservative resection of the anterior temporal lobe may reduce the risk of post-surgical naming difficulties.

Neuropsychological Testing: The effects of epilepsy, and surgery on cognitive function.

Neuropsychological testing has been used extensively with patients with intractable TLE, enabling comparison of pre-surgical baseline and post-surgical measures of cognitive functioning in order to determine the effects of surgery on cognitive functioning (Hermann, Seidenberg, Schoenfeld & Davies, 1997). The syndrome of Mesial Temporal Lobe Epilepsy (MTLE) is characterized by early age at seizure onset,

TLE and hippocampal sclerosis. Extensive neuropsychological research has focused on MTLE and memory function, where memory deficits are said to be associated with hippocampal pathology (Strauss, Loring, Chelune, et al., 1995). Hermann et al. (1997) stated that earlier research involving MTLE erroneously attributed more generalized cognitive difficulties to reduced hippocampal volume, and to memory difficulties. To better understand the cognitive difficulties experienced by patients with MTLE, they conducted a comprehensive study of cognitive function in 107 patients (62 left- and 45 right-sided pathologically confirmed MTLE) using measures from the Wechsler Adult Intelligence Scale – Revised (WAIS-R), Wide Range Achievement Test – Revised (WRAT-R), Multilingual Aphasia Examination (MAE), Wechsler Memory Scale (WMS-R), and Wisconsin Card Sorting Test (WCST). Consistent with earlier research, patients with left-sided MTLE performed worse on measures of verbal learning and memory than patients with right-sided MTLE. Conversely, patients with right-sided MTLE performed worse on measures of visual learning than patients with left-sided MTLE. Determination of laterality on the basis of differences in visual memory function is not without controversy. Using the WMS-III, Wilde, Strauss and Chelune (2003) found that confirmatory factor analysis did not support a visual memory difference between patients with left- and right-sided TLE. Furthermore, Cheung (2006) suggested that the differential performances on memory tasks may be instead related to illness duration.

Interestingly, Hermann et al. (1997) found that other aspects of cognitive functioning were not related to lesion laterality. Patients with left- and right-sided MTLE performed worse on measures of general intellectual functioning, academic achievement, language, and visuoperceptual skills than TLE patients without hippocampal sclerosis.

They proposed that the more generalized deficits identified on testing in the MTLE groups may be more related to the neurobiological consequences of interrupted neural development (particularly when the onset of seizures occurs early in life), effects of chronic intractable seizure activity, and long-term exposure to antiepileptic medications. In view of these findings, Hermann et al. (1997) cautioned that there may be cognitive consequences associated with delaying surgical intervention for MTLE.

Cognitive outcome following anterior temporal lobectomy for TLE was examined by Seidenberg et al. (1998) to determine if outcomes varied as a function of the presence or absence of hippocampal sclerosis. TLE patients with MTLE (31 left-, 21 right-) and without MTLE (non-MTLE; 23 left-, 13 right-) were compared on measures of the WAIS-R, MAE, Facial Recognition Test, California Verbal Learning Test, WMS-R, and WCST. Prior to surgery, the MTLE patients performed worse on cognitive testing than the non-MTLE group. Following surgery, memory decline was evident in the MTLE groups relative to their pre-surgical scores, which was possibly related to the hippocampal resection (with the extent of resection controlled for using a graded classification system). However, the left non-MTLE group experienced the most detrimental outcome following surgery, with reduced performances in the domains of verbal memory, visual confrontation naming, and the WAIS-R Verbal Comprehension Index. It was hypothesized that this marked decline may occur due to disconnection of the fiber bundle connecting the anterior temporal and lateral frontal regions. It was evident that there were other influencing factors, given that all patients had ATL surgery, but only the left non-MTLE group exhibited the marked degree of language impairment.

Seidenberg and colleagues suggested that early neural reorganization of language function may be related to the extent of ATL involvement in language.

As previously mentioned, the use of antiepileptic medication may have an affect on cognitive function. Cognitive affects associated with long-term usage discussed by Bennet (1992) included impaired psychomotor speed, concentration, memory, and problem solving. In contrast, medication has been found to result in increased alertness, and improved functioning in school children (Barnes and Bower, 1975; Westerveld et al, 2000). Bennet (1992) cautioned that the effects of medication on cognitive function need to be considered because a cognitive deficit may be the result of medication toxicity, rather than a cognitive deficit per se.

From the aforementioned literature relating to the pre-surgical evaluation for anterior lobectomy, and the neuropsychological effects of epilepsy and surgery on cognitive function, it is apparent that there are many factors that contribute to the post-surgical difficulties experienced by patients with TLE. In particular, preservation of language function is an important consideration, given the vulnerability to language impairment in the TLE population due to chronic effects of seizure activity, and the effects of surgery in the language dominant cerebral hemisphere. A review of the anatomy of language is required, along with discussion of the methods used to localize language function prior to TLE surgery.

Anatomy of Language – Classical and Localization Models

In the 1860's Paul Broca introduced a lesion-based approach to language localization following autopsy of a patient with known language impairment that was

restricted to the production of speech (Saffran, 2000). Broca observed damage to the pars opercularis of the inferior frontal gyrus in the left hemisphere. After further investigating this region with many case studies, it was identified as the locus for articulate speech, and termed Broca's area following release of his findings in 1865. Specific deficits involving articulation, production of speech, syntax, and naming were collectively known as Broca's Aphasia (Bookheimer, 2002).

In 1874, Carl Wernicke discovered a lesion in the posterior, superior left temporal lobe in a patient whose comprehension was markedly impaired (Kertesz, 1993). Wernicke believed this area to be involved with storage of word images and both the production and comprehension of speech. Subsequently, this region became known as Wernicke's area. Specific deficits involving reduced comprehension of speech, but with continued ability to produce speech was termed Wernicke's aphasia (Bookheimer, 2002). Wernicke also proposed the existence of a tract that linked the left posterior, superior temporal lobe with Broca's area, and hypothesized that damage to this tract would lead to an impairment of speech production, with intact comprehension. This tract became known as the arcuate fasciculus, with the disconnection described by Wernicke known as Conduction Aphasia (Saffran, 2000). Bookheimer (2002) noted that following Wernicke's discovery, the approach towards understanding brain function through connected regions became popular, and known as connectionism.

Carl Lichtheim furthered the research of Broca and Wernicke by proposing the existence of different forms of aphasia corresponding to the location of the lesion (Saffran, 2000). Sub-types of aphasia characterized by difficulties with speech production were described that included Conduction Aphasia and Transcortical Motor

Aphasia. The main deficit associated with conduction aphasia is the difficulty with repeating what others say, or reading aloud, but comprehension is intact (Kertesz, 1993). Transcortical Motor Aphasia occurs in the context of a lesion to the area anterior or superior to Broca's area. It is characterized by halting, or non-fluent speech with intact comprehension (Kertesz, 1993). Comprehension of speech is affected in Transcortical Sensory Aphasia, and believed to be associated with a lesion in the angular gyrus (Bookheimer, 2002). Problems with naming or word finding (anomia) were traditionally associated with more widespread damage such as that seen in traumatic brain injury or Alzheimer's Disease (Saffran, 2000). Widespread damage to the left hemisphere has been known to produce Global Aphasia, resulting in deficits in both speech production and comprehension of language (Kertesz, 1993).

The concept of localization of language is not universally accepted. Joseph, Noble and Eden (2001) argue that explanation of language functioning through localization is overly simplistic, in that it fails to consider the complexity of neural connections. An alternative interpretation proposed by Joseph et al. (2001) is that language is mediated through networks, with particular regions of the brain representing a portion of a particular network involved in a specific language function. An additional complication is outlined by Cabeza and Nyberg (2000), who explained that more modern methods of investigating language function, for example fMRI, are not capable of identifying the functional relationship of these networks. Mindful of these limitations, Joseph et al. (2001) explain that neural activation at a basic level signifies involvement in a function.

Functional Approaches to Localization of Language

In response to advancements in technology, a functional imaging approach evolved, with focus on the areas involved in specific components of language. Research using fMRI and PET indicates that the extrastriate cortex, and the lingual and fusiform gyri are involved in the function of reading (Kuriki, Takeuchi, & Hirata, 1998). Furthermore, the left posterior inferior temporal, left inferior frontal, and left inferior parietal regions are involved in lexical orthography, the ability to form abstract representations (Friedman et al., 1998; Frith, Friston, Liddle, & Frackowiak, 1991). Lexical phonology, the ability to discriminate between word sounds (Paulesu et al., 1996) is tested through word rhyming tasks where activation of many regions - including the perisylvian regions, left posterior superior temporal gyrus, left insula, inferior frontal gyrus, and the left-caudate - support the interpretation of language as being represented as specific networks. Sublexical phonology, the processing of sound units or syllables, is associated with activation in the left inferior frontal, premotor cortex, and the left orbital frontal regions (Demonet, Price, Wise, & Frackowiak, 1994). Phonological and phonetic encoding, and articulation, are also tested using pronunciation and decision making tasks, producing activation in the inferior frontal and superior temporal regions (Burton, Small, & Blumstein, 2000; Heim, Opitz, Muller, & Friederici, 2003; Rumsey et al., 1997).

Finally, the component of language that is of most relevance to the proposed study is semantic processing, or the conceptual understanding of word meaning (Joseph et al., 2001). Category judgements, verb generation, and verbal fluency tasks have been found to produce activation in the ATL, superior middle, and inferior temporal gyri, and the left inferior frontal cortex, which suggests that these regions are involved in semantic

processing (Demonet et al., 1994; Perani et al., 1996; Price, Moore, Humphreys, & Wise, 1997; Tzourio, Nkanga-Ngila, & Mazoyer, 1998). Semantic processing is of relevance to TLE due to the observed deficits in patients with left TLE in the naming of living things compared to non living things (Strauss et al., 2000), and nouns compared to verbs (Glosser & Donofrio, 2001). It is clear that object naming requires neural processing at many levels, including word selection, lexical retrieval, or semantic processing, and that naming difficulties may occur as a result of deficits at one or many of these levels (Caramazza, Berndt, & Brownell, 1982). Research findings that follow a functional approach are consistent with what is known about normal language processing as outlined in the classical, and localization models of language described earlier (Binder et al., 1997; Bookheimer, 2002; Cabeza & Nyberg, 2000; Ojemann et al., 1989)

Measures of Language Function

Advancements in imaging technology have been incorporated into the diagnosis, pre-surgical planning, and surgical treatment of many neurological conditions in an attempt to improve patient outcomes. In the past, the Wada test has been used as a 'gold standard' of pre-surgical language lateralization. The Wada procedure is an invasive test where the left or right carotid artery is injected with sodium amobarbital resulting in temporary disruption of cortical function in the cerebral hemisphere ipsilateral to the side of the injection (McDermott et al., 2005). During the few minutes of disrupted functioning, language abilities are tested using confrontation-naming tasks as well as other language tasks. Both hemispheres can be tested independently, with the language abilities of the left hemisphere assessed during a right carotid Wada test, and the

language abilities of the right hemisphere assessed during a left carotid Wada test. From this testing, it is possible to determine which hemisphere is predominantly involved in language. Sullivan, Bowden and Kneebone (2005) found that the Wada test had poor predictive validity, with only moderate prediction of post-surgical verbal memory scores. In contrast, pre-surgical neuropsychological assessment of memory provided the most valid prediction of post-surgical performances. It was concluded that the ability of the Wada test to predict post-surgical memory function is yet to be established

Another invasive method used to assess language function is Cortical stimulation Mapping (CSM). This procedure can be performed earlier, or immediately prior to surgery. Small electrodes are placed directly on the surface of the brain, and the patient is awake sufficiently to participate in language-based tasks. During the testing, small electrical currents are applied to specific areas in order to temporarily interrupt cerebral function in that region. The effect is similar to that observed during the Wada test, although with an effected area of only one square centimeter, specific regions can be targeted and tested (McDermott et al., 2005). Like the Wada test, the CSM has limitations; both are invasive, refused by some patients, time consuming, costly, and cannot be readily repeated if results are inconclusive. Sullivan et al (2005) suggested that structural and functional MRI may provide a more optimal outcome.

fMRI and Language

fMRI is increasingly employed to identify the brain regions involved in language prior to surgery for intractable epilepsy. It has the advantage of being a non-invasive procedure where the patient is required to rest inside an MRI scanner which uses a

rapidly rotating magnet (Binder et al., 1996). This magnet uses the differential magnetic properties of oxygenated and deoxygenated blood to generate images of the brain in real time (Krings, Reinges, Foltys, Cosgrove & Thron, 2001). fMRI is used to image the brain while it redistributes blood to compensate for the increase in deoxyhemoglobin (deoxygenated blood) as oxygen is consumed during neural activity (Krings et al., 2001). The BOLD, or oxygenated blood response involves an initial drop, then a rise to the maximum event, following by an undershoot before returning to baseline functioning (figure 1). Block- and event-related designs are typically used in fMRI designs; block designs have greater power than event-related designs when comparing the magnitude of BOLD responses. Event-related designs, however, enable the researcher to vary the presentation time to wait for associated activation.

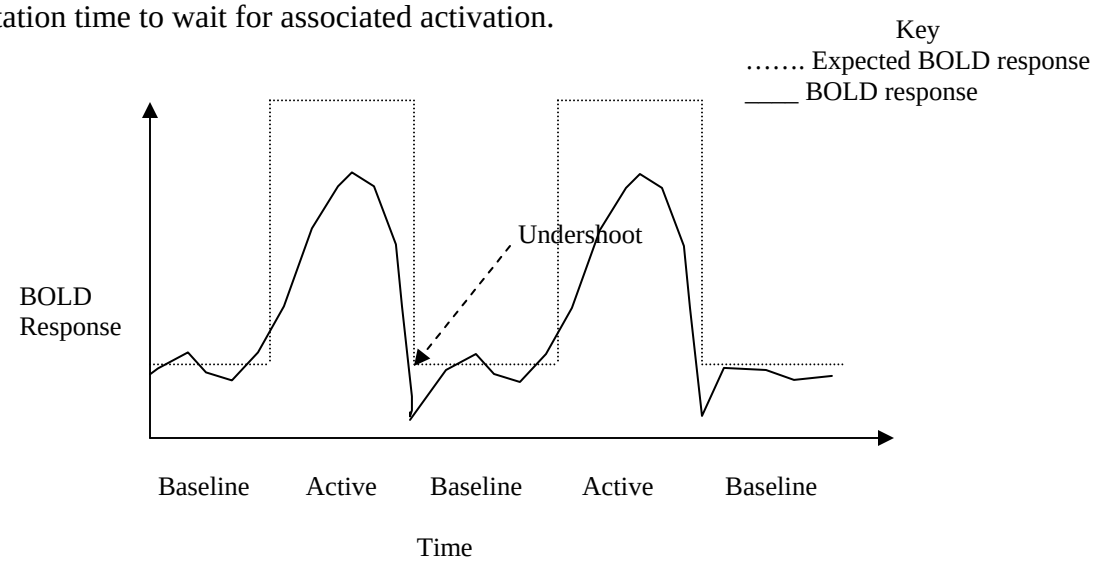

Figure 1. Depiction of baseline, active and undershoot components of an fMRI BOLD response.

When compared to the more invasive methods reviewed above, fMRI has been found to detect more areas involved in language processing, while the more invasive methods focus on the regions critical for language processing (Billingsley-Marshall,

Panagiotis, & Papanicolaou, 2004). In general, studies have reported very good concordance between the 'gold standard' Wada test and fMRI localization of language (for example, Bahn et al., 1997; Benbadis et al., 1998; Binder et al., 1996; Desmond, Sum, & Wagner, 1995; Hertz-Pannier et al., 1997). Furthermore, it has been argued that fMRI language localization can also be used to assess neuropsychological risk of language impairment following surgery (Binder et al., 1996).

Schwartz, Devinsky, Doyle and Perrine (1998) reported that neurosurgeons should be cautious when performing surgery on epilepsy patients with early seizure onset, poor verbal IQ, and left handedness. These criteria are considered to increase the probability of essential language areas being found in the left anterior temporal lobe. Schwartz et al. (1998) argued the importance of including naming and reading tasks in fMRI language localization to identify patients with anterior temporal lobe language involvement. However, other researchers (for example, Hermann et al., 1988) have reported increased risk of post-surgical language change associated with being left-hemisphere dominant and right handed, with high verbal IQ. It therefore appears that any disruption to the language- dominant temporal lobe is a risky endeavor.

Research using fMRI has identified many 'eloquent' areas of the brain involved in language functioning. Schwartz et al. (1998) recommended that any fMRI protocol should satisfy five criteria: it should elicit reliable, robust activation across individuals, it should result in activation in the frontal and temporal cortices; it should be usable with various clinical populations; it should be of short duration so that it could be tolerated well by most patients; and identified regions should correspond with those identified by Wada and CSM testing.

Brown (2007) raised concerns regarding the validity, reliability, standardization and the need for development of normative data relevant to the use of fMRI. Potential problems relating to an fMRI task's validity include the possibility that cerebral atrophy or complications with blood flow and metabolism can render reduced BOLD responses difficult to interpret. Furthermore, impaired motivation, inattentiveness, and failure to understand task directions can also impact on task validity. Brown stated that test-retest reliability in fMRI tasks has been found to generally low: statistics reported from average results generated from groups do not provide information about the stability for individual patients. Additionally, different methods, approaches and tasks are used in different research facilities, making standardization and comparison of research results difficult. Brown suggested that a collaborative approach between research centers is necessary to standardize testing and develop normative data in order to provide an informative assessment at the level of the individual.

In practice, it remains difficult to demonstrate reliable activity in specific cerebral regions, and it is unclear if the differences in activation represent individual variability, or a deficiency in the task (Ramsey, Sommer, Rutten & Kahn, 2001). Pre-surgical localization of language function is required because of individual variability in the representation of language. With this individual variability, and individually specialized organization of language networks, it is likely that one task will not result in activation in the same location across individuals. Considering these factors, Ramsey et al. (2001) suggest that a wide variety of tasks should be employed to test and image language. Specific fMRI studies that have investigated ATL language function in patients with TLE will be discussed in detail in Chapter 3.

The present study

Evidence reviewed previously in this chapter, and more extensively in Chapters 2 and 3 supports the involvement of the ATL region in language function, although it remains difficult to make inferences regarding the nature of the involvement of the ATL in language, and the impact of TLE surgery on language functioning. Anterior lobectomy is considered a successful surgical intervention for patients with intractable TLE due to the effect of surgery on seizure frequency: 40% of patients are seizure free, and 60 % experience a marked reduction in seizure frequency post-surgically (Hauser & Annegers, 1993), although 25 % of patients experience chronic naming difficulties following surgery for TLE.

Neuropsychological studies have investigated post-surgical naming difficulties, and functional imaging studies have investigated language function of the ATL. Neuropsychological studies of naming have been inconsistent, with reports of effects for lateralization of epilepsy (Davies et al., 1994 & Hermann & Wyler, 1988) and surgical status (Busch et al., 2005), while others have not found an effect for either variable using the 10^{th} percentile as the point at which to differentiate between normal and impaired naming function in patients with epilepsy (Kubu et al., 2001; Busch et al., 2004). Similarly, functional imaging studies that have attempted to localize ATL language function have produced inconsistent results, with some Famous Face naming and Sentence Reading studies finding ATL activation (Tsukiura, et al., 2002; Griffith et al., 2006; Huddy. Schweinberger, Jentzsch, & Burton, 2003 & Bavelier et al., 1997), whilst others have not (Leveroni et al., 2004).

The answer to these important research questions has the potential to vary markedly depending on the approach adopted for the interpretation of results. The present study was informed by the findings that a Bayesian approach offers greater clinical utility at the level of the individual than Null Hypothesis Significance Testing (NHST; Cohen, 1994). For the neuropsychological component of the study, analyses were performed using both NHST and Bayesian approaches. Results were reported using a NHST analysis in line with standard practice and Bayesian analysis in line with best practice (Elstein & Schwarz, 2002; Hunsley, 2007 and Loong, 2003). The use of both approaches for analysis was considered important given that the method of analysis may be a factor leading to the inconsistent findings of naming difficulties in patients with TLE. Similarly, results for the fMRI component of the study were analysed using the standard practice of reporting group averages, and best practice reporting of individual results. The present study offers a unique approach to the study of naming impairment in TLE by attempting to clarify the aforementioned inconsistencies with consideration of improving the tasks, and the approach taken for the analysis.

For the fMRI component of the study, two new fMRI tasks (Famous Faces naming, and Sentence Reading) were constructed, informed by the methodology of the previously mentioned research. The clinical utility of these tasks at the level of the individual was explored. For the neuropsychological component of the study, the CSNT was selected in an attempt to compensate for the problems of heterogeneous items, and the low ceiling in the BNT. CSNT items are divided into four categories (Animals, Fruit and Vegetables, Praxic, and Non-Praxic), therefore are not confounded by heterogeneous category grouping. In addition, the CSNT appears to have a higher degree of difficulty,

with normative data suggesting sensitivity for left-sided lesions (a mean of 8 out of 30 items in the Praxic category). The CSNT had not been previously validated with TLE patients, and has not been routinely used in Australia.

The present research aims to: validate the new neuropsychological and fMRI tests in patients with epilepsy; increase the understanding of the involvement of the ATL in language function; compare methods for evaluating pre- and post-surgical language function of the ATL region, and in doing so, clarify the inconsistencies within this area of research.

CHAPTER 2

Neuropsychological Assessment of ATL Language Function

Language Tests and Findings in Temporal Lobe Epilepsy

Chronic naming difficulties have been shown to occur in 25 % of TLE patients post-surgically (Langfitt & Rausch, 1996). This may be because surgical entry to the temporal lobe is gained via the Anterior Temporal Lobe (ATL), which subsequently sustains a certain degree of damage. Functional imaging studies have found ATL activation during naming (for example, Tsukiura et al., 2002) and verbal fluency (for example Demonet et al., 1994). This chapter examines neuropsychological tests for effective evaluation of pre- and post-surgical naming and verbal fluency aspects of language function. Neuropsychological assessment is used to predict risk of post-surgical language change and provides a quantitative measure of the effects of TLE surgery through comparison of base-line and post-surgical results, with confrontation naming and verbal fluency tests routinely used to assess language function. The present research aims to investigate a naming test in patients with epilepsy and compare methods for evaluating pre- and post-surgical language function of the ATL region.

The Boston Naming Test

Confrontation naming assessed using the Boston Naming Test (BNT; Kaplan, Goodglass, & Weintraub, 1983) has been found to differentiate left and right TLE, with left TLE patients performing worse than patients with right TLE (Davies et al., 1994; Hermann & Wyler, 1988). The 10^{th} percentile is commonly used as the cut-off point for

differentiating between normal and impaired naming function on the BNT (Spreen & Strauss, 1997), however the clinical utility of using the 10th percentile for predicting side of epileptic foci, and ultimate side of resection has been questioned (Kubu et. al., 2001; Busch et al., 2004). Using the 10th percentile cut-off for impairment, Kubu et al. (2001) compared the performances of 25 left- and 28 right-sided TLE patients on the BNT and the Visual Naming subtest of the MAE using likelihood ratios. In their sample, results indicated that neither test resulted in improved probability of predicting epileptic foci, or side of resection. The Kubu et al. (2001) study was later extended by Busch et al. (2004) using an increased sample of 175 left- and 173 right-sided TLE patients. Busch et al. (2004) found likelihood ratios between 1.03 and 9.89 using various BNT raw scores between 59 and 27. The 10th percentile was not found to be an effective point for differentiating left from right TLE; and Busch et al.(2004) recommended the use of BNT cut-off scores below the 10th percentile (raw score of 51) for effective clinical decision-making in patients with TLE. More recently, Busch et al. (2005) used the BNT, Wechsler Adult Intelligence Test – Third Edition (WAIS-III), and Wechsler Memory Scale – Third Edition (WMS-III) with a sample of 108 left- and 109 right-sided pre-surgical TLE patients. For this analysis, logistic regression was used rather than Bayesian analysis in Busch et al.'s previous work, and it was reported that the BNT predicted side of surgical resection more effectively than the measures of general intelligence and memory.

There are a number of problems associated with the original normative data of the BNT, for example, the normative sample did not adequately represent the elderly (over 75 years), or ethnic diversity within the community (Ross & Lichtenberg, 1998).

Furthermore, there is a ceiling effect on the BNT for those of above average intellectual abilities (Steinberg, Bieliauskas, & Smith, 2005). Normative data has been produced to provide greater clinical utility for assessment with the elderly (Ivnik et al., 1992), and better representation of ethnic communities (Ross & Lichtenberg, 1998), although little consideration has been directed towards compensating for the ceiling effect. Another weakness of the BNT is that it is comprised of heterogeneous items, belonging to many different categories, and the normative data relates to the overall score without provision of category specific sub-scores.

Lesion Studies and Object Naming

Evidence from invasive and non-invasive procedures suggests that there are category-specific naming networks, a factor not accommodated for by the heterogeneous grouping of items in the BNT. Krieman, Koch, and Fried (2000) used intracranial depth electrodes located in the amygdala, entorhinal cortex and the hippocampus on 11 patients with intractable epilepsy prior to surgery. They found that individual neurons responded selectively to visual stimuli of different categories (faces, natural scenes, famous people and animals). They concluded that the assessment of object naming is complicated, as it involves visual recognition of the object, knowledge of and memory for the name of the object, and ability to access and retrieve the name of the object (Krieman, et al., 2000). Research has also identified a difference between object processing at different levels of specificity (Grabowski et al., 2001). It has been proposed that the left ATL is involved in the mediation of word retrieval and is therefore involved in very unique and specific naming (Grabowski et al, 2001). With an anterior left temporal lesion, a patient may

recognize the object, but be unable to name it, with the deficit specifically relating to naming of the object (Grabowski et al, 2001). In contrast, the right temporal pole has been found to be involved in recognition. With an anterior right temporal lesion, the patient may not recognise the object, and therefore may not be able to associate a name with the object due to difficulties with recognition (Grabowski et al.2001; Tyler et al., 2004).

Other authors have explained the naming difficulty observed in patients with temporal lobe epilepsy as due to a disruption to the semantic memory network. Bell et al. (2001) compared the ability to name an object with the ability to describe the object. A relationship was identified between these abilities, where the Object Description Test (ODT; Hodges, Salmon & Butters, 1991) was the only significant predictor of performances on the BNT. For the ODT, patients with Alzheimer's disease were asked to describe six items from the BNT in detail, as if describing them to someone who has never seen them before. One point was awarded for each accurate component of the description that included physical appearances of the object, along with its corresponding function. The finding of a relationship between the naming difficulties (low BNT score) and impoverished semantic descriptions of BNT objects (low ODT score) supports the proposition that semantic impairment may contribute to object naming difficulties (Bell et al.). In another study of naming ability in patients with Alzheimer's disease, naming ability and conceptual knowledge were tested twice, with a 15 month interval between testing (Lambon, Patterson & Hodges, 1997). A relationship was shown between items named correctly at the first testing occasion, those named incorrectly at the second test session, and a general decline in conceptual knowledge (Lambon, et al., 1997). It was

concluded that object naming is likely to involve semantic memory, and that disruption to semantic memory networks, or retrieval of information from semantic memory, may contribute to the naming difficulties observed in patients with temporal lobe epilepsy. Furthermore, some researchers have postulated that the temporal lobe may be fundamentally involved in the storage of semantic information (for example, Chertkow, Bub, Deaudon, & Whitehead, 1997).

It has been proposed that the ability to name familiar people is mediated by its own neural network (Lyons, Hanley, & Kay, 2002). Consistent with the proposal that the left temporal lobe is associated with proper-name retrieval, and the right temporal lobe with recognition, fMRI studies have found proper-name anomia to be related with left temporal lobe damage (Fakatsu, Fujii, Tsukiura, Yamadori & Otsuki, 1999; Luchelli & De Renzi, 1992) and facial familiarity judgment with right temporal lobe damage (Evans, Heggs, Antoun, & Hodges, 1995). Furthermore, post-surgical naming of famous people and familiar objects has been found to be impaired in left TLE patients (Glosser, Salvucci, & Chiaravalloti, 2003). Glosser et al. (2003) also suggest that the ATL may also be involved in the processing and storage of names, given that some patients also have difficulty with the learning of new names after left temporal lobe resection.

The Category Specific Names Test

Through incorporating functional research involving the BNT and lesion studies, it is interesting to explore the idea that category-specific naming may result in a more sensitive identification of specific naming difficulties. The Category Specific Names Test (CSNT; McKenna, 1997) was developed in order to provide a clinical tool to detect a

category-specific naming deficit, and was driven largely by the type of lesion studies discussed above. The CSNT includes four categories; animals, fruit and vegetables, praxic, and non-praxic. The four sets of pictures are provided in colour, and are graded and matched in difficulty (McKenna, 1997). There are 30 items in each category. Unlike the BNT, the CSNT does not have time restrictions, and the four categories can be administered in any order. Normative data included a control sample of 400 volunteers, and 75 patients with unilateral left- (n=50) or right-sided (n=25) lesions. In the control group, there was a significant interaction between category and gender, with women better than men at naming fruit and vegetables, and worse than men at naming animals. The left-sided lesion group performed significantly worse across all categories when compared to the control and right-sided groups. The greater difficulty of some of the items, and the greater number of items overall, suggests that the CSNT would not have the same ceiling effects as the BNT. Further research is required to determine if this test adds to our understanding of naming difficulties following surgery for intractable temporal lobe epilepsy over and above the contribution of the BNT.

Verbal Fluency

Verbal fluency tasks have also been related to language function of the left anterior temporal lobe. Functional imaging studies have found activation in the ATL, superior middle, and inferior temporal gyri, and the left inferior frontal cortex during verbal fluency tasks, with phonemic fluency tasks eliciting activation in the frontal lobe, and semantic, or category fluency tasks eliciting activation in the temporal and mesial temporal regions (for example, Demonet et al., 1994; Perani et al., 1996; Price et al.,

1997; Tzourio et al., 1998). Suchy, Sands & Chelune (2003) investigated phonemic verbal fluency using the Controlled Oral Word Association Test (COWAT; Benton, Hammer & Sivan, 1983) in a sample of 94 left- and 80 right-sided TLE patients. They reported that COWAT scores improved following surgery, particularly in left TLE patients who remained seizure free. In addition, semantic fluency was examined using the Animal Fluency test (Tombaugh, Kozak & Rees, 1996) in a sample of 22 left- and 31 right-sided TLE patients, with left-sided TLE patients performing worse than right-sided TLE patients (Jokeit, Mara, Heger, Ebner & Markowitsch, 1998).

Post-surgical improvements have been shown on the COWAT in 15 patients with left-sided epilepsy (Hermann & Wyler, 1988). These results were consistent with the earlier research of Benton (1968) and Milner (1964). In contrast, Martin et al. (2000) did not find that lateralization of epilepsy, or surgical status predicted performance on the COWAT in a sample that included 81 left-sided and 71 right-sided TLE, and 8 left- and 14 right-sided patients with frontal epileptic foci. These findings were not consistent with the earlier research of Benton (1968) and Milner (1964), and may have been confounded by the mixed epileptic foci or methodological differences.

Analysis of Results: ATL Language Function in Patients with Epilepsy.

Language tests used in the present study were compared using conventional analyses of variance and covariance, or a Null Hypothesis Significance Testing (NHST) approach and Bayesian statistics. There is increasing recognition that a Bayesian approach has greater clinical utility for predicting individual outcomes than a NHST approach (for example, Loong et al., 2003; Hunsley, 2007, and Elstein & Schwarz, 2002),

although Bayesian analyses are not commonly included in neuropsychological research (Labarge, 2003).

Bayesian analysis: A worked example.

An example of a Bayesian analysis is provided in tables 1 and 2 using hypothetical results. Bayesian statistics are explained using definitions provided by Sackett, Straus, Richardson, Rosenberg, & Haynes (2000).

Table 1
Example of Bayesian Analysis: The Effectiveness of Test A in Detecting Disorder X.

Result of Experiment	Disorder X present	Disorder X not present	Total
Positive Test A Result (test result < 10^{th} % ile)	50 (a) (True +)	45 (b) (False +)	95
Negative Test A Result (test result > 10^{th} % ile)	50 (c) (False -)	855 (d) (True -)	905
Total	100	900	1000

Table 2
Bayesian Formulae Applied to Results of the Hypothetical Example Depicted in Table 1.

Variable	Formula	Results
N	a + b + c + d	1000
Base-rate (pre-test probability)	(a + c) / N	.10
Sensitivity	a / (a + c)	.50
Specificity	d / (b + d)	.95
Positive Predictive Value	a / (a + b)	.53
Negative Predictive Value	d / (c + d)	.94
Likelihood Ratio	sensitivity / (1 - specificity)	10
Pre-test odds	Base-rate / (1 – Base-rate)	.11
Post-test odds	Pre-test odds x LR	1.1
Post-test probability	Post-test odds / (post-test odds + 1)	.53

The base-rate, otherwise known as the prior probability refers to the prevalence of the disorder in the population. In this example, 100 in 1000 patients, or a base-rate of 10 % had Disorder X. The sensitivity of the test (a/(a+c)), which represents the probability of a patient having the disorder given a positive test result, was low, with only 50 in 100 (50 %) patients with Disorder X obtaining a positive result on Test A. In contrast,

specificity (d/(b+d)), or the probability of the patient not having the disorder given a negative test result, was high, with 855 in 900 (95 %) of patients who did not have Disorder X obtaining a negative result on Test A. Sensitivity and specificity are not affected by the base-rate of Disorder X, but negative and positive predictive values take the base-rate into account. Positive predictive value (PPV; a/(a+b)) is the probability of a positive test result being someone with Disorder X was low. In this example, only 50 in 95 (53 %) of patients with a positive result on Test A had Disorder X. In contrast, the negative predictive value (NPV; d/(c+d)), or probability of a negative Test A result being found in someone who does not have Disorder X, was high: 855 in 905 (94 %) of patients with a negative result on Test A did not have Disorder X.

Sensitivity and specificity are used to calculate likelihood ratios, or how much a test result raised or lowered the post-test probability of Disorder X. A likelihood ratio of 1.0 indicates that the pre- and post-probabilities are the same, the test result does not raise or lower the pre-test probability. Likelihood ratios greater than 1.0 increase the probability that the target disorder is present. Sackett et al's guide to interpretation is reproduced in Table 3.

Table 3
Size of Likelihood Ratio and Degree of Change from pre- to post-test probability

Likelihood Ratio	Degree of Change
> 10	Large, conclusive
5 - 10	Moderate, important
2 - 5	Small, sometimes important
1 - 2	Very small, rarely important

Pre-test odds and Post-test odds (Pre-test odds x LR) were calculated to obtain the Post-test probability which is the probability of detecting Disorder X using Test A. In

this example, the base-rate was 10 %. Bayesian analysis showed that by using Test A, detection of patients with Disorder X could be improved from 10 % (base-rate) to 53 % (post-test probability). Although this is an improvement, this result should be interpreted with caution because the improved post-test probability of 53 % remains at the level of chance.

Comparison of Tests Used to Assess Language Function in Patients with Epilepsy

Confrontation naming routinely assessed using the BNT and analysed using NHST driven, logistic regression analysis has shown that patients with left-sided epilepsy perform worse on the BNT than patients with right-sided epilepsy (Busch et al., 2004). Standard regression has been predominantly used to assess the utility of the COWAT and Animal Fluency for predicting laterality in TLE with some inconsistency across studies (Martin et al., 2000 & Suchy et al., 2003; Jokeit et al., 1998). Bayesian statistics have not been used in published studies with the COWAT and Animal Fluency in the TLE population. As stated earlier, the inclusion of Bayesian statistics is recommended for determining clinically useful tests (for example, Loong, 2003, Hunsley, 2007 and Elstein & Schwarz, 2002). In the case of this research, it is clear that Bayesian statistics would be useful to determine effective tests and cut-off scores for evaluating pre- and post-surgical naming function with individual patients who have TLE, and for evaluating a test's ability to identify laterality of seizures.

As previously mentioned, invasive and non-invasive evidence supports the existence of category specific networks, with specific left temporal lobe neurons responding to faces, famous people, natural scenes and animals (Kreiman, et al., 2000). In finding that the BNT identifies left-sided naming deficits (Busch et al., 2005), and that

invasive evidence suggests a left temporal involvement in naming specific categories (Kreiman, et al., 2000), the potential added benefit of a category specific test is explored in the current study by comparison of the CSNT and the BNT. This comparison is theoretically important, given that the BNT includes items from different categories, and there is the potential that predictive utility could be improved by compartmentalizing and comparing results for the different categories. Furthermore, the CSNT may overcome the ceiling effect encountered in the BNT, as it appears to involve a greater degree of difficulty. For example, the mean score for the CSNT Praxic Objects subtest was only 23 out of 30 in controls, and 8 out of 30 in patients with left lesions (McKenna, 1997). A test of greater difficulty than the BNT is expected to be a useful addition to the assessment of naming abilities, particularly for patients of high cognitive functioning. In addition, the Animal Fluency test was used to explore the clinical utility of a category specific fluency task in differentiating left from right TLE.

In the present study, the BNT and CSNT were administered to compare the two tests, and to investigate the utility of the CSNT in patients with epilepsy. The clinical utility of the BNT for differentiating laterality is generally well demonstrated, although there are studies (reported above) that do not find an effect for lateralization of epilepsy using the 10^{th} percentile as a cut off point (Kubu et al., 2001; Busch et al., 2004). As mentioned before, the BNT may be restricted due to the heterogeneous grouping of categories, or the constraints of the low ceiling. Comparison of the BNT and CSNT will clarify this concern. Assessment of phonemic and semantic fluency was also included to clarify the inconsistent findings involving the COWAT, and to further explore the predictive utility of the Animal Fluency test in patients with epilepsy. A Bayesian

approach was applied to compare likelihood ratios and the positive and negative predictive values to determine if the ability of the naming and fluency tasks to differentiate between left and right TLE; there is an added benefit of using both the BNT and the CSNT in the assessment of naming abilities; and if the 10th percentile is an effective point at which to differentiate normal from impaired naming function. Specific hypotheses are detailed below.

Hypotheses

1. Confrontation naming abilities will be lower in patients with left- than right-sided epilepsy.
2. Verbal fluency will be lower in patients with left- than right-sided epilepsy.
3. The CSNT would be more effective than the BNT in distinguishing between left and right TLE patients (due to a higher ceiling).

Method

Participants

Ethics approval was obtained from St. Vincent's Hospital and Victoria University (Appendix A). An invitation to participate was extended to all patients with a history of intractable epilepsy who had been assessed to determine suitability for epilepsy surgery at St. Vincent's Hospital over the five years from 2002 to 2007. These included 108 pre- and 78 post-surgical patients. Forty-two patients (21 pre- and 21 post-surgical) expressed interest, and were subsequently recruited, with formal consent obtained through signing of the relevant PICF (Appendix B). Participants were not offered any form of remuneration for their involvement in the study. Participants who took part in the study

were all right-handed as measured by the Edinburgh Handedness Inventory (Oldfield, 1971). Patient demographics are represented in table 4.

Table 4
Patient Demographics

Variable	Surgical Status & Epilepsy Lateralization			
	Pre-surgical (n = 21)		Post-surgical (n = 21)	
	left	right	left	right
Age, years (*M*, *SD*)	45, *14.9*	46, *11.1*	42, *3.3*	38, *5.3*
Range	18 - 74	21 - 67	18 - 56	26 - 47
Gender (M: F)	1:8	10:2	1:11	3:6
Years of Edn (*M, SD*)	12, *2*	13, *3*	12, *2*	14, *2*
Range	10 - 17	8 - 17	8 - 15	12 - 18
Seizure onset, age (*M, SD)*	16, *12*	12, *10*	15, *12*	12, *11*
Range	2 - 36	2 - 45	2 - 40	1 - 35
Seizure frequency, for 1month (*M, SD)*	2, *7*	2, *9*	1, *2*	2, *2*
Range	1 - 20	1 - 18	1 - 6	1 - 6
Seizure status (*Present, not present)*	9, *0*	12, *0*	11, *1*	8, *1*
Medication (*Monotherapy, Polytherapy)*	6, *3*	8, *4*	8, *4*	7, *2*

Patients varied with respect to the type of epilepsy and focal localization as determined by previous EEG, SPECT and MRI investigations in pre-surgical patients and histologically confirmed in the post-surgical group (Table 5).

Table 5
Patient Group Epilepsy Localization

Localization	Lateralization (frequency)			
	Pre-surgical		Post-surgical	
	Left	Right	Left	Right
Frontal pole				1
Fronto-temporal	1	1		
TLE (unspecified)	3	5	8	5
Hippocampal sclerosis	2	2	3	1
Mesial Hippocampal sclerosis	2			2
Amygdala		2		
Cavernous cavernoma (temporal lobe)	1		1	
Choroidal fissure cyst (occipital lobe)		1		
Occipital		1		
Total	9	12	12	9
Total Pre- and Post-surgical	21		21	
	42			

Materials

Results from the WAIS-III and the WMS-III were obtained from the patients' previous routine pre- or post-surgical neuropsychological assessment as appropriate to their group membership. Language tests administered for the purpose of this study included: the Edinburgh Handedness Inventory (Oldfield, 1971), the BNT (Kaplan et al., 1983), the CSNT (McKenna, 1997), the COWAT (Benton, et al., 1983), and Animal Fluency (Tombaugh, et al., 1996).

Design and Procedure

Testing for this study was conducted at St. Vincent's Hospital, Melbourne. Participants were asked to complete language tests that predominantly assessed the confrontation naming (BNT & CSNT) and phonemic and semantic verbal fluency (COWAT & Animal Fluency) aspects of language functioning. Language testing was completed using the standardized test administration and scoring, and took approximately

one hour to complete. During the confrontation naming tests, participants were shown pictures and asked to name the depicted object. During the verbal fluency tasks, patients were asked to list as many exemplars of a specific category and according to specific rules as quickly as possible. A between-subjects design was used, with comparison between pre- and post-surgical groups and left- and right-lateralization groups.

Statistics.

Continuous variables were inspected for any values falling outside of the expected range (+/- 3SD) with no univariate or multivariate outliers evident. Two participants did not complete the CSNT, and consequently analysis was conducted with a sample size of 40 for the CSNT and 42 for the COWAT, Animal Fluency and the BNT. Results from routine neuropsychological testing (WAIS-III and WMS-III) existed for 41 of the 42 participants, with the remaining pre-surgical participant having not yet completed their pre-surgical neuropsychological assessment. Missing Values Analysis (SPSS, MVA) revealed that remaining missing data was random, and at an occurrence not greater than five per-cent (Table C1). Normality was assessed through examination of skewness, histograms, and normal probability plots. Skewness and kurtosis remained under the critical level of 4 for all variables (Table C2).

Effect size estimates were evaluated using Cohen's criteria, with a small *f*(.10) corresponding to η^2 =.0099, a medium *f*(.25) corresponding to η^2 = .0588 and a large *f*(.40) corresponding to η^2 = .1370 (Cohen, 1988). With the higher prioritization of type I errors in Null Hypothesis Significance Testing (NHST), Cohen recommended power of .80, with a 20 per-cent chance of falsely retaining the null hypothesis (Type I error), compared to a five per-cent chance of falsely rejecting the null hypothesis (Type II error)

when alpha is set at .05. In the present study power, and effect size were taken into consideration when evaluating nonsignificant results, and where relevant, an estimation of the additional participants required to achieve statistical significance was provided.

Bayesian statistics (sensitivity, specificity, negative and positive predictive values, and negative and positive likelihood ratios) were calculated to determine the clinical utility of each test (Sackett et al., 2000).

Results

Surgical status (pre- and post-surgical), and epilepsy lateralization (left- and right-sided) groups were equivalent in age, but participants with left-sided epilepsy were less educated than participants with right-sided epilepsy $F(2, 39) = 4.48$, $p < .05$, $\eta^2 = .10$. There was a significant laterality effect on WAIS-III VIQ $F(1, 37)$, 7.51, $p < .05$, $\eta^2 = .17$ and FSIQs $F(, 37)$, 3.95, $p < .05$, $\eta^2 = .11$ with the left-sided group performing worse than the right-sided epilepsy group, as revealed by multivariate analysis of variance (MANOVA; SPSS Version 14.0; Table C3). Although there was a laterality effect, on VIQ, this was not present for the Vocabulary subtest $F(1, 36)$, .342, $p < .05$, $\eta^2 = .01$ indicating group equivalence on knowledge of word meaning. The Vocabulary subtest and naming have been shown to be highly correlated, and the Vocabulary subtest is considered to be more indicative of group equivalence of verbal abilities than omnibus measures such as VIQ and FSIQ (Spreen & Strauss, 1997).

There were no significant main effects of surgical status on WAIS-III and WMS-III

index scores, and there were no significant interactions (all ps >.05; Table C4). Chi-square analysis (SPSS) revealed that there were significantly more male participants in the post-than the pre-surgical group χ^2 (1, 41) = 5.08, $p < .05$, more males in the right- than the left-sided epilepsy group, and more females in the left-sided epilepsy group χ^2 (1, 41) = 12.55, $p < .05$. There were however, no significant effects of gender on neuropsychological measures identified on MANOVA (all *p*s > .05). To account for difference in educational experience for left versus right groups, Years of Education was added as a covariate in

subsequent analyses. Patient demographics and measures of General Intellectual function are detailed in Table 6. Table 6

Patient Demographics and Measures of General Intellectual Function

Variable	Surgical Status & Epilepsy Lateralization			
	Pre-surgical		Post-surgical	
	left	Right	left	Right
Age, years (*M*, *SD*)	45, *14.9*	46, *11.1*	42, *3.3*	38, *5.3*
Range	18 - 74	21 – 67	18 - 56	26 - 47
Gender (Male : Female)	1:8	10:2	1:11	3:6
Years of Edn (*M*, *SD*)	12, *2*	13, *3*	12, *2*	14, *2*
Range	10 - 17	8 – 17	8 - 15	12 - 18
FSIQ (*M*, *SD*)	95, *16*	102, *17*	91, *15*	104, *11*
Range	70 - 114	70 – 127	70 – 113	85 – 119
VIQ (*M*, *SD*)	92, *13*	102, *18*	88, *12*	105, *14*
Range	70 – 111	70 – 124	71 – 105	84 – 123
WAIS-III Vocab subtest (*M*, *SD*)	9, *2.3*	10, *2*	9, *1.8*	10, *2.6*
Range	8 – 12	9 – 12	8 – 11	9 – 13
PIQ (*M*, *SD*)	100, *18*	103, *18*	96, *18*	102, *8*
Range	70 – 117	78 – 132	73 – 124	89 – 111
GM (*M*, *SD*)	84, *24*	91, *16*	84, *17*	98, *9*
Range	45 - 115	49 – 115	45 - 107	83 – 109

Comparison of groups for the CSNT was achieved using MANCOVA (SPSS Version 14.0) with two Between Subjects factors: Laterality (left, right) and surgical status (pre, post), and Years of Education as a covariate. Performances on the BNT, COWAT, and Animal Fluency were assessed independently using three separate

univariate Analyses of Covariance (ANCOVA) with the same between-subject factors and covariate as for the CSNT.

Category Specific Names Test.

Performances of the left- and right-sided epilepsy, and pre- and post-surgical groups on CSNT measures of confrontation naming were examined using a MANCOVA performed on the five dependent variables from the CSNT, that is, scores on the four subtests (Animals, Fruit and Vegetables, Praxic, and Non-praxic) and the CSNT Total Score (Table C6). The effect of the covariate, Years of Education was non significant for all measures (all *p*s > .05). (Group means and standard deviations are detailed in Table C5).

CSNT Animals.

Average group performances for the CSNT Animals subtest (Figure 2) appeared higher in the right- than the left-sided epilepsy group, and lower in both left- and right-sided post-surgical groups, but the main effects of laterality and surgical status were not statistically significant. However, the nonsignificant effect of surgical status for CSNT Animals was medium to large in size F (1, 35) = 3.02, p = .09, η^2 = .08. There were no significant interactions (p > .05). Using Cohen's (1988) guidelines for power and effect size analyses, a further 26 to 64 participants would be required to achieve sufficient power of .80 for the non-significant results to reach threshold for statistical significance.

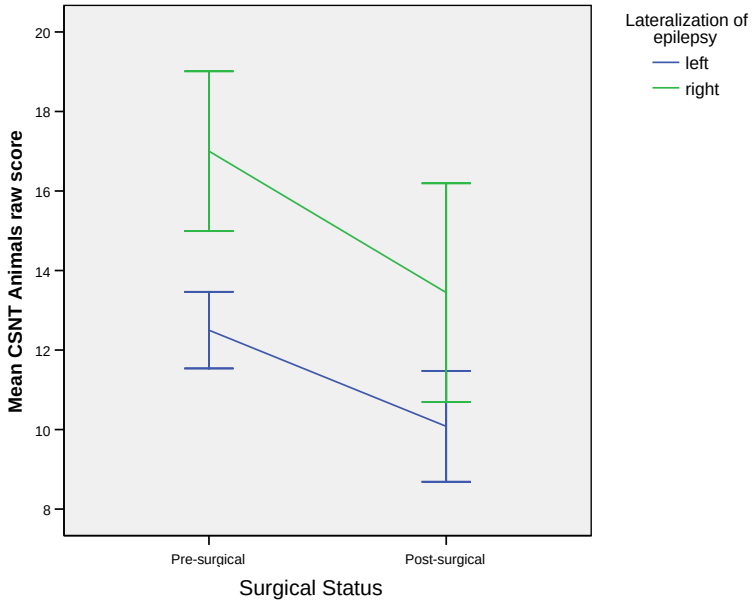

Figure 2. Mean scores on the CSNT Animals for patients with epilepsy (n=40). Note: error bars represent +/- 1 SE

The CSNT normative data shows that greater difficulty is experienced by females on the CSNT Animals subtest (males 25/30; females 20/30). Analysis was conducted separately for the female group (pre- and post-surgical groups combined) to determine if the nonsignificant finding observed in the mixed gender pre-surgical and post-surgical groups remained nonsignificant in female participants alone. Females and not males

were chosen because only two left TLE participants were male, and one did not complete the CSNT. The covariate Years of Education was not significant. In addition, the main effects for laterality and surgical status for CSNT Animals in females were nonsignificant, with small effect sizes, and there were no interactions.

CSNT Fruit and Vegetables.

Average group performances for the CSNT Fruit and Vegetables subtest appeared highly variable (Figure 3). There were no significant main effects or interactions for laterality or surgical status on CSNT Fruit and Vegetables (all *p*s > .05) and effect sizes were negligible.

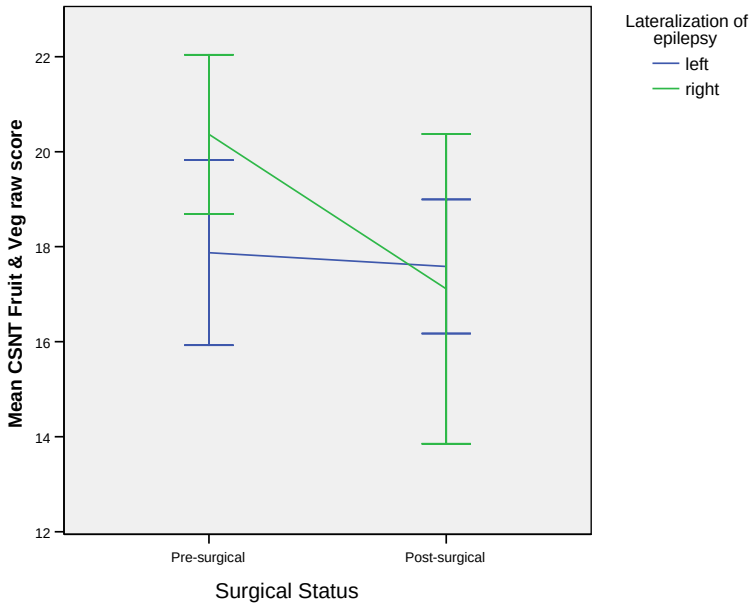

Figure 3. Mean scores on the CSNT Fruit and Vegetables subtest for patients with epilepsy (n=40). Note: Error bars represent +/- 1 SE.

CSNT Praxic.

The CSNT Praxic subtest (Figure 4), included utensils and tools used in the kitchen and household such as a whisk and a mallet. Average group performances appeared higher in the right- than the left group for both pre- and post-surgical groups. This was verified by a large, and statistically significant effect of lateralization F (1, 35) = 7.65, p = .009, η^2 = .18. The effect for surgical status was just below the statistical threshold for statistical significance F (1, 35) = 3.21, p = .08, η^2 = .08, with a medium to large effect size. There was no significant interaction (p > .05). Using Cohen's (1988) guidelines for power and effect size analyses, a further 26 to 64 participants would be required to achieve sufficient power of .80 for this non-significant effect to reach threshold for statistical significance.

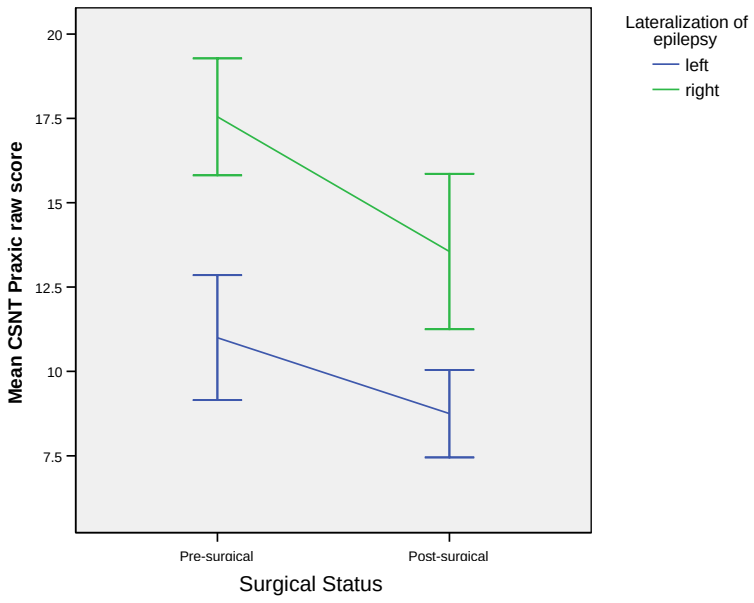

Figure 4. Mean scores on the CSNT Praxic subtest for patients with epilepsy (n=40). Note: Error bars represent +/- 1 SE.

CSNT Non-praxic.

For the CSNT Non-praxic subtest (Figure 5) items included objects encountered in the home and community such as a cameo broach and a wax seal. There were no significant main effects and effect sizes were small (Surgical status F (1, 35) = 2.18, p = .06, η^2 = .02, Lateralization of epilepsy F (1, 35) = 4.15, p = .06 η^2 = .06). There was no significant interaction (p > .05).

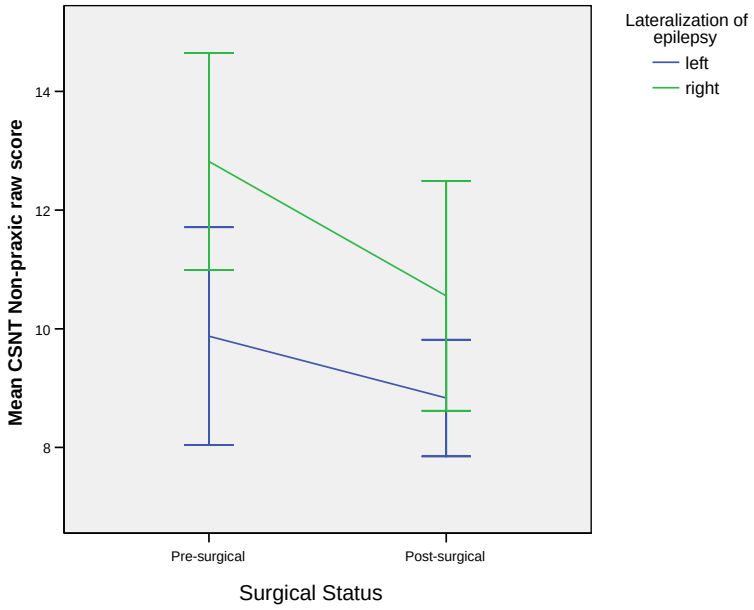

Figure 5. Mean scores on the CSNT Non-praxic subtest for patients with epilepsy (n=40). Error bars represent +/- 1 SE.

CSNT Total Score.

Figure 6 illustrates mean group performances for the CSNT Total Score. As expected given performances on the individual subtests, average group performances appeared higher in the right- than left-sided, in both pre- and post-surgical groups. The effects of laterality and surgical status were not statistically significant, with a small effect size for surgical status (F (1, 35) = 3.17, p = .08, η^2 = .05) and a medium effect size for lateralization of epilepsy (F (1, 35) = 5.35, .06, η^2 = .09). There was no significant interaction (p > .05). Using Cohen's (1988) guidelines for power and effect size analyses, a further 26 to 64 participants would be required to achieve sufficient power of .80 for these non-significant effects to reach threshold for statistical significance.

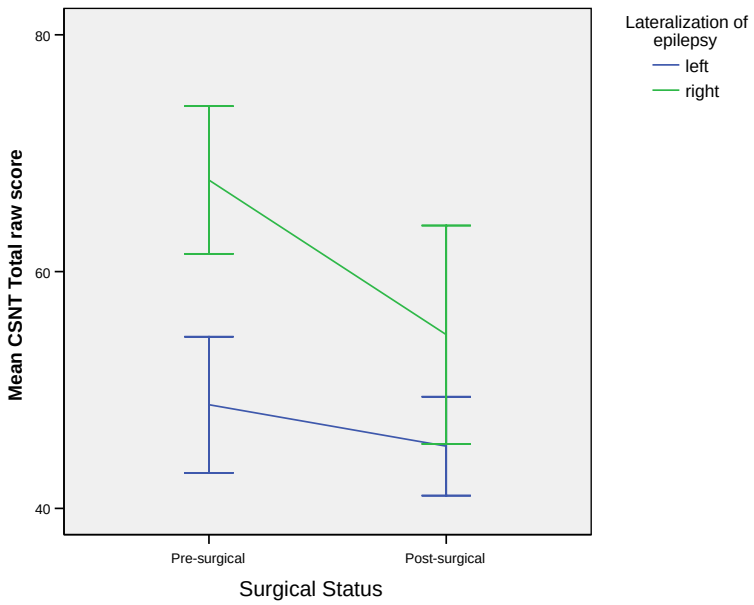

Figure 6. Mean scores on the CSNT Total Score for patients with epilepsy (n=40). Note: Error bars represent +/- 1 SE.

Boston Naming Test

Average group performances for the four groups are illustrated in Figure 7. Group performances appeared somewhat higher in the pre- than the post-surgical for both left- and right-sided epilepsy groups. A univariate ANCOVA was used to evaluate the effects of laterality and surgical status on the BNT. The effect of the covariate, Years of Education, was not significant but had a moderate effect size. Confirming the apparent difference between pre- and post-surgical groups in Figure 7, there was a significant effect for surgical status F (1, 37) = 6.24, $p < .05$, $\eta^2 = .14$, along with a moderate effect for lateralization that did not reach the level of statistical significance F (1, 37) = 3.12, $p = .09$, $\eta^2 = .08$. There was no significant interaction ($p > .05$). Power analysis revealed that 26 to 64 more participants would be required to reach threshold of statistical significance. There was no significant interaction.

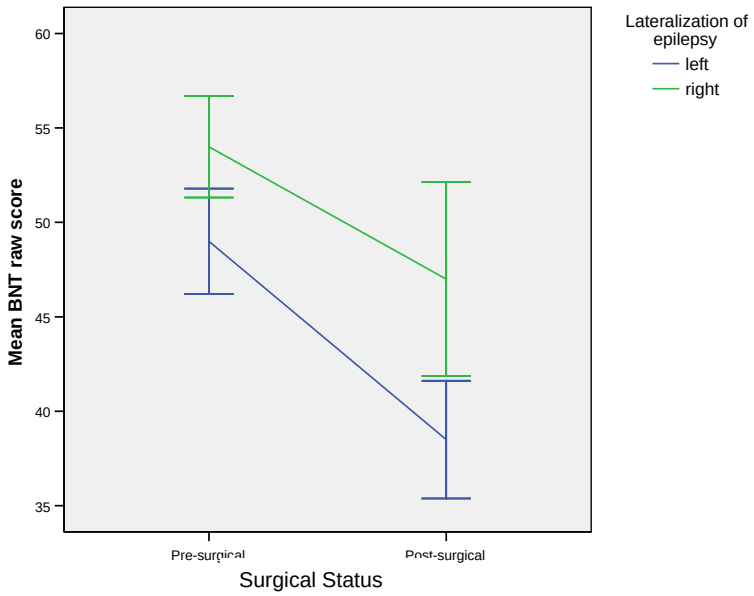

Figure 7. Mean scores on the BNT for patients with epilepsy (n=42). Note: error bars represent +/- 1 SE.

Controlled Oral Word Association Test

Controlled Oral Word Association Test

Average group performances for the four groups are illustrated in Figure 8. A univariate ANCOVA was used to evaluate the effects of laterality and surgical status on the COWAT. The effect of the covariate, Years of Education, was not significant. The effects for surgical status and lateralization were also nonsignificant, with small effect sizes. There was no significant interaction ($p > .05$).

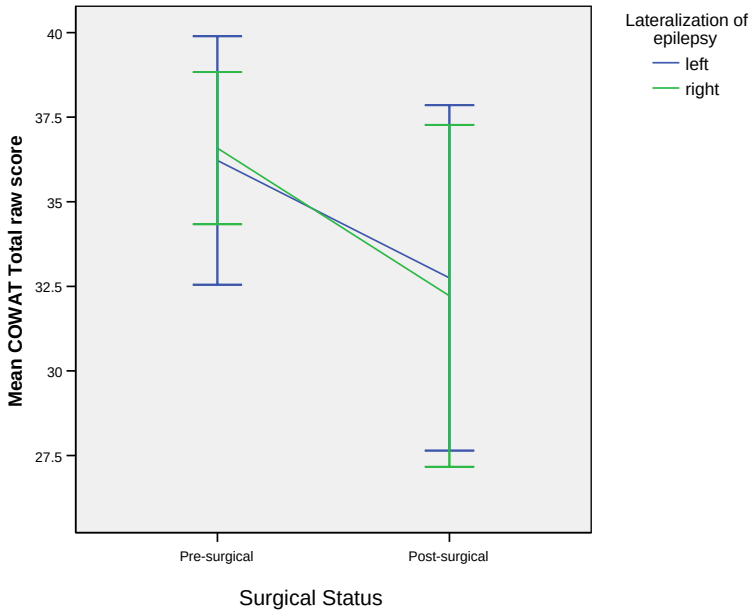

Figure 8. Mean scores on the COWAT for patients with epilepsy (n=42). Note: error bars represent +/- 1 SE.

Animal Fluency Test

Average group performances for the four groups are illustrated in Figure 9. There appears to be differences between left and right pre-operative and right pre- and post-operative groups, however univarite ANCOVA showed no significant effects for laterality or surgical status. The effect of the covariate, Years of Education, was not significant. The effects for surgical status and lateralization had only small effect sizes, and there was no significant interaction ($p > .05$).

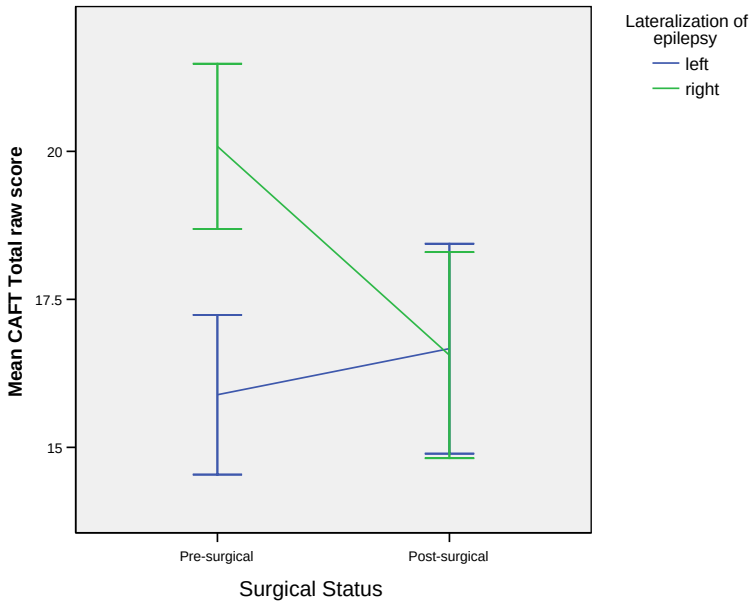

Figure 9. Mean scores on the Animal Fluency test for patients with epilepsy (n=42). Note: error bars represent +/- 1 SE.

Bayesian Analysis of Language Test Results

Bayesian statistics were used to determine the clinical utility of the tests examined in the present study via inspection of their sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios. The full data file was split into four groups (left pre-surgical, right pre-surgical, left post-surgical and right post-

surgical) with analysis performed for all confrontation naming (BNT and CSNT) and verbal fluency (COWAT and Animal Fluency) tests for left versus right pre-surgical patients, and for left versus right post-surgical patients. For the pre- and post-surgical groups, left- and right-sided epilepsy patients were compared to determine if the language tests were effective in identifying the language difficulties associated with left-sided pathology, and to determine if the 10^{th} percentile is an effective criterion point for differentiating left- from right-sided pathology**.** Pre- and post-surgery groups were separated in all analyses due to the potential confound of any effects of surgery on the results, as it is known that surgery results in changes in language function in LATL groups (Seidenberg, 1998). Although many of the CSNT subtests and verbal fluency tasks were found to be nonsignificant using a NHST approach, they were included in the Bayesian analysis to determine if the tests had any clinical utility despite the nonsignificant findings. Results for the CSNT, BNT, COWAT and Animal Fluency were examined in the context of criteria relevant to the practice of Evidence Based Medicine detailed by Sackett et al. (2000): Tests should be valid, capable of accurately distinguishing between patients who do and do not have a specific disorder, and applied to test for a specific disorder in individual patients.

The tests were evaluated in terms of their ability to detect left-sided pathology. Results were deemed to be valid by Sackett et al's criteria because they were obtained from a population that included both left- and right-sided pathology. Lateralization of pathology was determined by independent MRI, EEG and SPECT information for pre-operative patients, and confirmed pathology for post-operative patients. Independent

lateralization results were used to classify patient's disease laterality and combined with test results to determine numbers of true and false positive and negative outcomes.

Results of Bayesian analyses for all dependent variables are reported in Table 7. Base-rates, sensitivity and specificity, NPV and PPV, and positive and negative likelihood ratios were calculated to represent the probabilities associated with left-sided pathology in the pre- and post-surgical groups. Language tests were assessed using Bayesian formulae to determine if each test had the ability to accurately distinguish patients who do and do not have a specific disorder, where a positive test result was classified as a result *below* the 10th percentile, and a negative test result was classified as above the 10th percentile. The positive likelihood ratio and post-test odds were also used to determine if use of the tests resulted in increased post-test probability. Post-test probability needs to increase to over 80 % to demonstrate an improvement in clinical utility (Sackett et al., 2000). The BNT, the only test that met this criterion will be discussed here in detail. The implications of high sensitivity, specificity, and PPV and NPV have already been discussed in the introduction to this chapter (p. 28), and will be discussed for the BNT. The interpretation of high values for those variables would also apply where relevant, to other tests. However, although high sensitivity, specificity, PPV and NPV were observed in other tests, the clinical utility of these tests is less than the BNT because of the lower likelihood ratios, and small increases in post-test probabilities.

Results of the other naming and verbal fluency tests are only briefly discussed (in order of predictive utility) due to their small increases in post-test probabilities, and low clinical utility. For the naming tests, the CSNT Praxic subtest had a low likelihood of a positive test result ruling in left TLE with low specificity (45 %), low PPV (57 %) and a

small likelihood ratio (LR + = 3.22), but a high likelihood of a negative result ruling out left TLE (sensitivity, 100 %; NPV, 100 %, LR- 0) in the pre-surgical group, with similar results in the post-surgical group. The CSNT Non-praxic subtest had a low likelihood of a positive result ruling in left TLE (specificity, 36 %; PPV, 50%; LR+, 1.36) and moderate likelihood of a negative result ruling out left TLE (sensitivity, 87 %; NPV, 80%; LR,- .22) in the pre-surgical group, with similar results found for the post-surgical group. The CSNT Total score had a low likelihood of a positive result ruling in left TLE (specificity, 54 %; PPV, 54 %, LR + 1.34) and a low likelihood or a negative result ruling out left TLE (sensitivitiy, 75 %, NPV, 75 %, LR-, .46) in the pre-surgical group with similar results in the post-surgical group. The CSNT Fruit and vegetables subtest had a low likelihood of a positive result ruling in left TLE (specificity, 73 %, PPV, 40%; LR +, .92) and a low likelihood of a negative result ruling out left TLE (sensitivity, 25 %, NPV, 57 %, LR- 1.03) in the pre-surgical group, with similar results in the post-surgical group (Table 7).

For the verbal fluency tests, the Animal Fluency test had a low likelihood of a positive result ruling in left TLE (specificity, 75 %, PPV, 50 %; LR+, 1.32) and a low likelihood of a negative result ruling out left TLE (sensitivity, 67%; NPV, 75 %, LR- .44) in the pre-surgical group, with similar results in the post-surgical group. The COWAT had a low likelihood of a positive test result ruling in left TLE (specificity 75 %, PPV, 40 %, LR+, .88) and a low likelihood of a negative result ruling out left TLE (sensitivity 42 %, NPV, 46 %, LR- .86) in the pre-surgical group, with similar results in the post-surgical group (Table 7).

Table 7
Bayesian Analysis - Probability of Left-sided Pathology in the Pre- and Post-surgical Group

Test	Surgical status	Sensitivity	Specificity	PPV	NPV	LR (+)	LR (-)	Post-test Probability
Effective Test for Distinguishing left from right sided pathology								
BNT	Pre-surgical	.67	.92	.86	.78	8.37	.36	.86
	Post-surgical	.92	.78	.85	.87	4.18	.10	.85
Tests Deemed Not to be Effective for Distinguishing left from right sided pathology								
CSNT Animals	Pre-surgical	.87	.73	.70	.89	3.22	.18	70
	Post-surgical	.75	.55	.69	.62	1.67	.45	69
CSNT Praxic	Pre-surgical	1.0	.45	.57	1.0	1.82	0	.57
	Post-surgical	1.0	.33	.67	1.0	1.49	0	.67
CSNT Non-Praxic	Pre-surgical	.87	.36	.50	.80	1.36	.22	.49
	Post-surgical	.92	.22	.61	.67	1.18	.36	.61
CSNT Total score	Pre-surgical	.75	.54	.54	.75	1.34	.46	.49
	Post-surgical	.92	.44	.69	.80	1.64	.18	.68
Animal Fluency	Pre-surgical	.67	.75	.50	.75	1.32	.44	50
	Post-surgical	.50	.55	.60	.45	1.11	.91	59
COWAT	Pre-surgical	.22	.75	.40	.56	.88	1.04	40
	Post-surgical	.42	.67	.62	.46	1.27	.86	.62
CSNT F & V	Pre-surgical	.25	.73	.40	.57	.92	1.03	.40
	Post-surgical	.25	.67	.50	.40	.76	1.12	.50

Note: The 10th percentile was used to differentiate between normal and impaired naming function. Pre-surgical base rate = .42, post-surgical base-rate = .57.

The BNT was identified as the only valid and effective test using Bayesian analysis. Results are used as a worked example (Tables 8 and 9).

Table 8

*Bayesian Analysis – Lateralization of Epilepsy in the Pre-surgical Group * BNT (n=21).*

Result	Left-sided pathology present (null hypothesis false)	Left-sided pathology absent (null hypothesis true)	Total
BNT score < 10 %ile Positive (reject null hypothesis)	6 a (True +)	1 b (False +)	7
BNT score > 10 %ile Negative (retain null hypothesis)	3 c (False -)	11 d (True -)	14
Total	9	12	21

Table 9

*Bayesian Formulae: Laterlization of Epilepsy * BNT in the Pre-surgical Group*

Variable	Formula	Results
N	a + b + c + d	21
Base-rate	(a + c) / N	.43
Sensitivity	a / (a + c)	.67
Specificity	d / (b + d)	.92
Positive Predictive Value	a / (a + b)	.86
Negative Predictive Value	d / (c + d)	.78
Positive Likelihood Ratio	sensitivity / (1 - specificity)	8.37
Negative Likelihood Ratio	(1 – sensitivity) / specificity	.36

Using a score less than the 10^{th} percentile on the BNT to classify pre-surgical patients as having left-sided pathology, the base-rate of left-sided pathology was 43 %. Sensitivity was moderate, with 6 in 9 (67 %) patients with left-sided pathology obtaining a positive test result on the BNT. In contrast, specificity was high, with 11 in 12 (92 %) patients who did not have left-sided pathology obtaining a negative test result on the BNT. This means that with high specificity, a positive test result (< 10^{th} percentile) increased the likelihood of ruling in a diagnosis of left-sided pathology. In the pre-surgical group, the moderate positive likelihood ratio of 8.37 indicated a significant increase from the base-rate of 43 % to a post-test probability of 86 %. This indicates that

the BNT significantly raised the pre-test probability of detecting left-sided pathology in the pre-surgical group. This means that a positive result was more likely to be found in a person with, rather than without left-sided pathology. With the low level of false positives, high NPV, and large positive likelihood ratio, the BNT alone provided clinically meaningful information that would be of assistance in differentiating patients with left- and right-sided pathology. This ability was also evident in the post-surgical group, with an increase from the base-rate of 57 % to a post-test probability of 85 %.

Additional calculations were performed using an arbitrarily chosen score below the 10th percentile (raw score of 45) to determine if the increased predictive utility found by Kubu et al. (2001) and Busch et al. (2004) of using a specific score lower than the 10th percentile was shown in the present research. Results of these calculations (Table 10) demonstrated that there was no improvement gained by reducing the cut off criterion to a given score lower than the 10th percentile (raw score of 51) for the BNT in the present study. Both positive and negative predictive values for the lower cut off point were less clinically useful than those found using the 10th percentile as a cut off point in pre- and post-surgical groups. Furthermore, Table 10 shows that the lower BNT cut off point would not differentiate left from right TLE in the pre-surgical group (LR+ = .36) compared with effective differentiation using below the 10th percentile as a cut-off point, being a score below the raw score of 51 (LR+ = 8.37).

Table 10
Comparison of Bayesian statistics for specific cut-off points on the BNT.

Test	Surgical status	Sensitivity	Specificity	PPV	NPV	LR (+)	Post-test odds
Effective Tests for Distinguishing left from right sided pathology							
BNT (10th %ile, raw score of 51)	Pre-surgical	.67	.92	.86	.78	8.37	.86
	Post-surgical	.92	.78	.85	.87	4.18	.85
BNT (raw score of 45)	Pre-surgical	.33	.09	.75	.65	.36	.42
	Post-surgical	.83	.78	.83	.78	3.77	.59

Note: A raw score of 45 was used to differentiate between normal and impaired naming function. Pre-surgical base rate = .42, post-surgical base-rate = .57.

CSNT Animals Subtest.

The CSNT Animals subtest was nonsignificant on MANCOVA, however, on Bayesian analysis the test differentiated well between pre-surgical patients who had left-sided pathology and those who did not. This result needs to be further investigated given that the CSNT normative data indicated that males performed significantly better than females on the CSNT Animals subtest (males: 25/30, females 20/30), and there was a significant gender imbalance in the groups (left pre-surgical 1 male, 8 female; right pre-surgical 10 male, 2 female; left post-surgical 1 male, 11 females; right post-surgical 3 males, 6 females). Bayesian analysis was conducted separately for the female group (pre- and post-surgical groups combined) to determine if the predictive utility demonstrated on the mixed gender pre-surgical and post-surgical groups remained within an acceptable level for detecting left-sided pathology in female participants alone. As mentioned earlier, females, and not males were chosen because only two left TLE participants were male, and one did not complete the CSNT. Bayesian analysis for the female participants showed that PPV remained high (77 %), although NPV was

significantly less (33 %) than for the mixed gender pre-surgical (89 %) and post-surgical (62 %) groups. Therefore, there was a low likelihood that a female did not have left-sided pathology given a negative test result, and low likelihood of a positive test result ruling in a diagnosis of left-sided pathology (due to low NPV). While the positive likelihood ratio was very small (LR+ 1.28), this represented a very small increase from the pre-test odds compared to the small, but more clinically significant positive likelihood ratio of 3.22 in the mixed gender pre-surgical group. This shows a decrease in clinical utility of the CSNT Animals subtest for female participants, suggesting that the gender effect for CSNT Animals contributed to the high likelihood ratios observed for the mixed gender pre-operative and post-operative groups. This is consistent with the nonsignificant findings obtained using MANCOVA (reported on page 39).

Test Deemed Not Effective for Identifying Left-sided Pathology Determined Using Bayesian Analysis

The CSNT, COWAT, and Animal Fluency did not make a meaningful contribution to differentiating between those with, and those without left-sided pathology. To be effective, tests needed to increase the base-rate to post-test probabilities greater than 80 % to demonstrate improved clinical utility (Sackett et al., 2000). In this sample of patients with epilepsy with mean FSIQs and WAIS-III Vocabulary subtest scores within the Average range, increases from base-rate to post-test probability did not exceed 70 %.

Discussion

The present research aimed to investigate the utility of the CSNT and other conventional tests of naming and fluency in patients with epilepsy, compare methods for evaluating pre- and post-surgical language function of the ATL region, and in doing so, clarify the inconsistencies within this area of research.

Patients with left-sided epilepsy were expected to perform worse on tests of confrontation naming than right-sided epilepsy patients, and this hypothesis was supported. The BNT was not identified as significant for lateralization of epilepsy on ANCOVA, but Bayesian analysis revealed that it was useful for identifying left TLE using a cut-off below the 10th percentile in the pre-operative group. Furthermore, in the post-surgical group a score below the 10th percentile was associated with an increased likelihood of left-sided pathology. This finding was not consistent with Kubu et al. (2001) and the extension of this study by Busch et al. (2004) where both studies reported that the 10th percentile (recommended by Spreen and Strauss, 1997) was not an effective cut-off point to differentiate normal from impaired naming function. It is possible that the inconsistency between the earlier findings of Kubu et al (2001) and Busch et al (2004), and those of the present research could be due sampling differences. The results of Kubu et al. (2001) and Busch et al.(2004) were presented at American Epilepsy Society (AES) Conferences in 2001 and 2004 respectively, and have not yet been published so it was not possible to do a more detailed analysis of the differences between the methodology and results of these studies, and the classification of left and right TLE. This comparison would be needed to better understand these inconsistent findings. For the CSNT, MANCOVA revealed a statistically significant difference between left- and

right-sided epilepsy patients on the CSNT Praxic subtest, however the CSNT was not found to be effective for differentiation of left and right TLE on Bayesian analysis.

The hypothesis that patients with left-sided epilepsy would perform worse than patients with right-sided epilepsy on tests of verbal fluency was not supported on ANCOVA or Bayesian analysis. Results were not consistent with Suchy et al. (2003), Hermann and Wyler (1988), Benton (1968), Milner (1964), and Jokeit et al. (1998), but were consistent with Martin et al.(2000) who found an effect for lateralization on verbal fluency tasks, with left TLE patients performing worse than right TLE patients.

It was predicted that the CSNT would be more effective at distinguishing between those who have left-sided pathology and those who do not have left-sided pathology than the BNT due to the lower ceiling on the latter. This hypothesis was not supported. The CSNT was not found to be effective at differentiating left from right-sided epilepsy, and resulted in only modest increases from base-rate to post-test probability on Bayesian analysis. There were no main effects, or interactions for surgical status or lateralization on the CSNT Animals subtest, and although there appeared to be an acceptable level of clinical utility in the mixed gender pre- and post-surgical groups, this was not found for the female group, and suggests that the small likelihood ratio observed in the mixed gender group may be due to sampling differences. To be an effective test, an increase to a post-test probability of 80 % would be expected (Sackett et al., 2000). The BNT achieved this increase but the CSNT did not. Further research is required to determine if the CSNT is effective for differentiating left from right TLE in highly functioning TLE patients (due to the high ceiling).

On appearances, the neuropsychological tests used in the present study show a decline in right TLE groups post-surgically (Figures 2 to 9). This is likely to be due to sampling differences, rather than an effect of surgery due to the cross-sectional study design.

Results of neuropsychological testing strongly supported the clinical use of the BNT in patients with epilepsy, consistent with earlier research (Davies et al., 1994; Hermann & Wyler, 1998; Busch et al., 2005). The 10th percentile was found to be effective for differentiating between left and right TLE using the BNT in this sample, and this effect was not found for the lower cut off point (raw score of 45). This was inconsistent with the results of Kubu et al. (2001) and Busch et al (2004). All other tests (CSNT, COWAT and Animal Fluency) were associated with only modest increases from pre-test odds and were not effective tests for differentiating left from right sided pathology in TLE patients. The criterion of the 10th percentile was chosen to enable comparison with earlier research, although future research involving a larger sample may consider calculation of the Receiver Operating Curve to obtain sensitivity and specificity values to provide Likelihood Ratios for different scores between 51 and 45 to determine the optimal cut-off score relevant to the sample.

Due to the small number of participants scheduled for surgery during the time-frame of the present study, it was not possible to recruit a sufficient number of patients to enable a longitudinal focus. Instead, the present study was cross-sectional with comparison on the basis of laterality (left, right) and surgical status (pre, post). Further research is needed with a longitudinal focus to facilitate a better understanding of the

impact of surgery for epilepsy at the level of the individual, and to further investigate the use of the CSNT in Australia in highly functioning patients with epilepsy.

CHAPTER 3

Functional Magnetic Resonance Imaging Assessment of Language Function

Overview of Functional Evidence Involving the Anterior Temporal Lobe Region

Surgical entry to the temporal lobe is gained via the Anterior Temporal Lobe (ATL), which subsequently sustains a certain degree of damage. It is important to lateralize the language function of the ATL region prior to surgery to reduce the risk of post-surgical language difficulties (discussed in Chapter 2). Identification of effective tests for localizing the language function of the ATL has been the focus of the present study. As discussed in Chapter 1, fMRI has been used to investigate language in people with TLE, with ATL activation identifying the language dominant hemisphere (Schwartz, Haglund, Lettich, & Ojemann, 2000). Robust ATL activation has also been associated with early onset of TLE (Devinsky et al., 1993). Activation elicited through fMRI has also indicated involvement of the ATL in naming, and in comprehending nouns (Glosser & Donofrio, 2001; Ojemann, et al.,1989). Patterns of activation have also been found to be category-specific (Spitzer, Kwong, Rosen, & Belliveau, 1995), with ATL activation being associated with naming faces (Tsukiura et al., 2002; Glosser, et al., 2003; Seidenberg et al., 2002) and sentence reading (Bavelier et al., 1997). The findings of category-specific ATL activation on fMRI are consistent with the lesion studies discussed in Chapter 2, where focal lesions were associated with specific impairment of language function.

Facial naming was investigated by Tsukiura et al. (2002), who tested 10 post-surgical TLE patients and 10 matched controls on four face retrieval tasks. Names and occupations associated with previously unfamiliar faces were learned, with the first two tasks testing new learning of this information. The final two tasks involved retrieval of the names, and subsequently, occupations of famous people. When compared with the control group, left-sided TLE patients had difficulty with retrieving names, irrespective of facial familiarity, and interestingly, right-sided TLE patients also had difficulty with the retrieval of newly learned names. fMRI scanning was conducted with control participants during tasks, with significant group average activation identified in the ATL, superior frontal gyrus, cingulate gyrus, striate cortex, and cuneus during both the newly learned and Famous Faces tasks.

Leveroni et al. (2004) also compared fMRI activation during viewing of newly learned faces and Famous Faces with control participants (n=11). Their methodological approach was somewhat different. They asked participants to decide if the depicted face was familiar, and to press the left button if the face was familiar, and the right button if the face was unfamiliar. The participants were not required to think of the name associated with the familiar face. Bilateral activation was present in the medial frontal, superior frontal, and middle temporal regions. ATL activation was evident on the right but not on the left.

Griffith et al. (2006) used Famous Faces in a PET study with 12 TLE patients (3 LTLE, 6 RTLE, 1 bilateral, & 2 not verified). In this study, participants were asked to decide if the depicted face was familiar, and furthermore, to think of the person's name,

and any other information known about the person. The study focused exclusively on ATL activation using PET, and found significant left, but not right, ATL activation. It was noted that the left ATL activation was strongly associated with retrieval of specific semantic information about a familiar individual. It was proposed that the ATL may be involved in a co-ordinating role, or organising retrieval of semantic information.

Huddy, Schweinberger, Jentzsch and Burton (2003) adopted a different form of decision-making task in an EEG study. Twenty control participants were shown pairs of photographs that were either semantically congruent (for example, two actors) or name congruent (same name). Participants were asked to press one of three different buttons if the faces matched semantically, by name, or neither. The extent of ATL activation was greater during the naming of faces than during determination of semantic congruency

Post-surgical activation during naming tasks was examined by Grabowski et al (2003) with a sample of 8 post-surgical left-sided TLE patients in a PET study to determine if there was associated activation in the remaining regions surrounding the left ATL. A series of photographs of famous people were presented, with the participant required to indicate by button press if the person was familiar, and instructed to try to name the person sub-vocally. The left anterior superior temporal gyrus that is active in this task in normal individuals was not active in post-surgical patients at either the group, or individual level of analysis. It was proposed that resection of the left ATL may have resulted in a functional disruption of the left anterior superior temporal gyrus. Increased activation in visual regions was interpreted as visual processing compensation for inefficient functioning in the anterior temporal region (Grabowski et al, 2003). The study

was limited by the absence of pre-surgical PET scans: it is not possible to exclude the possibility that inactivity in the residual left ATL, and superior temporal gyrus was due to factors other than surgery, such as pre-existing language representation, the chronic effects of seizures, or long-term anti-epileptic medication.

ATL involvement in Sentence Reading was examined by Bavelier et al. (1997) with a sample of eight control participants. The study involved two fMRI sessions; the first session included alternating blocks of sentences and consonant strings. The second session included alternating blocks of American Sign Language (ASL) sentences and ambiguous hand signs. None of the participants were familiar with ASL. Results were reported at both the individual, and group average levels. Activation during the Sentence Reading task was present in the traditional language areas of the left hemisphere (Broca's, Wernicke's and the angular gyrus) along with the left ATL. It was noted that there was marked inter-individual variability. The general pattern of functional organisation was broadly consistent across individuals, although the extent of activation, and the location, varied considerably.

Following review of the studies discussed above, it is clear that there has been considerable variability in the methodology used to localize language function of the ATL, and that there are limitations inherent in the localization of language arising from these studies. One limitation was the absence of individual results in four of the six studies. Individual results would be necessary to determine consistency of an activated region across individuals, and satisfaction of the criteria recommended by Schwartz et al. (1998) in Chapter 1 (p. 16). Comparison across studies was difficult due to the different

methodologies, samples, and absence of neuropsychological data for comparison (Table 11).

It appears that left ATL activation occurs in the context of naming Famous Faces, and Sentence Reading, although the methodology required to elicit reliable activation has not yet been well established. ATL activation was reported in four of the six reviewed studies, and appears to be associated with naming, although its involvement with Sentence Reading is suggestive of a more complex semantic role. The language areas established through lesional and functional language studies that were mentioned in Chapter 1 are well represented by the reviewed tasks, particularly in the Famous Faces studies by Tsukiura et. al. (2002), Leveroni et al. (2004), and the Sentence Reading study by Bavelier et. al. (1997). The remaining studies focussed on ATL language function and did not report the activation of additional language areas (Table 11).

Table 11

Regions Activated During Famous Faces and Sentence Reading fMRI Studies

Region of Activation	Study Tsukiura et al. (2002) Famous Faces	Leveroni et al. (2004) Famous Faces	Griffith et al. (2006) Famous Faces	Huddy et al. (2003) Famous Faces	Bavelier et al. (1997) Sentence Reading
Left Hemisphere					
Superior Frontal Gyrus (BA 8, 10)	*	*			
Middle Frontal Gyrus (BA 9)	*	*			
Inferior Frontal Gyrus (BA 47)					*
Central Sulcus					*
ATL (BA 38)	*		*	*	*
Middle Temporal Gyrus (BA 21)		*			*
Middle Temporal Gyrus (BA 39)		*			*
Superior Temporal Gyrus (BA 22)					*
Cingulate (BA 31)	*	*			*
Cingulate (BA 32)	*				*
Striate cortex (BA 17)	*	*			
Cuneus (BA 18)	*				
Cuneus (BA 19)	*				
Right Hemisphere					
Superior Frontal Gyrus (BA 8, 10)		*			
Middle Frontal Gyrus (BA 9)		*			
Inferior Frontal Gyrus (BA 47)		*			
ATL (BA 38)		*			
Middle Temporal Gyrus (BA 21)		*			
Middle Temporal Gyrus (BA 39)		*			
Superior Temporal Gyrus (BA 22)		*			*
Superior Temporal Gyrus (BA 41)		*			*
Cingulate (BA 32)		*			

The Present Study

The present study aimed to find, and determine if Famous Faces naming and Sentence Reading fMRI tasks are capable of eliciting consistent ATL language function across individual control participants and patients with epilepsy. It is important to validate fMRI tasks that elicit left ATL activation because it has been shown that the ATL is involved in language function (Tsukiura et al., 2002; Griffith et al., 2006 &

Huddy et al., 2003), and it is the site through which the surgeon gains entry to the mesial temporal structures during surgery for intractable TLE. A Famous Faces naming task was used because it involves recognition and naming, and has been shown to elicit ATL activation, and a Sentence Reading task because it has been shown to elicit ATL and other frontal, and temporal lobe activation on fMRI for control, and epilepsy patient participants. Specific hypotheses are detailed below.

Hypotheses

1. The Famous Faces task would elicit consistent left-sided ATL activation in individuals and averaged group results.
2. The Sentence Reading task would elicit consistent left-sided ATL activation in individuals and averaged group results.

Method

Participants

The fMRI component of the study involved a pilot and an imaging study. For the fMRI pilot study, 20 participants (11 men, 9 women) with a mean age of 38 were recruited to ensure that the faces chosen for the Famous Faces naming task were indeed familiar, thus validating the task. Control participants in the pilot study did not take part in the imaging study. A non-clinical volunteer (male, aged 31) participated in a preliminary fMRI scan to test methodology and procedures.

The fMRI control group consisted of 10 non-clinical participants ranging in age from 23 to 42 years. The sample included 4 men with a mean age of 32 (range: 27 to 42),

and 6 women with a mean age of 27 (range: 23 to 30). All control participants were associates of the student researcher, were over the age of 18, and were initially approached in person and the aims of the study and requirements of participation were explained verbally. They were informed that their decision to participate, or not to participate would not have any effect on their relationship with the researcher. Those interested in participating were provided with the relevant PICF to review (Appendix D), and following clarification of any questions, formal consent was obtained through signature of the PICF. Exclusion criteria were prior diagnosis of a neurological condition, or visual difficulties. A non-clinical control group was considered to be the most appropriate because of the need to compare fMRI results obtained from epilepsy patients to the healthy, normally functioning brain and to compare language activation of epilepsy patients to the results of healthy individuals.

The fMRI patient group consisted of two male patients with right-sided TLE, and four female patients with left-sided TLE awaiting epilepsy surgery at St. Vincent's Hospital, Melbourne. Laterality of seizures was determined by various procedures including MRI, EEG, and SPECT. Potential participants in the patient group were identified by the epilepsy surgery program co-ordinator, and the patient was contacted by telephone and invited to participate. Patients were informed that their decision to participate or not would not influence the timing of their surgery or their treatment at St. Vincent's Hospital. Those interested in participating were mailed the relevant PICF to review, and any questions were subsequently clarified. Formal consent was obtained through the patient signing the consent to participate section of the relevant PICF.

Participants that took part in the study were all right-handed as confirmed by the Edinburgh Handedness Inventory (Oldfield, 1971). They were not offered any form of remuneration for their involvement in the study. Participants were classified according to their membership in the control (c) or patient (p) group. For example, participant 1 in the patient group was identified as 'p1'. Patient demographics and suspected pathology are detailed in Table 12.

Table 12
fMRI Patient Demographics

Demographics & suspected pathology

Patient	Gender	Age	Education	Age at onset of seizures	Seizure Frequency (for 1 month)	Medication (Monotherapy, Polytherapy)	Suspected Pathology
p1	F	42	8	13	4	P	Left mesial temporal sclerosis.
p2	F	38	9	8	7	P	Left TLE
p3	M	27	8		9	P	Left TLE
p4	M	29	12		4	M	Left TLE, and bilaterally reduced hippocampal volume.
p5	F	37	9		10	P	Right fronto-temporal mass effect.
p6	F	55	8		8	M	Right TLE with left-sided frontal and parietal gliosis & small vessel ischemia.

Materials

All fMRI scanning sessions were conducted at St. Vincent's Hospital, Melbourne using a Siemens Magnetom Avanto 1.5 Telsa. Structural and volumetric scans were performed initially followed by two functional tasks; a name retrieval activity that used Famous Faces accessed from free-ware internet pictures (Table E1) and a Sentence

Reading activity that used sentences with general knowledge content (Table E2). Famous Faces were presented in greyscale format on a white background, with adjustments made to brightness and contrast to ensure consistency. As the original picture sizes varied, adjustments were made to maintain the quality of the picture and to ensure that the pictures were approximately 4.5cm high by 3.5cm wide. Sentences were presented in black Times New Roman font at a size of 54 points on a white background. Sentence length ranged from six to 12 words with a mean length of 8.66 across two lines of reading text. All material was counterbalanced by subject topic and general period (year). For example, some of the photographs related to famous people of the 1970s, and others of people famous in the 1990s. Similarly, some sentences were representative of events that occurred in earlier years, and others of more recent events. The fMRI tasks were constructed on the basis of tasks described by Tsukiura et al. (2002), Glosser, Salvucci & Chiaravalloti (2003) and Seidenberg et al. (2002).

Design and Procedure

The fMRI component involved a pilot phase in order to evaluate the efficacy of the new fMRI tests, prior to use with the imaging groups. The pilot control participants were asked to view a series of photos presented on a computer. They were required to indicate if the featured person was familiar, and secondly if they could identify the person by name. The responses were used to select photos with the highest familiarity for the fMRI protocol. Four faces were replaced due to levels of familiarity below 70% (Table E1).

After validation of the Famous Faces task, a control volunteer participated in an fMRI scan to test the fMRI method and procedures. Following this initial testing, the control group participated in fMRI testing. The functional tasks were presented using Microsoft Powerpoint presentation software and an overhead projector. The projector was programmed to present the Powerpoint slides in reverse image, and the image was projected through the back of a blank white screen so that the slides appeared in the correct orientation when viewed by the participant. The screen was positioned between the projector and the MRI scanner. The participant viewed the image presented on the screen whilst in the scanner through a mirror attached to the MRI headpiece. Adjustments were made with each individual to ensure that the mirror and screen were in the correct position to ensure comfortable viewing of the presented material.

For each task respectively, the Famous Faces naming task slides were counterbalanced by age period, and the Sentence Reading task slides by sentence length, and presented in alternating blocks of 15 (ABAB design) at a presentation rate of 4 seconds. The famous faces slides in the Famous Faces naming task and sentences in the Sentence Reading task, represented the active (A) components for each task, and consonant strings represented the baseline (B) component of the functional study. Consonant strings were chosen for the baseline component in line with the previous research mentioned above, and is intended to subtract the reading component from the experimental task. For example, during the Famous Faces naming task, a participant would firstly view 15 slides of famous faces (A), followed by 15 slides of consonant strings (B), and then 15 slides of famous faces (A) with this series repeated for three

blocks of faces and three blocks of consonant strings resulting in a total of 45 active, and 45 baseline slides. Prior to commencement of the fMRI scan, participants were asked to think of the person's name without verbalizing it for the Famous Faces task, and to read the sentences without verbalizing the words during the Sentence Reading task. Participants were asked to read the string of letters during presentation of consonant strings. Instructions were given verbally prior to entering the scanner, and then projected on the screen in written format immediately prior to each task, when the person was in the scanner. fMRI scanning took approximately 30 minutes for each patient.

Structural, volumetric and functional data files that were generated following an individual fMRI scan are described in Table 13.

Table 13
fMRI Testing of ATL Activation. Data Generated from fMRI Scanning Sessions

File	Number of slices/files
Localizer of the temporal lobe	
High-resolution structural image	256 slices
Structural image	25 slices
Famous Faces functional task	180 files
Famous Faces functional task (with motion correction applied on site)	180 files
Sentence Reading functional task	180 files
Sentence Reading functional task (with motion correction applied on site)	180 files
Intermediate t-maps	
Mean and t-maps	

Note. Functional task files were subsequently converted to 4D 90 volume files.

Analysis of fMRI results was carried out using FMRI Expert Analysis Tool Version 5.43, part of FSL (FEAT; FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). The focus was predominantly to identify if either of the fMRI tasks resulted in consistent activation in the ATL, as shown by greater BOLD responses during the active blocks of

famous faces and sentences when compared to the baseline blocks of consonant strings. A lower-level FEAT analysis was used at the level of the individual, and a higher level FEAT analysis at the group level. Furthermore, the study aimed to determine if there was a difference in the areas of language activation between the control and patient participants.

Analysis of Individual Cases.

The following pre-statistics processing was applied. Motion artefacts were corrected using Motion Correction applied to FLIRT, FMRIB's Linear Registration Tool (MCFLIRT), an intra-modal motion tool designed for use in fMRI studies (Jenkinson, 2002). MCFLIRT corrections are reported in Table F1 for the Famous Faces naming task and in Table F2 for the Sentence Reading task. Non-brain material (for example, the skull) was removed using the Brain Extraction Tool (BET; Smith 2002). Spatial smoothing was conducted using a Gaussian kernel of 3mm (FMRIB Manual). Mean-based intensity normalisation was applied to all 90 volumes of each task by the same factor. Highpass temporal filtering was selected (Gaussian-weighted straight line fitting, with sigma = 50.0s). Registration to a 25-slice high-resolution structural image and subsequently with standard images was carried out using FLIRT (Jenkinson 2001, 2002). Time-series statistical analysis was carried out using FMRIB's Improved Linear Model with local autocorrelation correction (FILM, Woolrich 2001). Z (Gaussianised T/F) statistic images were thresholded using clusters determined by $Z > 2.3$ and a (corrected) cluster significance threshold of $p < 0.05$ (Worsley 1992).

For each individual participant, cluster analysis and high-resolution rendered images were used to illustrate the active regions of the brain during the fMRI Famous Faces and Sentence Reading tasks respectively. Significant regions of activation were identified through cluster analysis at the level of the individual participant. Rendered images of the functional data depict significant activation pictorially in standard radiologic format (left = right / right = left).

Analysis of Group Data.

Higher-level analysis at the group average level was also conducted using FEAT, with all of the individual (lower-level) analyses fed into the higher-level analysis. Because all pre-processing (for example, motion correction and non-brain material extraction) was completed during lower-level analyses, the only processing options available for higher-level analysis are FEAT 'Stats' and 'Post-stats' (FMRIB Manual). For set-up of the Statistics, the options of Fixed Effects (FE) and Mixed Effects (ME) are available. The FE model uses within-session, across-time variances (varcopes) from the lower-level analyses. Higher FE group average estimation is achieved through comparing the lower and higher-level varcopes. In contrast, Mixed-effects (ME) variance uses the sum of FE variance and random-effects variance ('true' variances of first-level parameter estimates) providing a result that is more generalizable to the wider population from which the participants were selected (FEAT Manual). In summary, FE analysis is sensitive to activation, and ME is both sensitive, and has greater generalizability to the sample population through control of random error (FEAT

Manual). When FE is selected, there are no further processing options to consider. For ME, the options are ordinary least squares (OLS), and local analysis of mixed effects (FLAME). OLS is the least accurate, but fast technique that ignores all lower-variance and focuses only on higher level variance. The most accurate higher-level estimate is provided by FLAME.

For the present study, an ME FLAME 1 design was applied. For the 'Post-stats', a Single Group Average (one sample t-test) design was chosen, and applied to the control and patient groups separately. In the Single Group Average design, the lower-level analyses were initially registered to their individual high-resolution structural image, and then to a standard image defined by Taliarchic space. Comparison was then made across control and patient groups participants to identify regions that activated at the group average level.

Patient group results were analysed at the group average level in line with standard practice, although the difficulties with comparing patients with heterogeneous pathologies (reported in table 20) were considered during interpretation of results. Different brain structure, and individual variability in the representation of language function observed in patients with epilepsy suggest that analysis of individual data is more appropriate, and clinically meaningful (Brown, 1997). Individual and group average results for the control group are presented first, followed by results for the patient group.

Results

Famous Faces Naming Task – Individual Results

Control group.

Areas of activation during the fMRI Famous Faces task identified during cluster analysis were classified on the basis of lateralization, brain region, and individual participant (summarized in Table 14), with individual control group results represented in Appendix G. Activation was reported at the level of the individual with the threshold set at $Z > 2.3$ ($p < .05$). The threshold of activation is commonly set at this level to retain maximum sensitivity to detect activation, and reduction of activation not related to the task (noise). If the threshold is set too low, the level of noise is high and it is difficult to differentiate task-related activation from noise. If the threshold is set too high, noise is reduced, but task-related activation is also mistaken as noise and is conservatively reduced (FMRIB Manual). ATL activation was identified in only one control participant in the left and one in the right. On inspection of individual activation figures (Appendix G), there was, however, activity in anterior regions in close proximity to the ATL, for example, the anterior aspect of the Middle Temporal Gyrus. Other language areas were also activated in a low number of controls (<40%).

Table 14
Summary of fMRI Famous Faces Naming Task Activation in Language areas in the Control Group (n=10)

			Participant									
Region	BA	# of controls showing activation	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10
Left Hemisphere												
Superior Frontal Gyrus	8, 10	0										
Superior Frontal Gyrus	11, 19	3			*	*			*			
Middle Frontal Gyrus	10, 11	3			*		*	*				
Medial Frontal Gyrus	9, 10	2				*			*			
Precentral Gyrus	4, 6	2	*								*	
Inferior Frontal Gyrus	13, 45, 47	3		*				*			*	
Central Sulcus		0										
Anterior Temporal Lobe	38	1							*			
Superior Temporal Gyrus	22	2			*					*		
Middle Temporal Gyrus	19, 21	1				*						
Middle Temporal Gyrus	39	2								*		*
Inferior Temporal Gyrus	20	1				*						
Cingulate	31, 32	2		*							*	
Striate Cortex	17	0										
Cuneus	18, 19	0										
Right Hemisphere												
Superior Frontal Gyrus	9, 10, 11	3		*					*	*		
Middle Frontal Gyrus	9	0										
Middle Frontal Gyrus	6, 10, 11, 46	4	*					*	*		*	
Precentral Gyrus	4, 6	4	*				*		*			*
Inferior Frontal Gyrus	47	3						*			*	*
Anterior Temporal Lobe	38	1		*								
Middle Temporal Gyrus	21, 39	0										
Superior Temporal Gyrus	22	1							*			
Superior Temporal Gyrus	41	0										
Inferior Temporal Gyrus	19, 20	2			*					*		
Cingulate	32	1			*							
Fusiform Gyrus	19, 37	4	*	*			*					*

Note: BA = Brodmans Area. Only activation for areas above the threshold for significance Z > 2.3 are reported.

Significant ATL activation on either side was only evident for participant's c2 and c7. Specific results for participant c2 are included as an example of elicited ATL

activation, with a high resolution rendered image in Figure 10, and results reported in Table 15. For participant c2, activation was identified in the right temporal pole, indicating right ATL involvement in the Famous Faces naming task for this particular participant. Activation in this person was also elicited in the left Anterior Cingulate Gyrus, and in the right Superior Frontal Gyrus, ATL and Cingulate Gyrus.

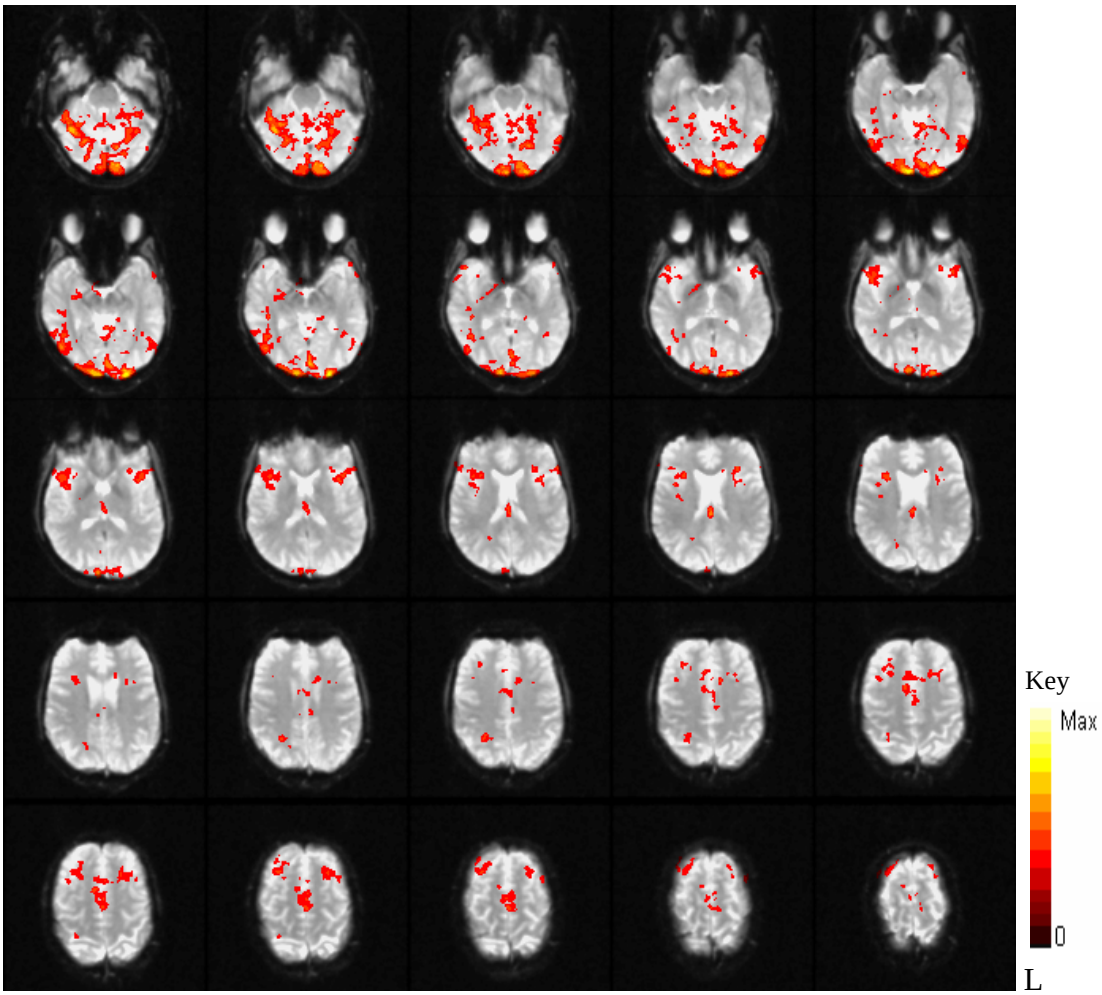

Figure 10. High resolution 25-slice rendered functional image for control group participant c2 during the fMRI Famous Faces naming task.

Table 15
Famous Faces Naming Task: fMRI Activation of Language Areas for Participant c2

Region	No. of voxels	Brodmann's Area	Talairach Coordinates *x*	*y*	*z*	Z Value
Left Hemisphere						
Inferior Frontal Gyrus	676	47	-43.3	16	-8.1	5.74
Anterior Cingulate	180	32	-10.7	29.4	22.5	4.67
Cuneus	3530	19	-23	-97	32.6	10.9
Right Hemisphere						
Superior Frontal Gyrus	332	9	30.4	46.1	27.2	4.87
Fusiform Gyrus	1370	37	38.4	-62	-11	8.98
Anterior Temporal Lobe	646	38	50.3	19.1	-21	5.5
Cingulate Gyrus	643	23	1.56	-18	23.5	6.29

Note: Only activation above the threshold of Z = 2.3 are reported.

Specific results for participant c7 are included as an example of left-sided ATL involvement in naming, with a high resolution rendered image in Figure 11 and results in Table 17. Activation was also present in the left Superior Frontal and Medial Frontal gyri, and ATL, and right Superior Frontal, Middle Frontal, Medial Frontal, and Superior Temporal gyri.

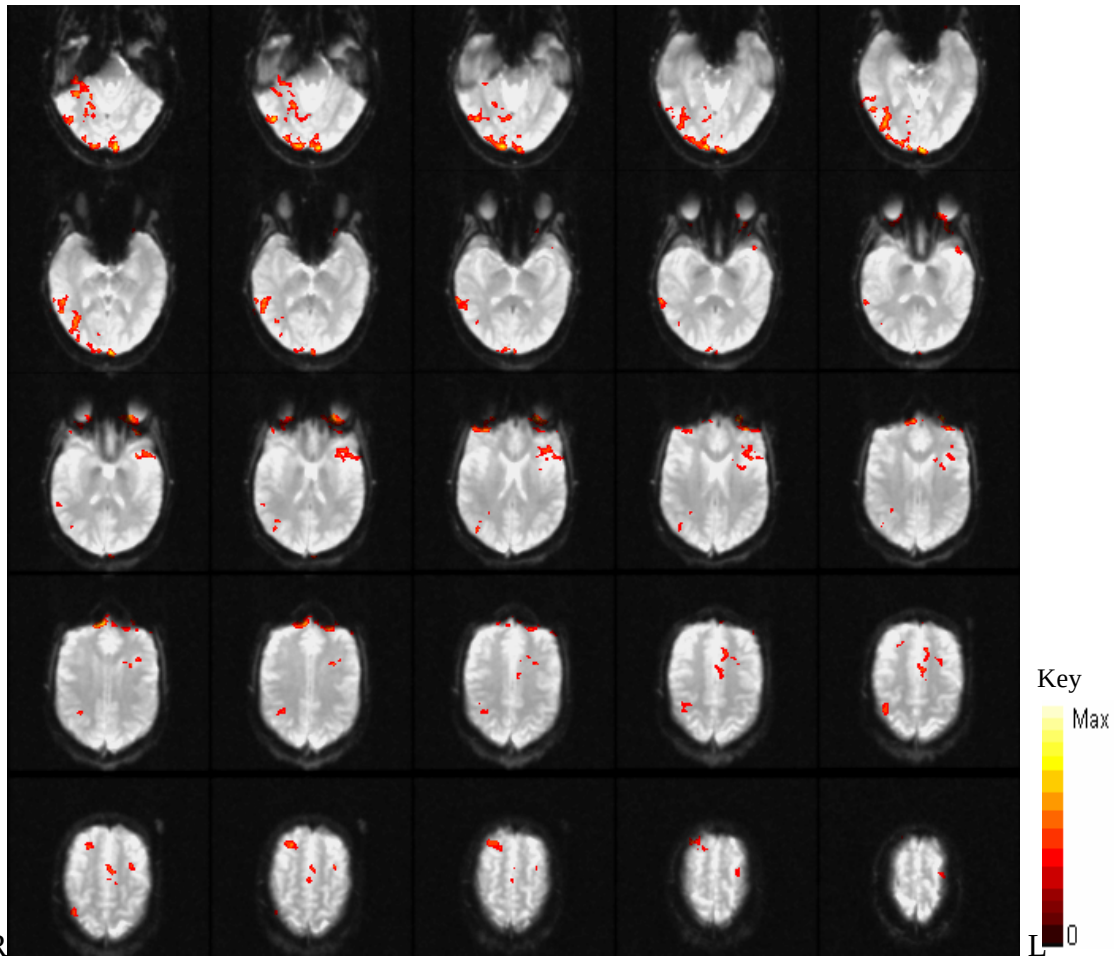

Figure 11. High resolution 25-slice rendered functional image for control group participant c7 during the fMRI Famous Faces naming task.

Table 16
Famous Faces Naming Task: fMRI Activation of Language Areas for Participant c7

Region	No. of voxels	Brodmann's Area	Talairach Coordinates *x*	*y*	*z*	Z Value
Left Hemisphere						
Superior Frontal Gyrus	551	19	-24.2	64.6	-27	5.81
Medial Frontal Gyrus	117	9	-3.04	30.8	31.5	4.15
Anterior Temporal Lobe	285	38	-43.4	17.8	-15	4.28
Unsula	181	13	-27.4	25.2	13	4.44
Cuneus	272	18	-11.2	-102	26.4	7.4
Right Hemisphere						
Precentral Gyrus	127	6	37.2	-13	60.5	4.1
Superior Frontal Gyrus	201	11	35.5	46.1	-22	5.09
Middle Frontal Gyrus	145	10	25.6	57.8	18	4.71
Medial Frontal Gyrus	140	11	10.4	63.1	-19	6.3
Superior Temporal Gyrus	259	22	58.7	-47	15.8	5.02
Cuneus	1069	19	10.1	-98	30	7.61

Note: Only activation above the threshold of Z = 2.3 are reported.

Patient Group.

As with the control group, activation for the patient group was reported at the level of the individual with the threshold set at $Z > 2.3$ ($p < .05$). For the Famous Faces naming task, individual patient results are summarized in Table 17, and illustrated in Appendix H. ATL activation was not present in any individuals of the patient group for the Famous Faces naming task. Additional frontal and temporal regions associated were activated infrequently by the Famous Faces Naming test (< 30 %).

Table 17
Summary of fMRI Famous Faces Task Activation in Language Areas in the Patient Group (n=6)

			Participant					
Region	BA	# of patients showing activation	p1	p2	p3	p4	p5	p6
Left Hemisphere								
Superior Frontal Gyrus	6	1						*
Superior Frontal Gyrus	8, 10	0						
Middle Frontal Gyrus	46	1					*	
Medial Frontal Gyrus	9	0						
Medial Frontal Gyrus	6, 8, 11	2				*	*	
Precentral Gyrus	44	1						*
Inferior Frontal Gyrus	47	0						
Inferior Frontal Gyrus	44	1	*					
Central Sulcus		0						
Anterior Temporal Lobe	38	0						
Superior Temporal Gyrus	13, 22	2		*				*
Middle Temporal Gyrus	39	1	*					
Striate Cortex	17	0						
Cingulate	30	1					*	
Cingulate	31, 32	2	*	*				
Right Hemisphere								
Superior Frontal Gyrus	8, 10	0						
Superior Frontal Gyrus	11	1					*	
Middle Frontal Gyrus	6	2		*				*
Middle Frontal Gyrus	9	0						
Inferior Frontal Gyrus	45, 47	1				*		
Anterior Temporal Lobe	38	0						
Middle Temporal Gyrus	21	2		*		*		
Middle Temporal Gyrus	37, 39	1				*		
Precentral Gyrus Gyrus	4, 6	2		*			*	
Cingulate	32	0						

Note: BA = Brodmans Area. Only activation for areas above the threshold for significance Z > 2.3 are reported.

Famous Faces Naming Task - Analysis of Group Average Results

Control Group.

Higher-level cluster analysis at the group level revealed significant regions of activation for the fMRI Famous Faces naming Task (Table 18). Rendered images of the functional data depict significant activation pictorially (Figure 12). Left ATL activation was significant at the group level. There was also group average activation other language areas that included the left-Middle Temporal Gyrus, and right Inferior Frontal Gyrus.

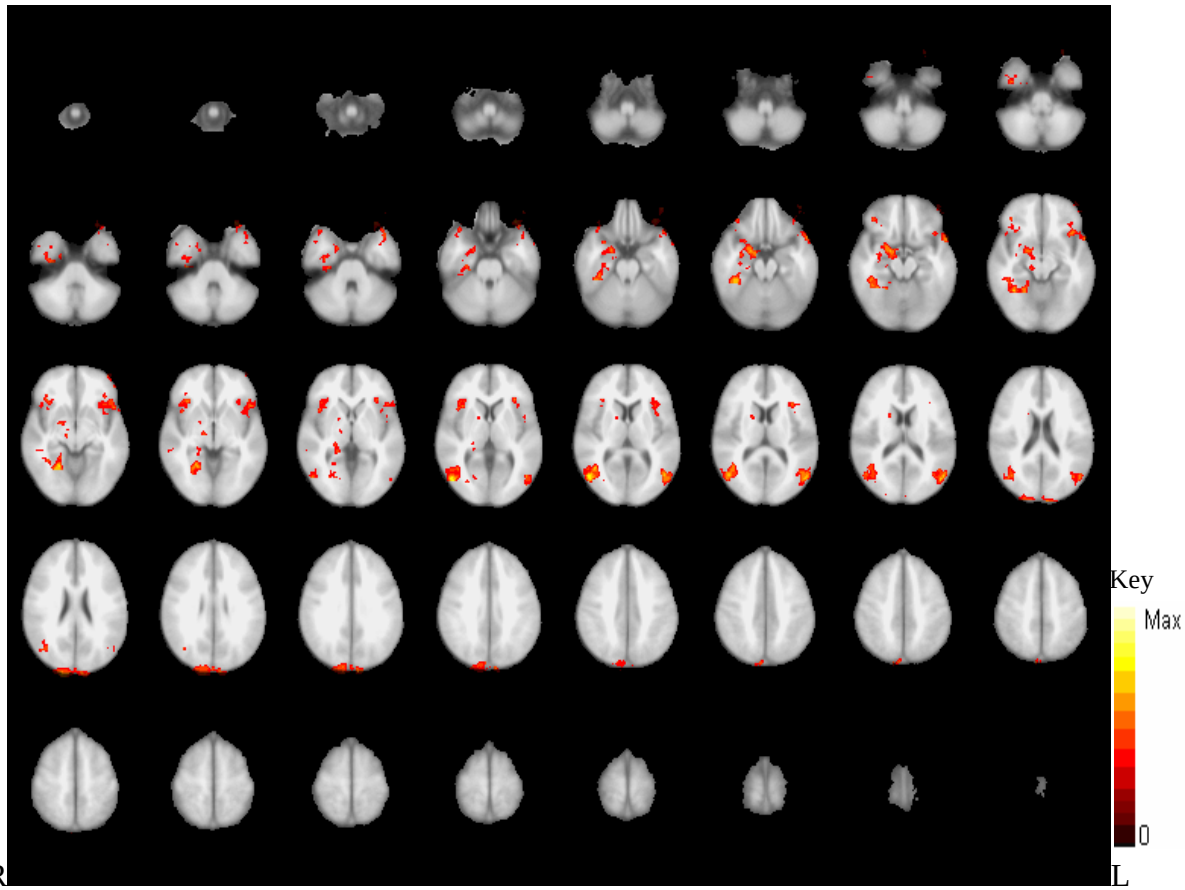

Figure 12. High resolution rendered functional image for the control group during the fMRI Famous Faces naming task (Flame 1 analysis).

Table 18
Famous Faces Naming Task Higher Analysis Control Group Average (Flame 1)

Region	No. of voxels	Brodmann's Area	Talairach Coordinates *x*	*y*	*z*	Max Z Value
Left Hemisphere						
Anterior Temporal Lobe	1239	38	-54	12	-16	3.62
Middle temporal gyrus	534	39	-52	-70	12	4.05
Insula	297	13	-46	-4	4	2.89
Right Hemisphere						
Inferior frontal gyrus	483	47	36	26	-4	3.32
Middle occipital gyrus	777	37	50	-72	4	4.69
Anterior lobe, Culmen	8026		42	-46	-18	10.8

Note: Only activation above the threshold of Z = 2.3 are reported.

Patient Group.

For the patient group, the fMRI Famous Faces task was initially analysed using FSL (Flame 1 analysis), although the task was not associated with reliable activation of language regions (Figure 13).

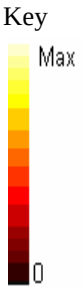

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Figure 13. High resolution rendered functional image for the patient group during the fMRI Famous Faces task (Flame 1 analysis).

Further analysis was performed using less stringent criteria (FSL, Fixed Effects analysis) and significant anterior temporal activation (for example, the anterior aspect of the Superior Temporal Gyrus) was evident, although not directly in the ATL region. Results are represented in and Figure 14 and Table 19.

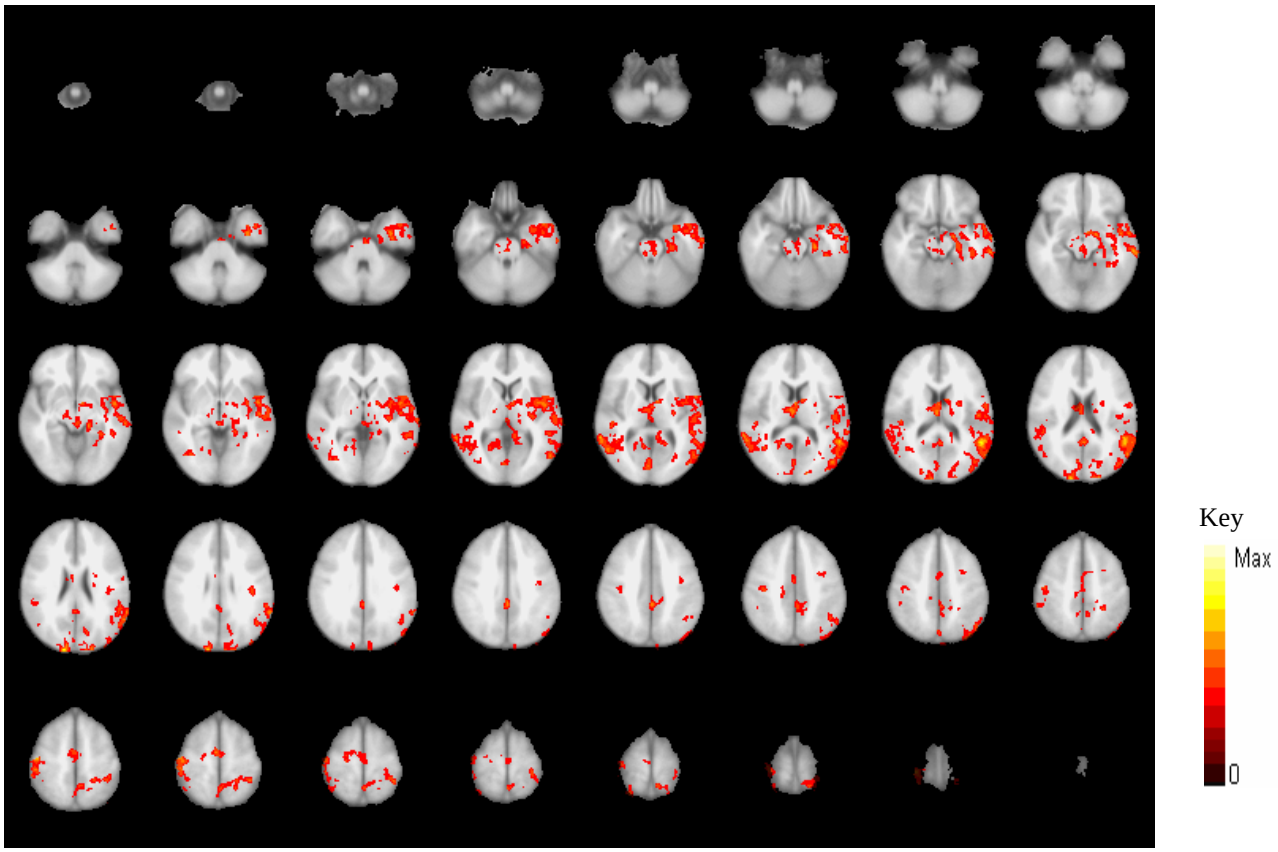

Figure 14. High resolution rendered functional image for the patient group during the fMRI Famous Faces task (Fixed Effects analysis).

R L

Table 19

Famous Faces Task Higher-level Analysis Patient Group Average (Fixed Effects)

Region	No. of voxels	Brodmann's Area	Talairach Coordinates *x*	*y*	*z*	Max Z Value
Left Hemisphere						
Superior temporal gyrus	7205	21	-52	-52	18	6.95
Postcentral gyrus	668	5	-38	-44	62	4.51
Right Hemisphere						
Medial frontal gyrus	424	6	4	-8	60	4.26
Middle temporal gyrus	966		64	-46	8	5.86
Postcentral gyrus	747	3	50	-16	56	6.24
Cuneus	462	18	16	-98	22	7.54

Note: Only activation above the threshold of Z = 2.3 are reported.

Sentence Reading Task - Analysis of Individual Results

Control Group.

Areas of activation during the fMRI Sentence Reading task in the control participants identified via cluster analysis were classified on the basis of lateralization, and then brain region (Table 20), with detailed individual results in Appendix I. It is evident that the Sentence Reading task elicited both left- and right sided activation, and again, left ATL activation was infrequent. The Sentence Reading task was more sensitive to activation in the left middle temporal gyrus, or Wernicke's Area, consistent with the role performed by this region, and the demands of the task. Only two participants demonstrated significant ATL activation in the control group (c4 and c9).

Table 20

Summary of fMRI Sentence Reading Task Activation in Language Areas in the Control Group (n=10)

			Participant									
Region	BA	# of controls showing activation	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10
Left Hemisphere												
Superior Frontal Gyrus	11, 19	1		*								
Superior Frontal Gyrus	8, 10	4		*					*	*		*
Middle Frontal Gyrus	10, 11	1				*						
Middle Frontal Gyrus	6	2				*		*				
Medial Frontal Gyrus	9, 10	0										
Precentral Gyrus	4, 6	2	*								*	
Inferior Frontal Gyrus	13, 45, 46, 47	6		*	*			*	*		*	*
Central Sulcus		0										
Anterior Temporal Lobe	38	2				*					*	
Middle Temporal Gyrus	19, 21	5	*	*	*		*		*	*	*	
Middle Temporal Gyrus	39	3		*			*				*	
Middle Temporal Gyrus	22 2			*			*					
Superior Temporal Gyrus	22	1								*		
Inferior Temporal Gyrus	20	3		*		*		*				
Cingulate	30	1										*
Cingulate	32	3	*			*					*	
Striate cortex	17	0										
Cuneus	18	0										
Right Hemisphere												
Superior Frontal Gyrus	8, 10	1								*		
Middle Frontal Gyrus	9	0										
Middle Frontal Gyrus	10, 11, 46	3						*		*	*	
Precentral Gyrus	4, 6	2		*	*							
Inferior Frontal Gyrus	9	1							*			
Inferior Frontal Gyrus	45, 46, 47	4		*	*				*			*
Anterior Temporal Lobe	38	0										
Middle Temporal Gyrus	21	2			*						*	
Middle Temporal Gyrus	39	0										
Superior Temporal Gyrus	22	0										
Superior Temporal Gyrus	41	0										
Inferior Temporal Gyrus	20, 21	1								*		
Fusiform	37	1		*								

Note: BA = Brodmans Area. Only activation for areas above the threshold for significance Z > 2.3 are reported.

Specific results for participant c4 are provided as an example of left ATL activation during the Sentence Reading task. Results are depicted in Table 21, and a high resolution rendered image in Figure 15.

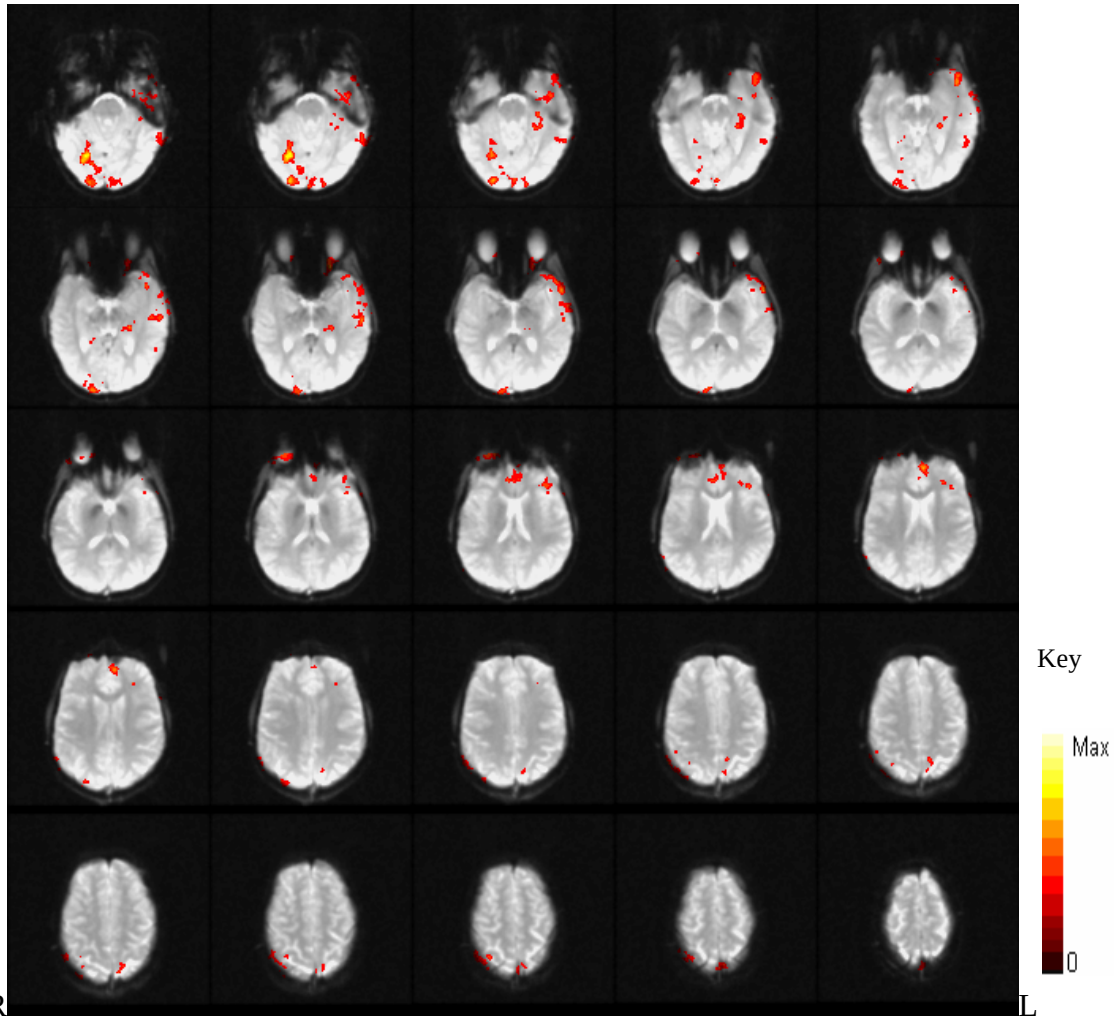

Figure 15. High resolution 25-slice rendered functional image for control group participant c4 during the fMRI Sentence Reading task.

Table 21
Sentence Reading Task: fMRI Activation in Language Areas for Participant c4

Region	No. of voxels	Brodmann's Area	Talairach Coordinates *x*	*y*	*z*	Z Value
Left Hemisphere						
Medial Frontal Gyrus	201	11	-5.06	50.5	-16.7	6.46
Medial Frontal Gyrus	135	6	-10.2	-28.4	60.3	4.05
Anterior Temporal Lobe	703	38	-56.2	12	-19.1	6.19
Inferior Temporal Gyrus	150	20	-43.6	-11.5	-35	4.56
Inferior Temporal Gyrus	155	20	-59.9	-51.8	-11.2	4.29
Parahippocampal Gyrus	166	27	-23.8	-32.5	-5.21	4.95
Cuneus	132	18	-.547	-94.5	21.4	4.8
Right Hemisphere						
Lingual Gyrus	301	19	28.9	-72.8	-0.483	8.91
Middle Occipital Gyrus	273	19	25.6	-96.5	16.3	6.89

Note: Only activation above the threshold of Z = 2.3 are reported.

Specific results for participant c9 are included as an example of left ATL activation, and bilateral language representation. Results are reported in Table 22, and a high resolution rendered image depicted in Figure 16. Activated language areas included the left Inferior Frontal Gyrus, ATL, and Wernicke's area. Right-hemisphere involvement in language was evident, particularly in the Inferior Frontal Gyrus and Middle Temporal Gyrus, and suggests bilateral representation of language for participant c9.

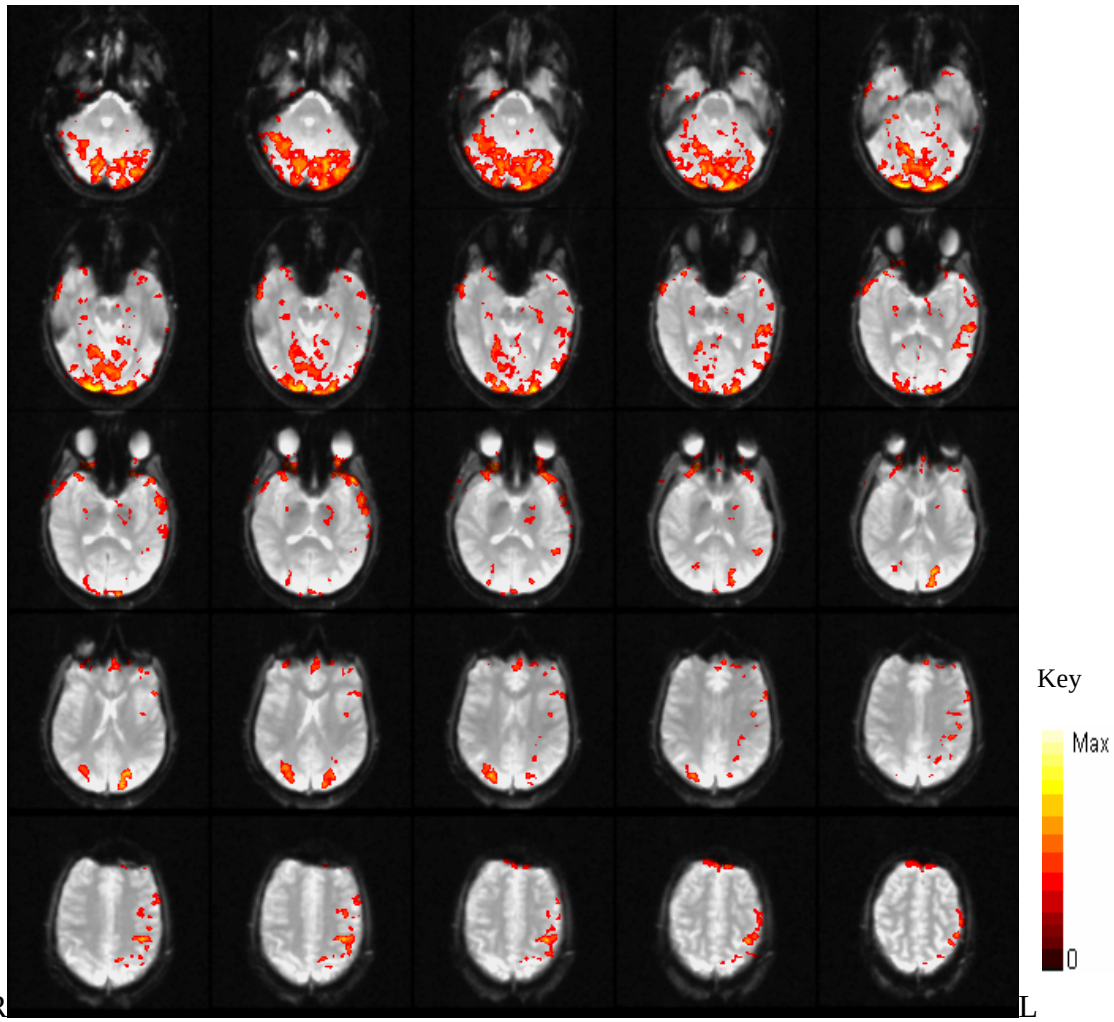

Figure 16. High resolution 25-slice rendered functional image for control group participant c9 during the fMRI Sentence Reading task.

Table 22
Sentence Reading Task: fMRI Activation for Participant c9

Region	No. of voxels	Brodmann's Area	Talairach Coordinates *x*	*Y*	*z*	Z Value
Left Hemisphere						
Precentral Gyrus	635	6	-38.5	-6.58	45.9	7.36
Precentral Lobule	131	6	-11.3	-30.5	56.9	4.05
Inferior Frontal Gyrus	167	45	-57.1	27.5	7.33	4.88
Anterior Temporal Lobe	798	38	-45.3	26.5	-27.6	6.73
Middle Temporal Gyrus	327	21	-55.8	2.71	-16	5.57
Middle Temporal Gyrus	207	39	-48	-68.8	18.4	5.6
Parahippocampal Gyrus	224		-28.5	-20.7	-15.4	4.63
Precuneus	296	7	-19.8	-58.5	46.2	7.76
Right Hemisphere						
Medial Frontal Gyrus	182	11	0.842	52.8	-16.4	4.79
Middle Temporal Gyrus	396	21	65.1	6.09	-25.6	5.01
Cuneus	6818	19	20.4	-98.3	27.5	9.21
Anterior Lobe, Culmen	117		27.7	-32.8	-23.3	4.33

Note: Only activation above the threshold of Z = 2.3 are reported.

Patient Group.

For the Sentence Reading task, individual patient results are summarized in Table 23 and depicted in Appendix J. Left-sided ATL activation was not observed in any of the patients. Right-sided ATL activation was present for one patient (p6), and anterior left-sided activation was present for one participant (p1).

Table 23
Summary of fMRI Sentence Reading Task Activation in Language Areas in the Patient Group (n=6)

Region	BA	# of patients showing activation	Participant p1	p2	p3	p4	p5	p6
Left Hemisphere								
Superior Frontal Gyrus	8, 10	0						
Middle Frontal Gyrus	6, 8, 46	3	*	*			*	
Medial Frontal Gyrus	9, 10	1				*		
Precentral Gyrus	4, 6	4	*	*	*	*		
Inferior Frontal	13, 45, 47	4	*		*	*		*
Central Sulcus		0						
Anterior Temporal Lobe	38	0						
Middle Temporal Gyrus	19, 21	3	*					*
Middle Temporal Gyrus	39	0						
Superior Temporal Gyrus	22	2				*		*
Inferior Temporal Gyrus	20	0						
Cingulate	30	2					*	*
Cingulate	32	0						
Striate cortex	17	0						
Cuneus	18, 19	0						
Right Hemisphere								
Superior Frontal Gyrus	8, 10	0						
Superior Frontal Gyrus	11	1				*		
Middle Frontal Gyrus	9	1						*
Middle Frontal Gyrus	46	1				*		
Precentral Gyrus	4	2				*	*	
Inferior Frontal Gyrus	47	0						
Anterior Temporal Lobe	38	1						*
Middle Temporal Gyrus	21, 39	0						
Superior Temporal Gyrus	22, 41	0						
Superior Temporal Gyrus	39	1				*		
Inferior Temporal Gyrus	20	1				*		
Cingulate	32	0						

Note: BA = Brodmans Area. Only activation for areas above the threshold for significance Z > 2.3 are reported.

Specific results for participant p1 are illustrated in Figure 17, showing left anterior temporal activation (anterior aspect of the middle temporal gyrus) during the Sentence Reading task in the patient group that was not specifically localized in the ATL region, and also activation in Inferior Frontal, and Middle Temporal Gyrus (Table 24).

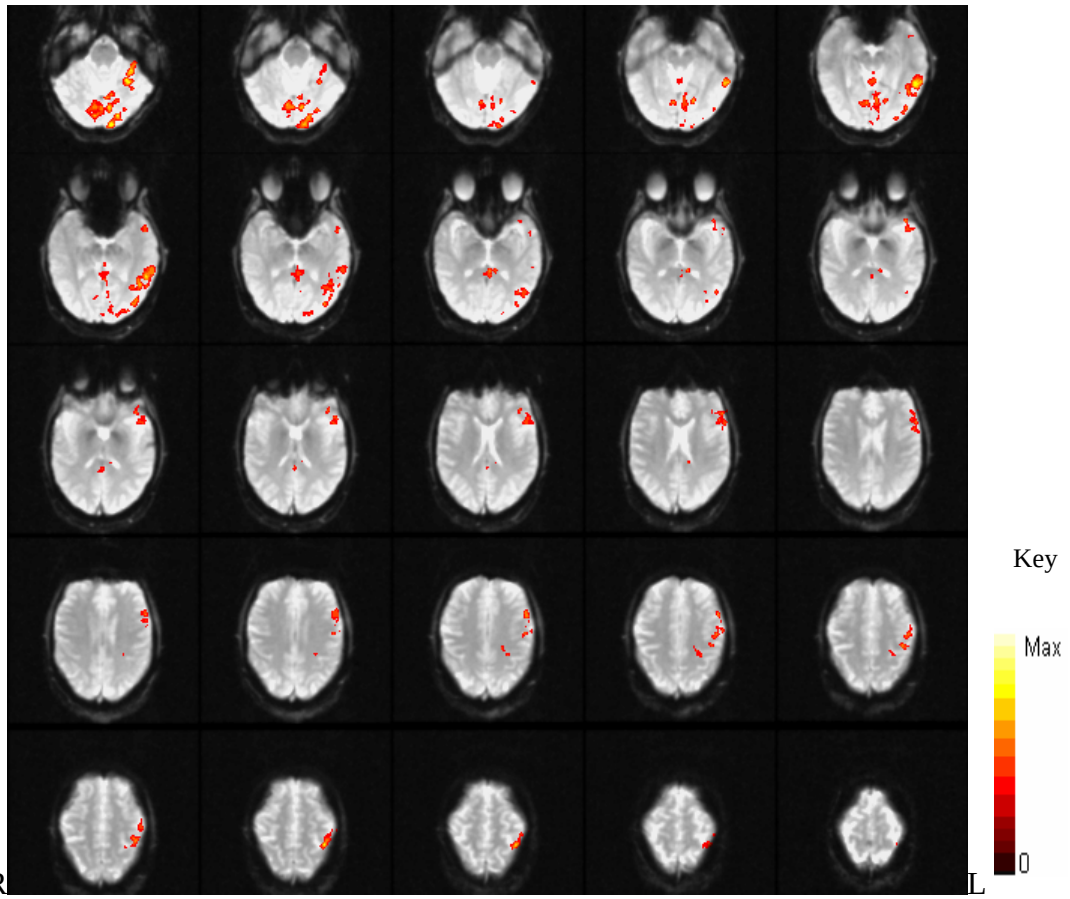

Figure 17. High resolution 25-slice rendered functional image for patient group participant p1 during the fMRI Sentence Reading task.

Table 24
Sentence Reading Task: fMRI Activation in Language Areas for Participant p1

Region	No. of voxels	Brodmann's Area	Talairach Coordinates *x*	*y*	*z*	Z Value
Left Hemisphere						
Middle Frontal Gyrus	224	6	-38.7	-1.34	57.8	6.16
Inferior Frontal Gyrus	433	46	-50.4	30	16.8	4.89
Middle Temporal Gyrus	506	21	-55.5	-49.1	-0.49	6.77
Cuneus	995	18	-12.1	-104	14.4	6.67

Note: Only activation above the threshold of Z = 2.3 are reported.

Sentence Reading task – Analysis of Group Average Results

Control Group.

For the control group, fMRI Sentence Reading task activation was identified using FSL (Flame 1 analysis) with results represented in Table 25 and Figure 18. There appeared to be considerable variability between individuals, and there was no consistent activation of the ATL, Wernicke's area, or other frontal or temporal areas associated with language function on control group analysis during the Sentence Reading task.

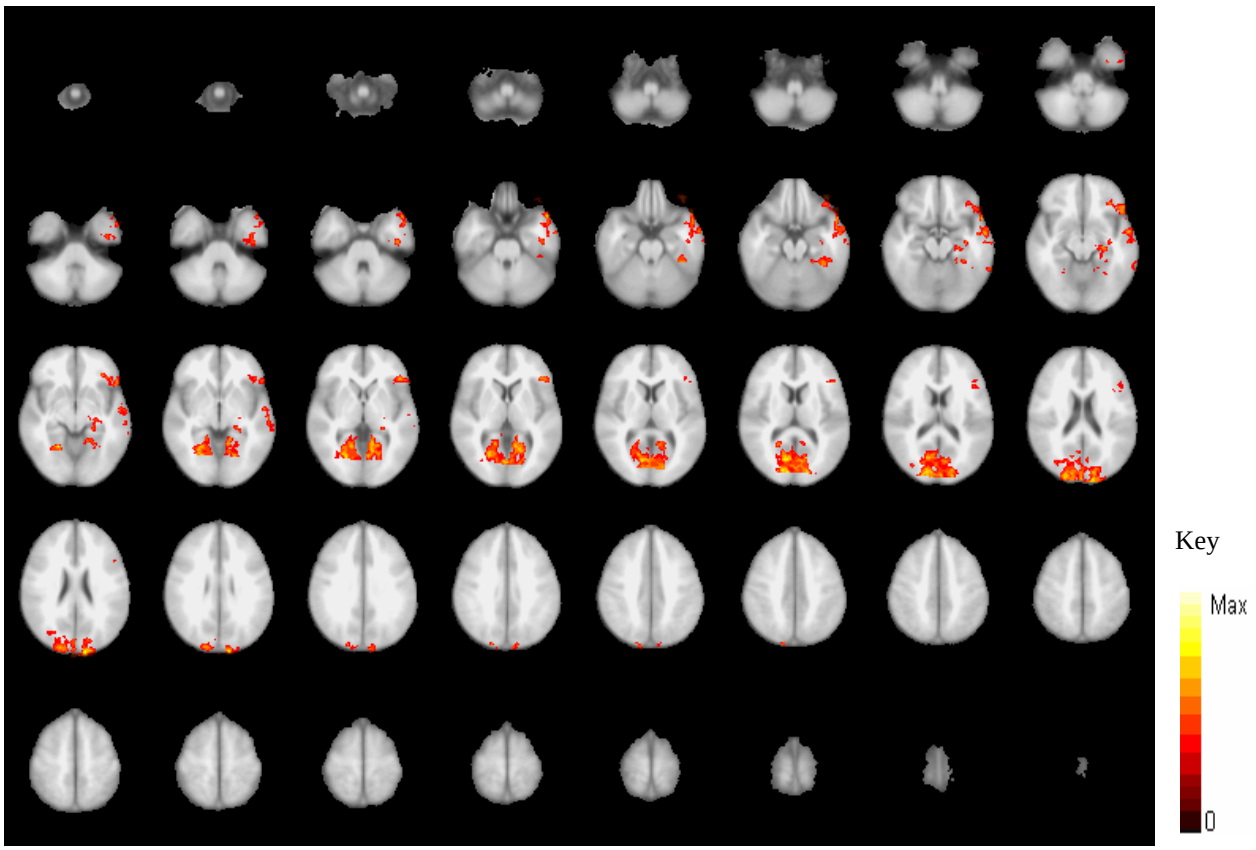

Figure 18. High resolution rendered functional image for the control group during the fMRI Sentence Reading task (Flame 1 analysis).

Table 25
Sentence Reading Task: Higher Analysis Control Group Average (Flame 1)

Region	No. of voxels	Brodmann's Area	Talairach Coordinates *x*	*y*	*z*	Max Z Value
Left Hemisphere						
Middle temporal gyrus	1948	21	-58	-4	-16	3.77

Note: Only activation above the threshold of Z = 2.3 are reported.

Patient Group.

For the patient group, fMRI Sentence Reading task activation was identified using FSL (Flame 1 analysis) with results represented in Table 26 and Figure 15. The left ATL region was identified as a significantly active area at the group average level.

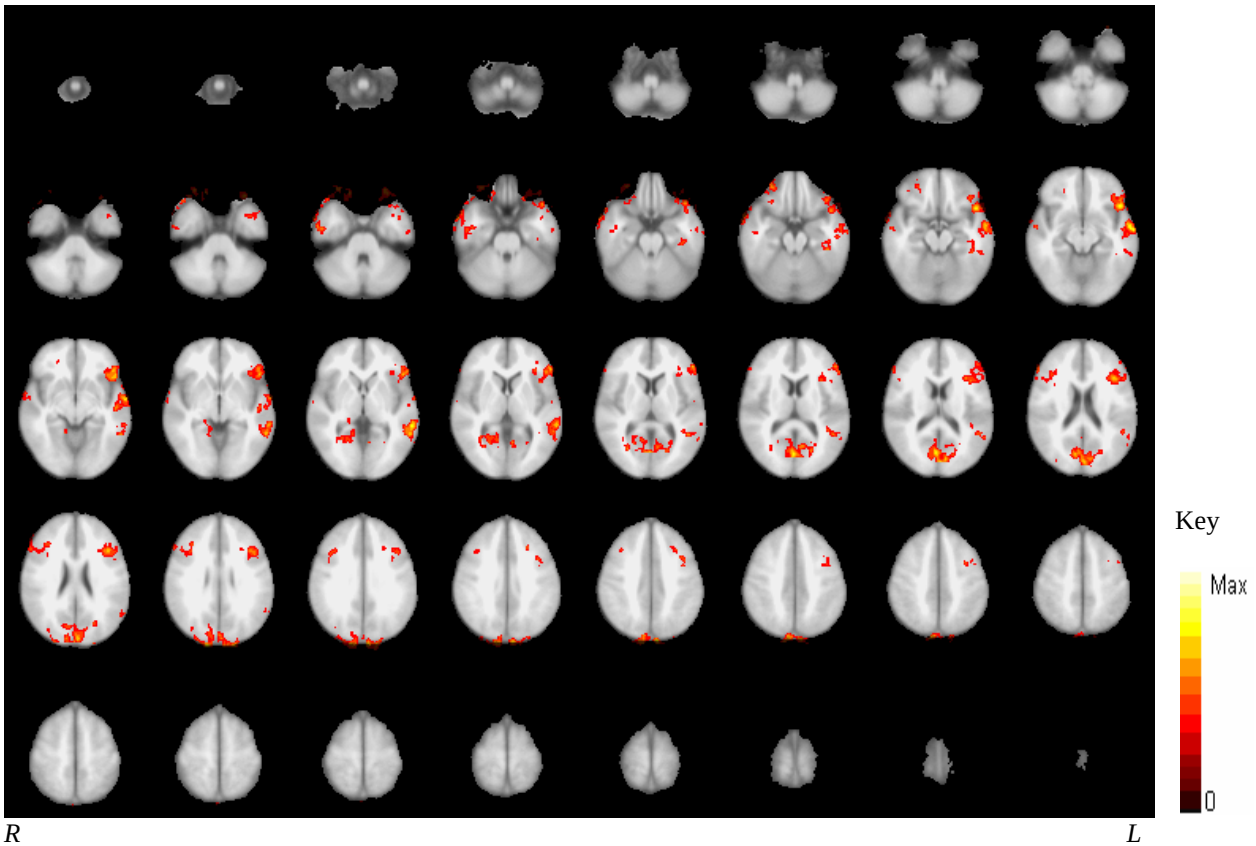

Figure 19. High resolution rendered functional image for the patient group during the fMRI Sentence Reading task (Flame 1 analysis).

Table 26

fMRI Sentence Reading task Higher Analysis Patient Group Average (Flame 1)

			Talairach Coordinates			
level 2 location	No. of voxels	Brodmann's Area	*x*	*y*	*z*	Max Z Value
Left Hemisphere						
Anterior Temporal Lobe	2566	38	-48	20	-14	6.89
Middle temporal gyrus	681	21	-62	-8	-12	6.47
Middle temporal gyrus	905	21	-62	-38	0	6.55
Right Hemisphere						
Middle frontal gyrus	443	46	58	34	18	3.9
Middle temporal gyrus	584	21	66	8	-22	4.62
Cuneus	2703	19	16	-98	28	6.42

Note: Only activation above the threshold of Z = 2.3 are reported.

Comparison of fMRI Activation for Control and Patient Participants

Individual results for control and patient participants for both the Famous Faces and Sentence Reading Tasks are summarized in Table 27 in order to facilitate comparison of any apparent group differences in regions of activation across groups. Inconsistent results are discussed and interpreted in the Discussion section.

Table 27
Frequency of fMRI Activation of Language Areas during the Famous Faces and Sentence Reading Tasks

		Famous Faces Task				Sentence Reading Task			
Region	BA		Control Group (n=10)		Patient Group (n=6)		Control Group (n=10)		Patient Group (n=6)
Left Hemisphere			%		%		%		%
Superior Frontal Gyrus	6		0		17		20		50
Superior Frontal Gyrus	8, 10		0		0		40		0
Superior Frontal Gyrus	11, 19		30		0		10		0
Middle Frontal Gyrus	6, 8, 46		0		0		0		0
Middle Frontal Gyrus	10, 11		30		33		10		0
Medial Frontal Gyrus	9, 10		20		0		0		17
Precentral Gyrus	4, 6		20		0		20		67
Inferior Frontal Gyrus	13, 45, 47		30		0		60		67
Central Sulcus			0		0		0		0
Anterior Temporal Lobe	38	**	10		0		20	**	0
Middle Temporal Gyrus	19, 21		10		0	**	50	**	50
Middle Temporal Gyrus	39	**	20		17		20		0
Superior Temporal Gyrus	21, 22		20	**	22		30		33
Inferior Temporal Gyrus	20		10		0		30		0
Cingulate	30		20		17		10		33
Cingulate	32		0		0		30		0
Striate cortex	17		0		0		0		0
Cuneus	18, 19		0		0		0		0
Right Hemisphere									
Superior Frontal Gyrus	9, 10, 11		30		17		10		17
Superior Frontal Gyrus	9		0		0		0		17
Middle Frontal Gyrus	6, 10, 11, 46		40	**	33		40	**	17
Inferior Frontal Gyrus	9		0		0		10		0
Precentral Gyrus	4		40		33		10		33
Inferior Frontal Gyrus	47	**	30		17		40		0
Anterior Temporal Lobe	38		10		0		0		17
Middle Temporal Gyrus	21, 39		0	**	50		20	**	0
Superior Temporal Gyrus	22, 41		10		0		0		0
Superior Temporal Gyrus	39		0		0		0		17
Inferior Temporal Gyrus	20		20		0		10		17
Cingulate	32		10		0		0		0
Fusiform Gyrus	19, 37		40		0		10		0

Note: Frequency of participants with activation (Freq); percentage of total group (%).
** *Activation present for Higher-level Group Average Analysis*

Discussion

The present study expected to find consistent ATL activation in individuals and groups for the Famous Faces naming and Sentence Reading tasks. These hypotheses were not supported. Results of fMRI testing did not support the inclusion of either the Famous Faces or Sentence Reading task in an fMRI protocol for the purpose of localizing ATL language function in individuals. While significant left-sided ATL activation was identified at the control group average level, there was a relatively low frequency of either left- or right-sided ATL activation across individual control and patients.

The ATL region was the focus of the present study due to the independent findings of ATL activation during; naming of faces (for example, Seidenberg et al., 2002), sentence reading (Bavelier et al., 1997), and neural specific responding during naming of faces, famous people, natural scenes and animals (Kreiman, Koch & Fried, 2000). Furthermore, Schwartz et al. (1998) stated the importance of including naming and reading tasks in fMRI protocols to identify patients with ATL involvement in naming, due to the increased probability of ATL involvement in patients with early seizure onset, poor verbal IQ, left-handedness, and right hemisphere language dominance. Two functional tasks were constructed to specifically target functioning of the ATL; a Famous Face naming task, and a Sentence Reading task, and to report activation of other areas of the brain involved in naming (Famous Faces naming task), and in reading (Sentence Reading task).

The Famous Faces naming task was expected to elicit activation in the ATL, Superior Middle Temporal Gyrus, Inferior Temporal Gyrus, and Inferior Frontal Gyrus.

Activation commensurate with expectations, and consistent with Tsukiura et al. (2002), Griffith et al. (2006) and Huddy et al. (2003) was demonstrated in the left ATL and Middle Temporal Gyrus on analysis of control group average results. The Sentence Reading task was expected to elicit activation in the extrastriate cortex, lingual and fusiform gyri, left middle temporal gyrus, and left inferior frontal gyrus (Bavelier et al. 1997). Activation consistent with expectations was evident in the middle temporal gyrus for the control group. On the basis of the control group average findings, results appear promising, although analysis at the level of individual members of the group is more clinically informative. Results of individual cluster analyses were considered to determine the frequency of ATL activation across individual members of the control and patient groups. The Famous Faces task elicited left-sided ATL activation in only one of the control participants, and none of the patients. Furthermore, right ATL activation was identified in only one of the control participants. For the Sentence Reading task, left ATL activation was found in one of the control participants, and none of the patient group participants. Right ATL activation was also evident during the Sentence Reading task, occurring in two patient group participants. Task utility for localizing ATL language function was determined to be very limited because the tasks were not sensitive to ATL language function across testing (activation in < 20% of participants). It is likely that the tasks would not be sensitive enough to image the language functions of the ATL region of individual patients presenting for a pre-surgical fMRI.

Specific areas identified during the control group average analysis for the Famous Faces naming task were infrequently identified across control participants (left ATL 10

%, left middle temporal gyrus 20 %, and the right inferior frontal gyrus 30 %). For the Sentence Reading task, the left inferior frontal gyrus and Wernicke's area (middle temporal gyrus) activated in 60 and 50 % of control participants respectively, and Wernicke's area was also identified at the control group average level. For the patient group, activation during the Famous Faces naming task was not greater than 50 % across individuals with the most frequent activation in the right middle temporal gyrus. Specific areas of activation identified during the patient group average analysis for the Famous Faces naming task were infrequently identified across individual patients (left superior temporal gyrus 22 % of patients: and right middle frontal gyrus: 33 %; and middle temporal gyrus: 50 %). Activation during the Sentence Reading task was infrequent across patients (left superior frontal gyrus: 50 %; precentral gyrus: 67 %; inferior frontal gyrus: 67 % and middle temporal gyrus: 50 %). Significant activation was also infrequent at the group level (left ATL 0 % and middle temporal gyrus 50 %, and right middle frontal gyrus 17 % and middle temporal gyrus 0 %).

Due to their poor consistency across individuals, and infrequent activation in the frontal and temporal cortices, both tasks fail to meet the criteria recommended for fMRI tasks by Schwartz et al. (1998) which stated that fMRI protocols should: elicit reliable, robust activation across individuals, result in activation in the frontal and temporal cortices, be usable with various clinical populations, be of short duration and tolerated well by most patients, and correspond with results of Wada and CSM testing. The poor concordance between individual and group results in the patient group could be due to the difficulties of comparing patients with heterogeneous pathology (Brown, 2007).

There was the additional concern of poor concordance between individual and group average analyses in the control group. For example, for the Famous Faces naming task, activation was elicited for only one in ten (10%) control participants, and this low frequency was discordant with the finding of significant activation in this region at the control group average. The finding of discordant control data implicates a more fundamental problem with the analysis of group average results. Although the tasks were not sensitive to ATL activation, the Sentence Reading task was found to elicit relatively consistent activation of the inferior frontal gyrus and middle temporal gyrus, and may be a useful inclusion in an fMRI protocol where identification of reading related language areas is required.

Limitations of the present study included difficulties with recruitment of patients. Furthermore, bilateral pathology in three of the six participants reduced the validity of comparison between participants.

It would have been valuable to do a language outcome study after fMRI has been used to localize function of the ATL, and surgery has been performed (not yet reported in the literature) to determine if fMRI helps to improve language outcomes. An additional complication was inherent in the approach to fMRI analysis adopted by FSL, and other fMRI analysis programs. Activation thresholds, along with the minimum number of active voxels are used to differentiate important active regions of the brain. Areas that overlap at the group level may not be identified at the level of the individual due to a small number of active voxels. In the present study, ATL activation was demonstrated at the group average, and not consistently at the level of the individual. It is possible that

ATL activation was present, although did not meet the criteria for inclusion, or alternatively was removed during Bonferroni corrections. It is important to consider however that when there are only a small number of active voxels, there may be clinical implications; it may not be possible to localize this small region and avoid it during surgery.

Generally, the Famous Faces and Sentence Reading tasks did not have the level of sensitivity required for clinical decision-making (Schwartz et al., 1998). Interpretation at the group average level was considered to be somewhat misleading because results of this analysis do not provide insight into the probability of detecting ATL, or other regions associated with language functioning in patients with TLE, with clinical utility at the group average level compromised by the heterogeneous pathology, and greater group variability in the representation of language in this patient population. The high incidence of language re-organization in patients with epilepsy compounds the problem of individual variation that is normally expected in control participants. With increased variability in the neural representation of language function, there may be a reduced probability of detecting significant activation associated with functioning of a specific region. Comparison of individual group member's results is likely to be more clinically useful because adoption of this approach focuses on frequencies and probability of detecting the targeted regions in individuals. It therefore has greater potential of directing research to the development and clinical use of a task that is more likely to elicit activation in the targeted regions than the tested Famous Faces naming and Sentence Reading tasks of the current study.

An extended study involving a larger sample, and pre- and post-surgical neuropsychological assessment of language outcome would be necessary to further explore the effectiveness of these tasks at the level of the individual. At present, there is not sufficient evidence to support inclusion of the tasks in a functional protocol aimed at localization of the ATL, although the study found modest support for inclusion of the Sentence Reading task for localization of the involvement of the left Inferior Frontal, and Middle Temporal Gyri in reading. Further research, and a conservative approach must be employed given that results are used to inform the surgical plan, surgical decisions, and the extent of surgery (Bookheimer, 2007).

CHAPTER 4

General Discussion

Following surgery for intractable TLE, it is common for patients to experience transient, and occasionally more chronic, language difficulties (Saykin et al., 1992). The ATL has been implicated in language function, although the extent of ATL involvement and the specific role of the ATL are not well understood. The present study aimed to make unique contributions to the research involving the role of the ATL in language function, and methods for evaluating pre- and post-surgical language function of the ATL in patients with intractable epilepsy through two studies. The first employed neuropsychological testing of pre- and post-surgical TLE patients on routinely used tests of language function (BNT, COWAT and Animal Fluency) and the CSNT, a neuropsychological naming test in Australia for patients with epilepsy. The CSNT appeared not to have the problems associated with the BNT of heterogeneous items and a low ceiling, due to the inclusion of four categories (animals, fruit and vegetables, praxis, and non-praxis), and higher degree of difficulty (and higher ceiling). Bayesian analyses were used, in addition to covariate parametric statistics, in order to evaluate clinical utility of the fluency and naming tasks in lateralizing language function in patients with epilepsy. The second study looked at ATL activation in healthy controls and TLE patients with two new fMRI tasks (Famous Faces naming and Sentence Reading). For a more detailed overview, refer to the brief discussion section beginning on page 56 for the first study and page 96 for the second study.

Validation of these new tests in patients with epilepsy was considered important due to the methodological differences in previous research. Previous neuropsychological investigations of naming using the BNT have produced inconsistent results (Davies et al., 1994, Hermann & Wyler, 1988, Busch et al., 2005 & Kubu et al., 2001). fMRI studies of naming using Famous Faces and Sentence Reading tasks have predominantly reported group average findings (Tsukiura et al., 2002; Leveroni et al., 2004, Griffith et al., 2006; Haddy, 2003 & Bavelier et al., 1997), although Brown (2007) cautioned that significant group average results do not ensure consistent and reliable activation in individual group members.

Bayesian analysis was incorporated into the analysis of results to determine the predictive utility of the neuropsychological naming tests at the level of the individual patient in order to evaluate new methods for predicting, and hopefully reducing post-operative language difficulties. This approach was in contrast to the standard practice use of group average based parametric statistics. Neuropsychological research typically uses a NHST approach as standard practice, evaluating strength of evidence against the null hypothesis. Bayesian analysis is a less commonly used approach for practice, but is a better approach for determining the applicability of research results to individuals. The clinical utility of the various naming and fluency tests were demonstrated in Chapter 2 using Bayesian analysis. Similarly, fMRI results are typically interpreted at the group average level, although analysis at the level of the individual may provide more clinically meaningful information. Despite interesting activation at the group average level, the research presented in Chapter 3 showed that two fMRI tasks thought to be sensitive to ATL activation did not produce frequent or consistent ATL activation in individuals.

Furthermore, the tasks did not elicit consistent activation in language areas, and did not demonstrate strong lateralizing activation of left-temporal lobe language areas, with a high degree of right involvement observed in the majority of individuals.

For the neuropsychological study, MANCOVA identified a significant effect for lateralization of epilepsy on the CSNT Praxis subtest and for surgical status, but not lateralization on the BNT. In contrast, when a Bayesian approach was applied, the BNT was the only effective test for differentiating between left and right TLE. This inconsistency may be due to the cross-sectional design. Remaining tests (CSNT, COWAT and Animal Fluency) resulted in only modest increases from prior to post-test probability, and because they did not even come close to increasing post-test probability to the required level of 80 % (Sackett et al., 2000), the CSNT, COWAT and Animal Fluency were deemed not to be effective for differentiating left from right TLE.

The finding that the BNT is sensitive to lateralization of epilepsy, with left TLE patients performing worse than right TLE patients was consistent with Davies et al. (1994), Hermann & Wyler (1988) and Busch et al. (2005). Verbal fluency tasks were not found to sensitive to left temporal disruption in this sample, and therefore, findings were not consistent with Suchy et al.(2003) and Jokeit et al. (1998). The post-surgical improvements on the COWAT in patients with left TLE found by Hermann and Wyler (1988), Benton (1968) and Milner (1964) were not found in the present study.

For the fMRI tasks, significant ATL activation was identified at the group average level for the Famous Faces naming task in the control group. During the Famous Faces naming task, findings of group average ATL activation was consistent with Tsukiura et al. (2002) and Griffith et al. (2006), and findings of middle temporal activation was

consistent with Leveroni et al. (2004). The Sentence Reading task did elicit moderately consistent activation in left inferior frontal, and middle temporal gyri (consistent with Bavelier et al., 1997), and it was concluded that the Sentence Reading task may a useful inclusion in a fMRI protocol for the localization of areas involved in reading. In contrast, consistent ATL activation was not present in either task across individual group members. These findings are consistent with the concern expressed by Brown (2007) regarding the validity of using group average data analysis and results for pre-operative fMRI protocols, where results are used to inform surgical decision-making.

Limitations

The cross-sectional approach used in the neuropsychological aspect of this study prevented a within-subjects comparison of pre- and post-operative language results, therefore the utility of the CSNT in detecting post-operative language change is as yet untested. The cross-sectional design also prevented neuropsychological pre- and post-operative follow-up of patients to determine if fMRI results were useful in guiding the surgical approach, and hence reducing the occurrence, or severity of post-operative language change.

The fMRI study was limited to the use of only two functional tasks due to funding constraints limiting scanner time. In addition, the unequal proportion of right (n = 2) and left (n = 4) TLE patients, and heterogeneity of pathology in the fMRI test sample limited generalizability to mesial TLE patients. Heterogeneity may have affected patterns of activation via reorganization of language function, but similar low levels of activation in control participants suggests that the fMRI tasks were not sensitive. Furthermore, as the

sentence reading task was carried out sub-vocally, it could not be verified that patients were actually performing the task.

Recommendations for Future Research

Ongoing advancements in neuropsychological test development and technology (fMRI) offer useful new research opportunities in the area of pre- and post-surgical evaluation of language in patients with epilepsy. With their psychometric and statistical training, neuropsychologists are considered to be a valuable member of epilepsy research and surgery evaluation teams (Bookheimer, 2007). Continued research is required to ensure that test and technological advancements are applied appropriately at the clinical level.

Bayesian analysis provided a more useful basis for interpreting the clinical utility of the neuropsychological tests than the group differences detected through NHST, and provided clinically meaningful information that could be used to interpret individual results. Despite being recognized as useful, Bayesian analyses have not been incorporated into many of the relevant studies. It is recommended that incorporation of a Bayesian approach has the potential to add value to any study, and reduce misleading reporting based solely on NHST. Bayesian analysis indicated that the BNT was the only language test effective for predicting left-sided pathology. It is therefore recommended that the BNT should continue to be used for the assessment of confrontation naming abilities, and for differentiating between left and right TLE. Further research is needed to determine if the CSNT is effective at differentiating left from right sided pathology in highly functioning TLE patients due to the higher ceiling of the CNST. Comparison with

any newly published naming tests should be considered in an effort to continuously improve neuropsychological assessment protocols.

The clinical effectiveness of fMRI in pre-surgical planning has not been extensively studied. To be effective, fMRI tasks need to satisfy the criteria recommended by Schwartz et al. (1998) and Brown (2007). These criteria were not met by the tasks used in the current study. The fMRI study did not find support for the functional tasks, although provided a valuable insight into the limitations and methodological difficulties inherent in research involving fMRI. fMRI research that reports group average activation without consideration of individual results is not clinically useful because an understanding of average activation is not likely to be of assistance when making clinical, and surgical decisions for individual patients. Longitudinal neuropsychological and fMRI research is needed to test the validity, and clinical utility of methods used to assess language function in patients with epilepsy to ensure that new developments in test publication and technology are considered, and appropriately incorporated into standard practice to reduce the risk of post-surgical naming difficulties in patients with epilepsy.

Given that results are used to inform surgery, and influence the extent of surgery, the consistency and sensitivity of fMRI tasks to activation in individuals should be considered, and the effects of pre-surgical fMRI language scanning on post-operative language function should be evaluated. To do so a large scale longitudinal neuropsychological and fMRI study with fMRI tests that produce consistent activation in individuals is required. With this approach, it would be possible to determine if pre-surgical fMRI informed the surgical approach, and if this information resulted in a reduction of post-surgical naming difficulties as assessed via neuropsychological testing.

There is indeed a need for effective program evaluation, and further research of naming difficulties in patients with epilepsy.

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APPENDIX A

Ethics Approvals

APPENDIX B

Invitation to Participate, and PICF for the Neuropsychological Assessment of Language Study.

[Address]

[Date]

Dear [name],

Re: invitation to participate in research project

A research project looking at language function in people with epilepsy is being undertaken at St. Vincent's Hospital, Melbourne.

You have been identified as a potentially suitable participant in this research project because you have already had neuropsychological testing at St Vincent's.

The research involves naming pictures of objects and faces, and some other naming tasks which you may have done before. Testing will take about 1 hour, and we will provide you with detailed feedback on your performance, plus some strategies that may be helpful.

If you decide to participate in this study please contact **Nancy Salton on 0412 284 162** or at St. Vincent's Hospital on 9288 3559.

Please be assured that your decision to participate or not will in no way affect your ongoing clinical care at St. Vincent's Hospital.

Thank you kindly for taking the time to consider this project.

Yours Sincerely,

Dr. Fiona Bardenhagen
Senior Clinical Neuropsychologist
Neuropsychology Unit

Enc: Participant information and consent form

ST. VINCENT'S HEALTH

PARTICIPANT INFORMATION AND CONSENT FORM

CLINICAL PARTICIPANTS

Version 1 Dated 28 September 2006

PROTOCOL NO. (SVH): HREC-A 010/05 (VU HRETH 024/05)

NAME OF PARTICIPANT:

U.R. NO:

FULL PROJECT TITLE:
Project 1: fMRI and Neuropsychological Investigation of Anterior Temporal Pole Language Function in Patients with Temporal Lobe Epilepsy (Language assessment).

NAME/S OF INVESTIGATOR/S: Dr. Fiona Bardenhagen; Professor Mark Cook; Associate Professor Stephen Bowden; Associate Professor Michael Murphy; Dr. Kevin Morris; Dr Nick Trost.

Student Researchers: Nancy Salton

This Participant Information and Consent Form is **6** pages long. Please make sure you have all the pages.

1. Your Consent

You are invited to take part in this research project. Your participation is voluntary.

This Participant Information contains detailed information about the research project. Its purpose is to explain to you as openly and clearly as possible all the procedures involved in this project before you decide whether or not to take part in it.

Please read this Participant Information carefully. Feel free to ask questions about any information in the document. You may also wish to discuss the project with a relative or friend or your local health worker. Feel free to do this.

Once you understand what the project is about and if you agree to take part in it, you will be asked to sign the Consent Form. By signing the Consent Form, you indicate that you understand the information and that you give your consent to participate in the research project.

You will be given a copy of the Participant Information and Consent Form to keep as a record.

2. Purpose and Background

The purpose of this project is to investigate the involvement of the temporal lobe in language, and to chart the recovery of language functioning following surgery for temporal lobe epilepsy.

A total of 80 people will participate in this project.

Previous experience has shown that following surgery for left temporal lobe epilepsy, it is common for patients to experience transient, and occasionally more long-term language difficulties. This has led to the need for better tests in order to understand language functioning in people with epilepsy.

You are invited to participate in this research because you have temporal lobe epilepsy, or because you have already had surgery for epilepsy. This project may help us to better understand the specific language functions affected by temporal lobe epilepsy and by surgery for temporal lobe epilepsy, and will assist us in developing measures that more accurately measure language function in people with seizure disorders.

The results of this research may be used to help Nancy Salton to obtain a degree.

3. Procedures

Participants will patients with temporal lobe epilepsy.

For patients in the language component of this research, you will be asked to do psychological testing of language abilities. An example of the type of language assessment that you will encounter is one where you will be shown a picture of a household item and asked to identify it by name.

Testing will take about 1 hour if you have already had neuropsychological testing at St. Vincent's, and if you give us permission to access those results. If you have not had a previous neuropsychological assessment at St. Vincent's, we will also test other intellectual abilities, and testing will take up to 2.5 hours. All of these tests will be explained to you.

The results of these tests will be combined to provide a better understanding of language function in people with temporal lobe epilepsy, and the effects of surgery on language function.

4. Possible Benefits

We cannot guarantee or promise that you will receive any benefits from this project. However, if the research is successful, a better understanding of the effects of language function in seizure disorders should benefit people in the future and improve outcomes for patients due to undergo surgery for temporal lobe epilepsy in the future.

You will be provided with detailed feedback and recommendations based on your test results.

5. Possible Risks

The procedures used in this study are not harmful to you, apart from some mild fatigue, frustration, or anxiety associated with doing the tests. There may be additional unforeseen or unknown risks.

6. Alternatives to Participation

The alternative to participation, is to not participate.

7. Privacy, Confidentiality and Disclosure of Information

Any information obtained in connection with this project and that can identify you will remain confidential and secure in the Victorian Epilepsy Centre and the Neuropsychology Unit in the department of Clinical Neurosciences. Only the researchers associated with this project will have access to this information. Electronic data will be kept secure through the use of password protection. Personal data will only be disclosed with your permission, except as required by law. If you give us your permission by signing the Consent Form, we plan to publish the results in a collated, de-identified format in an international medical journal.

In any publication, information will be provided in such a way that you cannot be identified. The consent form that you sign will be kept separately and securely in the Neuropsychology Unit for a period of ten years after which paper records will be shredded and electronic files deleted.

8. New Information Arising During the Project

During the research project, new information about the risks and benefits of the project may become known to the researchers. If this occurs, you will be told about this new information. This new information may mean that you can no longer participate in this research. If this occurs, the person(s) supervising the research will stop your participation. In all cases, you will be offered all available care to suit your needs and medical condition.

9. Results of Project

If you would like to receive information about the results of this project, please advise the student researcher. Upon completion of the project, participants who have registered their interest will be provided with a brief written summary of the results.

10. Further Information or Any Problems

If you require further information or if you have any problems concerning this project (for example, any side effects), you can contact the principal researcher, Dr. Fiona Bardenhagen or Associate Professor Stephen Bowden.

Dr. Fiona Bardenhagen, Mobile 0404 062 082

Associate Professor-Stephen Bowden, Mobile 0429 115 907

11. Complaints

If you have any complaints about any aspect of the study or the way in which it is being conducted you may contact the Patient Representative at St. Vincent's

Health on Telephone: 9288 2211. You will need to tell the Patient Representative the name of the person who is noted above as principal investigator. As this study has also been approved by Victoria University, the Patient Representative will discuss all complaints with the Secretary of the Victoria University Ethics Committee. If you prefer, you may contact the University directly, by contacting the Secretary, University Human Research Ethics Committee, Victoria University of Technology, PO Box 14428 MCMC, Melbourne, 8001 (telephone: 9677 4710). A complaint to either the hospital or the university will be discussed with the other party.

12. Research Participant Rights

If you have any questions about your rights as a research participant, then you may contact Jill Rambling, Executive Officer Research at St. Vincent's Health on Telephone: 9288 3930.

13. Participation is Voluntary

Participation in any research project is voluntary. If you do not wish to take part you are not obliged to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine treatment, your relationship with those treating you or your relationship with St. Vincent's Hospital.

Before you make your decision, a member of the research team will be available to answer any questions you have about the research project. You can ask for any information you want. Sign the Consent Form only after you have had a chance to ask your questions and have received satisfactory answers.

If you decide to withdraw from this project, please notify a member of the research team before you withdraw. This notice will allow that person or the research supervisor to inform you if there are any health risks or special requirements linked to withdrawing.

14. Ethical Guidelines

This project will be carried out according to the *National Statement on Ethical Conduct in Research Involving Humans* (June 1999) produced by the National Health and Medical Research Council of Australia. This statement has been developed to protect the interests of people who agree to participate in human research studies.

The ethical aspects of this research project have been approved by the Human Research Ethics Committee of St. Vincent's Hospital, Melbourne and Victoria University, St. Albans.

15. Reimbursement for your costs

You will not be paid for your participation in this

project.

CONSENT FORM - CLINICAL PARTICIPANTS
Version 1 Dated 28 September 2006 Site St. Vincent's Hospital, Melbourne.

Full Project Title:

Project 1: fMRI and Neuropsychological Investigation of Anterior Temporal Pole Language Function in Patients with Temporal Lobe Epilepsy (Language assessment).

I have read, and I understand the Participant Information version 1 dated 28 September 2006.

I freely agree to participate in this project according to the conditions in the Participant Information.

I will be given a copy of the Participant Information and Consent Form to keep

The researcher has agreed not to reveal my identity and personal details if information about this project is published or presented in any public form.

Participant's Name (printed) .....

Signature Date

Name of Witness to Participant's Signature (printed) .....

Signature Date

Researcher's Name (printed) .....

Signature Date

Note: All parties signing the Consent Form must date their own signature.

REVOCATION OF CONSENT FORM - CLINICAL PARTICIPANTS

Revocation of Consent Form

Full Project Title:

Project 1: fMRI and Neuropsychological Investigation of Anterior Temporal Pole Language Function in Patients with Temporal Lobe Epilepsy (Language assessment).

I hereby wish to WITHDRAW my consent to participate in the research proposal described above and understand that such withdrawal WILL NOT jeopardise any treatment or my relationship with St. Vincent's Hospital, Melbourne.

Participant's Name (printed) .....

Signature Date

APPENDIX C

Statistics

Table C1
Missing Values Identified using SPSS MVA

Variable	N	No. of cases missing	Percentage of cases
Year of surgery	19	23	54.8
Years of education	42	0	0
Lateralization	42	0	0
Surgical status	42	0	0
CSNT Animals	40	0	4.8
CSNT Fruit & Vegetables	40	2	4.8
CSNT Praxis	40	2	4.8
CNST Non-praxis	40	2	4.8
CSNT Total Score	40	2	4.8
COWAT Total Score	42	0	0
CAFT Total Score	42	0	0
BNT Total Score	42	0	0

Table C2

Neuropsychological Testing of Language: Skewness and Kurtosis

Variable	N	Skewness	Kurtosis
Age	42	0.03	0.86
Years of Education	42	1.33	2.51
CSNT Animals	40	1.46	0.11
CSNT Fruit & Vegetables	40	1.09	0.53
CSNT Praxis	40	1.95	1.13
CSNT Non-praxis	40	1.18	0.43
CSNT Total score	40	0.61	0.69
COWAT Total score	42	0.59	0.68
CAFT	42	0.81	0.36
BNT	42	2.95	0.11
VIQ	28	1.25	0.39
PIQ	28	1.32	0.09
FSIQ	28	1.90	1.07
GM	28	1.97	1.59

Table C3

*Multivariate Analysis of Variance for Surgical Status * Lateralization in Patients with Epilepsy on Measures of General Intellectual and Memory Abilities.*

Source	Variable	*SS*	*df*	*F*	η^2	*p*
	n = 41					
			Between subjects			
Surgical status	VIQ	18.59	1	.09	.00	.77
	PIQ	87.32	1	.33	.01	.57
	FSIQ	60.36	1	.25	.01	.62
	GM	59.34	1	.19	.00	.66
Lateralization	VIQ	1605.63	1	7.51	.17	.01*
	PIQ	130.00	1	.49	.01	.49
	FSIQ	934.68	1	3.95	.11	.05*
	GM	765.18	1	2.49	.06	.12
*Surgical status * Lateralization*	VIQ	80.11	1	.37	.01	.54
	PIQ	8.22	1	.03	.00	.86
	FSIQ	33.13	1	.14	.01	.71
	GM	37.55	1	.42	.00	.73
Error	VIQ	7909.35	37	(213.77)		
	PIQ	9762.35	37	(263.85)		
	FSIQ	8748.93	37	(236.46)		
	GM	11386.22	37	(307.74)		

Note: Values enclosed in parentheses represent mean square errors.
**p<.05.*

Table C4
*Mulivariate Analysis of Variance for Surgical Status * Lateralization and Patient Group Demographics*

Source	Variable	*SS*	*df*	*F*	η^2	*p*
	n=40					
			Between subjects			
Surgical status	Age	358.38	1	2.62	.06	.11
	Edn	2.16	1	.40	.01	.53
Lateralization	Age	40.57	1	.30	.01	.59
	Edn	24.45	1	4.48	.10	.04*
Error	Age	5325.52	39	(136.55)		
	Edn	212.60	39	(5.45)		

Note: Values enclosed in parentheses represent mean square errors.
**p<.05*

Table C5

Patient Group Descriptive Statistics for Neuropsychological Tests

Neuropsychological Test	Descriptive Statistics							
	Pre-operative (n=19)				Post-operative (n=21)			
	Left (n=8)		Right (n=11)		Left (n=12)		Right (n=9)	
	M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
FSIQ	95	16	102	17	91	15	104	11
VIQ	92	13	102	18	88	12	105	14
WAIS III, Vocab	9	2.3	10	2	9	1.8	10	2.6
PIQ	100	18	103	18	96	18	102	8
GM	84	24	91	16	84	17	98	9
CSNT Animals	12.	2.	17.	7.	10.	5.	13.	8.
CSNT Fruit & Vegetables	18.	5.	20.	5.	18.58	5	17.	10
CSNT Praxis	11	5	17	6.	9.	4	14	7
CSNT Non-praxis	10	5	13	6	9	3	11	6
CSNT Total Score	49	16	68	21	4	14	55	28
COWAT	31	10	37	8	33	18	32	15
BNT	44	11	53	11	38	11	47	15

Table C6

*Multivariate Analysis of Co-variance for Surgical Status * Lateralization in Patients with Epilepsy*

Source	Variable	*SS*	*df*	*F*	η^2	*p*
	n=40					
			Between subjects			
Surgical status	CSNT Animals	103.12	1	3.02	.08	.09
	CSNT F & V	30.82	1	.70	.02	.41
	CSNT Praxis	101.53	1	3.21	.08	.08
	CSNT Non-praxis	24.39	1	.90	.02	.35
	CSNT TL raw score	727.32	1	1.77	.05	.19
Lateralization	CSNT Animals	74.46	1	2.18	.06	.15
	CSNT F & V	8.16	1	.18	.00	.67
	CSNT Praxis	242.28	1	7.65	.18	.009**
	CSNT Non-praxis	58.42	1	2.15	.06	.15
	CSNT TL raw score	1439.14	1	3.51	.09	.07
*Surgical status * Lateralization*	CSNT Animals	10.54	1	.31	..01	..58
	CSNT F & V	21.52	1	.49	.01	.49
	CSNT Praxis	11.05	1	.35	.01	.56
	CSNT Non-praxis	2.34	1	.09	.00	.77
	CSNT TL raw score	283.69	1	.69	.02	.41

Note: Values enclosed in parentheses represent mean square errors.
***p<.01.*

APPENDIX D

Invitation to Participate, and PICF for the fMRI Assessment of Language Study.

ST. VINCENT'S HEALTH

PARTICIPANT INFORMATION AND CONSENT FORM

Version 5 Dated 9 September 2005

PROTOCOL NO. (SVH): HREC-A 09/05 and 010/05 (VU HRETH 024/05 and 026/05)

NAME OF PARTICIPANT:

U.R. NO:

FULL PROJECT TITLE:
Project 1: fMRI and Neuropsychological Investigation of Anterior Temporal Pole Language Function in Patients with Temporal Lobe Epilepsy.

Project 2: Review of fMRI Language Mapping in Patients with Temporal Lobe Epilepsy.

NAME/S OF INVESTIGATOR/S: Dr. Fiona Bardenhagen; Professor Mark Cook; Associate Professor Stephen Bowden; Associate Professor Michael Murphy; Dr. Kevin Morris; Dr Nick Trost.

Student Researchers: Nancy Salton, Matthew Nairn

This Participant Information and Consent Form is 6 pages long. Please make sure you have all the pages.

1. Your Consent

You are invited to take part in this research project. Your participation is voluntary.

This Participant Information contains detailed information about the research project. Its purpose is to explain to you as openly and clearly as possible all the procedures involved in this project before you decide whether or not to take part in it.

Please read this Participant Information carefully- Feel free to ask questions about any information in the document. You may also wish to discuss the project with a relative or friend or your local health worker. Feel free to do this.

Once you understand what the project is about and if you agree to take part in it, you will be asked to sign the Consent Form. By signing the Consent Form, you indicate that you understand the information and that you give your consent to participate in the research project.

You will be given a copy of the Participant Information and Consent Form to keep as a record. **Purpose and Background**
The purpose of this project is to investigate the involvement of the temporal lobe in language, and to chart the recovery of language functioning following surgery for temporal lobe epilepsy.

A total of 30 people will participate in this project.

Previous experience has shown that following surgery for left temporal lobe epilepsy, it is common for patients to experience transient, and occasionally more long-term language difficulties. This has led to the need to better understand the areas of the brain involved in language functioning in people with epilepsy. In patients who undergo brain surgery for the treatment of the seizures, *we* also want to measure the recovery of language functioning after surgery.

You are invited to participate in this research because you are about to undergo surgery for temporal lobe epilepsy. This project may help us to better understand the specific parts of the brain involved in the language functions affected by surgery for temporal lobe epilepsy and will assist us in developing measures that more accurately pin point the location of language function in people with seizure disorders.

The results of this research may be used to help Nancy Salton or Matthew Nairn to obtain a degree.

2. Procedures

Participants will include healthy volunteers, and patients scheduled for temporal lobe epilepsy surgery.

Information will be obtained from your functional Magnetic Resonance Imaging (fMRI) scan that will be conducted before surgery, and through psychological testing conducted at St. Vincent's Hospital before surgery, and at intervals of one, three, six and twelve months after surgery. The psychological testing will take approximately 1 hour per session, and the questions will be limited to the assessment of language. An example of the type of language assessment that you will encounter is one where you will be shown a picture of a household item and asked to identify it by name. All of these tests will be explained to you.

The results of these tests will be combined to provide a better understanding of language function. The results of your fMRI and psychological tests will be combined with results of neurological, neurosurgical, and other clinical investigations or procedures conducted while you are at the hospital, to provide a comprehensive understanding of matters that affect your language functioning.

3. Possible Benefits

We cannot guarantee or promise that you will receive any benefits from this project. However, if the research is successful, a better understanding of the effects of language function in seizure disorders should benefit people in the future and improve outcomes for patients due to undergo surgery for temporal lobe epilepsy in the future.

S. Possible Risks

The procedures used in this study are not harmful to you, but the MRI scan may cause you a small level of discomfort and/or anxiety. This may arise from having to lie still in a small space for 30-40 minutes.

There may be additional unforeseen or unknown risks.

6. Alternatives to Participation

The alternative to participation, for patients, is to complete your neuropsychological assessment in the usual manner but not to make your results available for research.

7. Privacy, Confidentiality and Disclosure of Information

Any information obtained in connection with this project and that can identify you will remain confidential and secure in the Victorian Epilepsy Centre and the Neuropsychology Unit in the department of Clinical Neurosciences. Only the researchers associated with this project will have access to this information. Electronic data will be kept secure through the use of password protection Personal data will only be disclosed with your permission, except as required by law. If you give us your permission by signing the Consent Form, we plan to publish the results in a collated, de-identified format in an international medical journal.

In any publication, information will be provided in such a way that you cannot be identified. The consent form that you sign will be kept separately and securely in the Neuropsychology Unit for a period of ten years after which paper records will be shredded and electronic files deleted.

S. New Information Arising During the Project

During the research project, new information about the risks and benefits of the project may become known to the researchers. If this occurs, you will be told about this new information. This new information may mean that you can no longer participate in this research. If this occurs, the person(s) supervising the research will stop your participation. In all cases, you will be offered all available care to suit your needs and medical condition.

9. Results of Project

If you would like to receive information about the results of this project, please advise the student researcher. Upon completion of the project, participants who have registered their interest will be provided with a brief written summary of the results.

10. Further Information or Any Problems

If you require further information or if you have any problems concerning this project (for example, any side effects), you can contact the principal researcher, Dr. Fiona Bardenhagen or Associate Professor Stephen Bowden.

Dr. Fiona Bardenhagen, Mobile 0404 062 082

Associate Professor Stephen Bowden, Mobile 0429 115 907

11. Complaints

If you have any complaints about any aspect of the study or the way in which it is being conducted you may contact the Patient Representative at St. Vincent's Health on Telephone: 9288 2211. You will need to tell the Patient Representative the name of the person who is noted above as principal investigator. As this study has also been approved by Victoria University, the Patient Representative will discuss all complaints with the Secretary of the Victoria University Ethics Committee. If you prefer, you may contact the University directly, by contacting the Secretary, University Human Research Ethics Committee, Victoria University of Technology, PO Box 14428 MCMC, Melbourne, 8001 (telephone: 9677 4710). A complaint to either the hospital or the university will be discussed with the other party.

12. Research Participant Rights

If you have any questions about your rights as a research participant, then you may contact Jill Hambling, Executive Officer Research at St. Vincent's Health on Telephone: 9288 3930.

13. Participation is Voluntary

Participation in any research project is voluntary. If you do not wish to take part you are not obliged to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine treatment, your relationship with those treating you or your relationship with St. Vincent's Hospital.

Before you make your decision, a member of the research team will be available to answer any questions you have about the research project. You can ask for any information you want. Sign the Consent Form only after you have had a chance to ask your questions and have received satisfactory answers.

If you decide to withdraw from this project, please notify a member of the research team before you withdraw. This notice will allow that person or the research supervisor to inform you if there are any health risks or special requirements linked to withdrawing.

14. Ethical Guidelines

This project will be carried out according to the *National Statement on Ethical Conduct in Research Involving Humans* (June 1999) produced by the National-Health and Medical Research Council of Australia. This statement has been developed to protect the interests of people who agree to participate in human research studies.

The ethical aspects of this research project have been approved by the Human Research Ethics Committee of St. Vincent's Hospital, Melbourne and Victoria University, St. Albans.

Reimbursement for your costs You will not be

paid for your participation in this project.

CONSENT FORM - CLINICAL PARTICIPANTS
Version 5 Dated 9 September 2005
Site St. Vincent's Hospital, Melbourne.

Full Project Title:

Project 1: fMRI and Neuropsychological Investigation of Anterior Temporal Pole Language Function in Patients with Temporal Lobe Epilepsy.

Project 2: Review of fMRI Language Mapping in Patients with Temporal Lobe Epilepsy.

I have read, and I understand the Participant Information version 5 dated 9 September 2005.

I freely agree to participate in this project according to the conditions in the Participant Information.

I will be given a copy of the Participant Information and Consent Form to keep

The researcher has agreed not to reveal my identity and personal details if information about this project is published or presented in any public form.

Participant's Name (printed) .....

Signature Date

Name of Witness to Participant's Signature (printed) .....

Signature Date

Researcher's Name (printed) .....

Signature Date

Note: All parties signing the Consent Form must date their own signature.

REVOCATION OF CONSENT FORM - CLINICAL PARTICIPANTS

Revocation of Consent Form

Full Project Title:

Project 1: fMRI and Neuropsychological Investigation of Anterior Temporal Pole Language Function in Patients with Temporal Lobe Epilepsy.

Project 2: Review of fMRI Language Mapping in Patients with Temporal Lobe Epilepsy.

I hereby wish to WITHDRAW my consent to participate in the research proposal described above and understand that such withdrawal WILL NOT jeopardise any treatment or my relationship with St. Vincent's Hospital, Melbourne.

Participant's Name (printed) .....

Signature Date

APPENDIX E

Famous Faces and Sentence Reading fMRI Tasks: Item Familiarity Analysis

Table E1

Pilot Study - Familiarity of famous faces

		Participants																				
Slide number	Famous faces	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	Frequency (%)
1	Frank Sinatra	*	*	*	*		*	*	*	*	*		*	*	*	*	*	*	*	*	*	90
2	Cate Blanchet	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*		*	*	*	95
3	Oprah Winfrey	*	*		*	*	*	*		*	*	*	*	*	*	*	*	*		*	*	85
4	Arnold Swarzenegger	*		*	*	*	*		*	*	*	*		*	*	*	*	*	*		*	80
5	Bill Cosby		*	*	*	*	*	*	*		*	*	*	*	*	*		*	*	*	*	85
6	Brittney Spears (replaced with Nicole Kidman)	*					*				*	*							*			25
7	Sarah Ferguson	*	*	*	*	*		*	*	*	*	*	*	*	*	*	*	*	*	*		90
8	Mel Gibson	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	100
9	Elvis Presley	*	*	*	*	*	*	*	*	*	*		*	*	*	*	*	*	*	*	*	95
10	Anna Kournikova	*	*			*	*	*		*	*		*	*	*		*	*	*	*	*	75
11	Elizabeth Taylor	*	*	*	*	*	*	*	*	*		*	*	*	*	*	*	*	*	*	*	95
12	Steve Bracks	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	100
13	Nelson Mandella	*	*	*	*	*	*	*		*	*	*	*	*	*		*	*		*	*	85
14	Princess Diana	*	*	*		*	*	*	*	*	*	*		*	*	*	*	*	*	*	*	90
15	Grace Kelly (replaced with Audrey Hepburn)					*		*							*							15
31	Ray Charles	*	*	*	*		*	*	*	*	*		*	*	*	*	*	*	*	*	*	90
32	George Bush Jnr	*	*	*	*	*	*	*		*	*	*	*			*	*	*	*			75
33	Angelina Jolie	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*		*	95
34	Dame Edna	*	*		*	*		*	*	*	*	*		*	*	*	*		*	*	*	80
35	Alec Baldwin	*	*	*	*	*	*	*	*	*	*	*	*	*	*		*	*		*	*	90
36	Bob Hope	*	*	*	*		*	*	*	*	*	*	*	*	*	*		*	*	*	*	90
37	Cameron Diaz	*	*	*	*	*	*		*	*	*	*	*	*		*	*	*	*	*	*	90

38	Bette Davis (replaced with Sofia Lauren)	*	*		*	*					*					*						30
39	Pierce Brosnan	*	*		*	*	*	*		*	*	*	*	*	*		*		*	*	*	80
40	Charlie Chaplan	*		*	*	*	*	*	*	*		*	*	*	*	*	*	*	*	*	*	90
41	Sandra Bullock	*		*		*	*	*	*		*	*	*	*	*	*	*	*	*	*	*	90
42	Kathryn Hepburn	*	*	*	*		*	*	*		*		*	*	*	*	*	*		*		75
43	Jim Carey	*	*		*	*	*	*	*	*	*	*			*	*		*	*	*	*	80
44	Prince Charles	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	100
45	Courtney Cox	*	*	*	*	*		*	*	*	*		*	*		*	*		*	*	*	80
61	Marilyn Munroe	*	*	*	*		*	*	*	*	*	*	*		*	*	*	*	*	*	*	90
62	Nicholas Cage		*	*	*	*	*	*	*	*		*	*	*	*	*	*	*	*	*	*	90
63	Fred Astaire		*	*		*	*	*	*		*	*		*	*		*	*	*	*	*	75
64	Jennifer Annisten	*			*	*		*	*	*	*	*	*	*	*	*	*	*	*	*	*	85
65	Ingrid Bergman	*	*	*	*	*	*		*	*		*	*		*	*	*	*		*	*	80
66	Russell Crowe	*	*	*	*		*	*		*	*		*	*	*	*	*	*		*	*	80
67	Humphrey Bogart	*	*			*		*	*		*	*	*	*		*	*	*	*	*	*	75
68	Neve Campbell	*	*	*	*	*	*	*	*	*	*	*	*	*		*		*		*	*	85
69	Dame Judy Dench	*	*		*	*	*		*	*		*	*		*	*	*	*		*		70
70	Robert De Niro		*	*	*		*	*		*		*	*	*	*	*	*	*		*	*	70
71	Kevin Costner	*	*	*		*	*	*	*	*	*	*	*	*	*	*	*		*	*	*	90
72	Julie Andrews	*	*	*	*	*	*	*	*	*	*		*	*	*		*	*		*	*	85
73	George Clooney	*		*	*		*	*	*		*	*	*	*	*	*		*	*	*	*	80
74	Cary Grant	*	*	*	*	*	*	*	*		*	*	*	*	*	*	*	*	*	*	*	95
75	Mickey Rooney	*	*	*	*	*	*		*	*	*	*	*		*	*	*	*	*			80
	Replacements																					
6	Nicole Kidman	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	100
15	Audrey Hepburn	*	*	*	*	*	*	*	*	*	*	*	*	*			*	*	*	*	*	90
38	Sofia Lauren	*	*	*	*	*	*	*	*	*	*	*		*	*	*	*	*	*	*	*	95
	Total familiar faces	43	41	37	40	39	41	41	38	38	41	38	39	39	40	39	40	40	36	42	40	
	%	90	85	77	83	81	85	85	79	79	85	79	81	81	83	81	83	83	75	88	83	

Table E2

fMRI Sentence Reading Task: Sentences

Slide number	Sentences	Word length
96	David Reyne is a popular travel reporter	7
97	Keifer Sutherland stars in the television program 24	8
98	The Prime Minister of Australia during 2005 was John Howard	10
99	Geoffrey Rush won many awards for the movie Shine	9
100	The Crown Prince of England is Prince Charles	8
101	Hippocrates is considered to be the father of modern medicine	10
102	During his travels Michael Palin met many interesting people	9
103	The first human to space walk was Alexei Leonov	9
104	Dr. Fiona Wood was the 2005 Australian of the Year	10
105	The oldest member of the Beatles was Ringo Starr	9
106	Alexander Graham Bell invented the telephone in 1876	8
107	Guglielmo Marconi pioneered the development of the radio	8
108	Dawn Frazer won Olympic gold in 1956, 1960 and 1964	10
109	Wolfgang Amadeus Mozart was born in 1756	7
110	Pavarotti is on of the Three Tenors	7
126	Jane Austin wrote Pride and Prejudice	6
127	John Wayne won his only oscar for the movie True Grit	11
128	Orphan Annie's dog was called Sandy	6
129	Delta Street took dictation for Perry Mason	7
130	Indiana Jones was a character in Raiders of the Lost Arc	11
131	A parrot taught Dr. Dolittle to talk to the animals	10
132	Neville Bonner was the first Aborigine elected to parliament	9
133	Sophia Loren won a best actress oscar for Little Women	10
134	Caroline Chisolm is the only woman featured on Australian currency	10
135	Vincent van Gogh partially cut off his left ear	9
136	Dame Nellie Melba was born Helen Porter Mitchell	8
137	Ian Flemming created the character James Bond	7
138	The author of the Scarlatti Inheritance was Robert Ludlum	9
139	Betty Cuthbert was the Golden Girl during the 1956 Olympics	10
140	Leonard Bernstein wrote the music for West Side Story	9
156	Humphrey Bogart starred in the movie Casablanca	7
157	Scarlet O'Hara's mansion was called Tara	6
158	The founder of the Boy Scout's was Robert Bayden-Powell	9
159	Pinocchio had a cat and a goldfish as pets	9
160	The Artful Dodger is a character in Oliver Twist	9
161	Rip van Winkle slept for twenty years	7
162	Charlie Chaplin was the first star to sign a million dollar contract	12
163	Sherwood Forest was the home of Robin Hood	8
164	Marie Curie has been awarded two Nobel Prizes	8
165	George Lucus wrote and directed American Graffiti	7
166	The King of Swing is Benny Goodman	7
167	The drug morphine was named after morpheus, the Greed God of dreams	12
168	Jamaica was discovered by Christopher Columbus	6
169	John Farnham was TV Weeks King of Pop from 1969 to 1973	12
170	Batman and Robin patrolled Gotham City in their batmobile	9
	Mean word length	8.64

APPENDIX F

fMRI Pre-processing

Table F1

MCFLIRT Pre-statistical Motion Correction Adjustments
Famous Faces Task

Participant	Absolute (mm)	Relative (mm)	Participant	Absolute (mm)	Relative (mm)
Control Group			*TLE Patient Group*		
cf1	0.31	0.28	pf1	0.14	0.08
cf2	0.08	0.06	pf2	0.15	0.11
cf3	0.09	0.08	pf3	0.09	0.06
cf4	0.10	0.08	pf4	0.12	0.09
cf5	0.10	0.09	pf5	0.19	0.19
cf6	0.06	0.06	pf6	0.08	0.08
cf7	0.08	0.07			
cf8	0.10	0.13			
cf9	0.16	0.07			
cf10	0.15	0.11			

Table F2

MCFLIRT Pre-statistical Motion Correction Adjustments
Sentence Reading Task

Participant	Absolute (mm)	Relative (mm)	Participant	Absolute (mm)	Relative (mm)
Control Group			*TLE Patient Group*		
cs1	0.24	0.24	ps1	0.12	0.09
cs2	0.04	0.04	ps2	0.20	0.12
cs3	0.08	0.07	ps3	0.07	0.10
cs4	0.13	0.07	ps4	0.10	0.08
cs5	0.11	0.08	ps5	0.19	0.19
cs6	0.10	0.05	ps6	0.09	0.06
cs7	0.07	0.06			
cs8	0.16	0.14			
cs9	0.09	0.06			
cs10	0.09	0.07			

APPENDIX G

Control Group: Individual fMRI Famous Faces Task Results

fMRI Famous Faces Task Control Group Participant c1.

Table G1

fMRI Famous Faces Task Cluster Analysis for Control Group Participant c1

					Talairach Coordinates			
Laterali zation	Level 1 location	level 2 location	No. of voxels	Brodmann's Area	*X*	*Y*	*z*	Z Value
		Left hemisphere						
Left	Frontal Lobe	Precentral Gyrus	5792	4	-39.2	-18	62.6	6.31
	Occipital Lobe	Middle Occipital Gyrus	1806	18	-44.6	-84	2.13	7.15
		Right hemisphere						
Right	Frontal Lobe	Precentral Gyrus	600	4	33	-21	52.1	6.16
		Medial Frontal Gyrus	260	6	0.55	-3.1	53.2	5.38
	Tempora l Lobe	Fusiform Gyrus	5795	19	48.1	-77	-15	7.4
	Occipital Lobe	Cuneus	803	18	14.4	-106	2.02	7.7

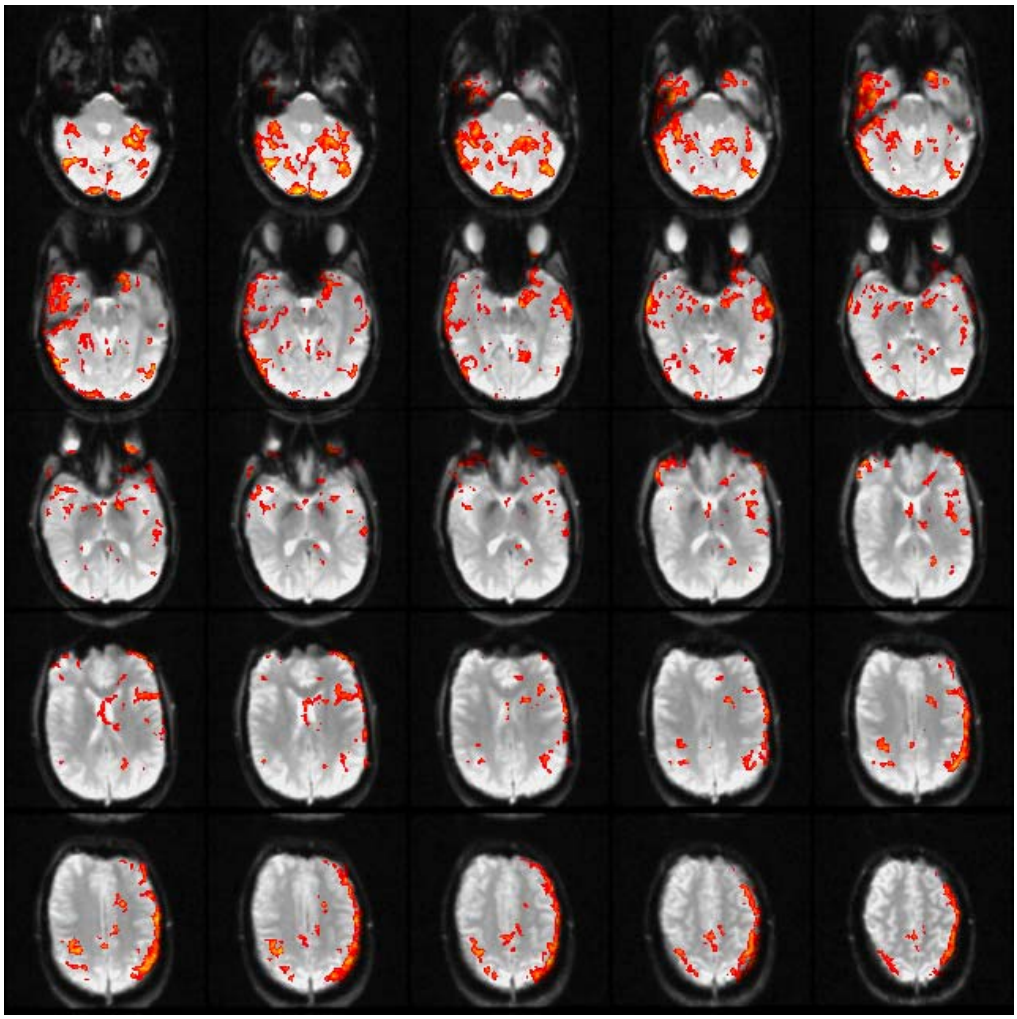

Figure G1. High-resolution 25-slice rendered functional image for control group participant c1 during the fMRI Famous Faces task.

fMRI Famous Faces Task Control Group Participant c3

Table G2

fMRI Famous Faces Task Cluster Analysis for Control Group Participant c3

					Talairach Coordinates			
Lateralization	Level 1 location	level 2 location	No. of voxels	Brodmann's Area	*x*	*y*	*z*	Z Value
Left	Frontal Lobe	Superior Frontal Gyrus	119	11	-29.3	56.7	-23	5.22
		Middle Frontal Gyrus	140	10	-27	37.9	20.9	3.94
	Temporal Lobe	Superior Temporal Gyrus	1712	22	-57.9	2.34	2.77	5.51
			139	22	-50.6	-5	3.68	4.69
	Occipital Lobe	Middle Occipital Gyrus	1064	18	-43	-77	-9.8	8.03
Right	Frontal Lobe	Cingulate Gyrus	678	32	12.8	10.9	34.6	5.19
	Temporal Lobe	Inferior Temporal Gyrus	127	19	47.9	-75	0.01	4.9
	Sub cortical	Insula	714	13	30.4	26.2	0.5	5.74
	Cerebellum	Anterior Lobe, Culmen	279		44.1	-48	-22	6

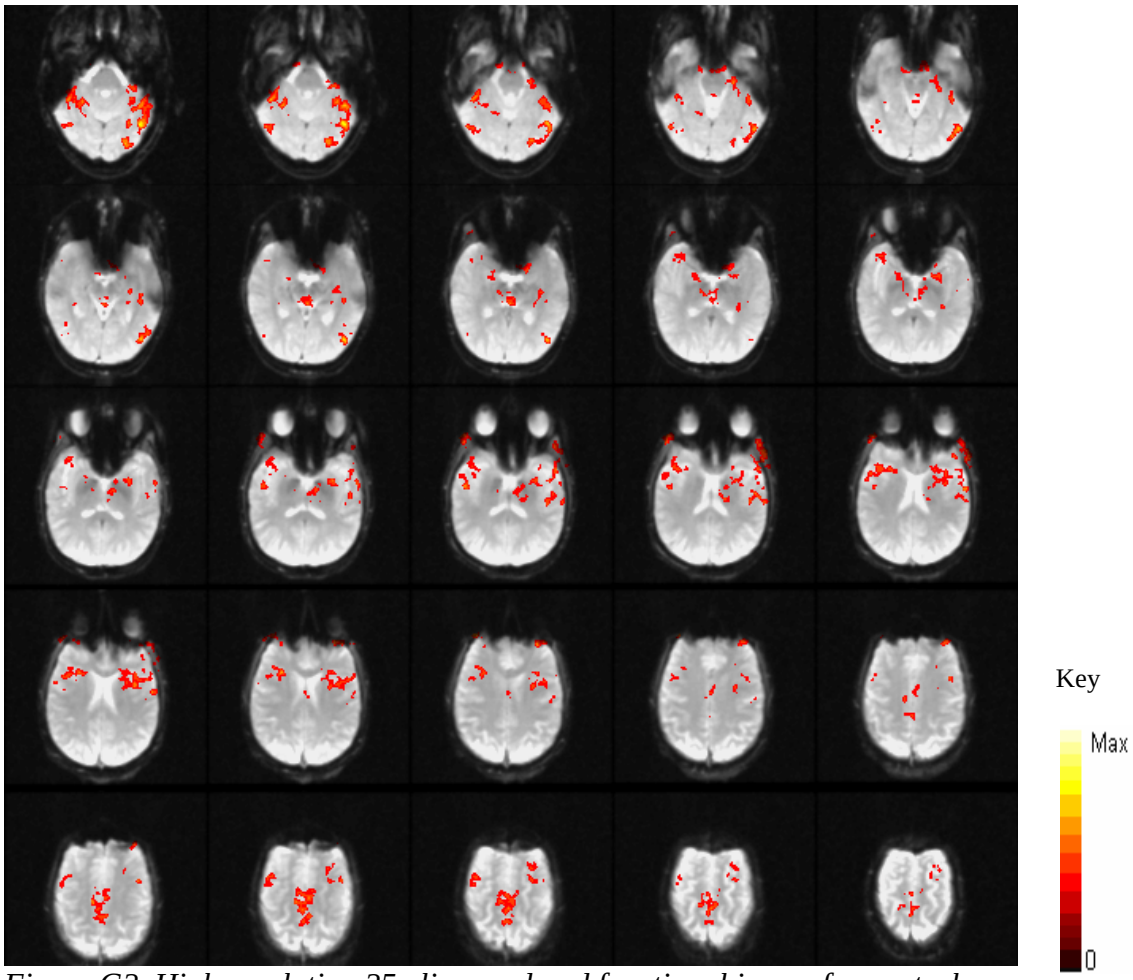

Figure G2. High resolution 25-slice rendered functional image for control group participant c3 during the fMRI Famous Faces task.

fMRI Famous Faces Task Control Group Participant c4

Table G3

fMRI Famous Faces Task Cluster Analysis for Control Group Participant c4

					Talairach Coordinates			
Laterali zation	Level 1 location	level 2 location	No. of voxels	Brodmann's Area	*x*	*y*	*z*	Z Value
Left	Frontal Lobe	Superior Frontal Gyrus	917	11	-22.2	47.2	-24	6.25
		Medial Frontal Gyrus	141	10	-8.67	38.7	-14	6
	Temporal Lobe	Middle Temporal Gyrus	270	19	-43.6	-81	23.9	5.6
			261	21	-61.4	-42	-7.7	5.12
	Temporal Lobe	Inferior Temporal Gyrus	124	20	-34	-11	-36	6.15
	Cerebellum	Anterior Lobe, Culmen	138		-29.9	-48	-21	6.39
Right	Limbic lobe	Posterior Cingulate	137	30	20.1	-52	11.5	5.1
	Occipital Lobe	Middle Occipital Gyrus	163	18	27.8	-96	20.9	6.58
		Inferior Temporal Gyrus	327		46	-73	-1.3	7.32
	Cerebellum	Anterior Lobe, Culmen	755		41.7	-46	-20	7.51

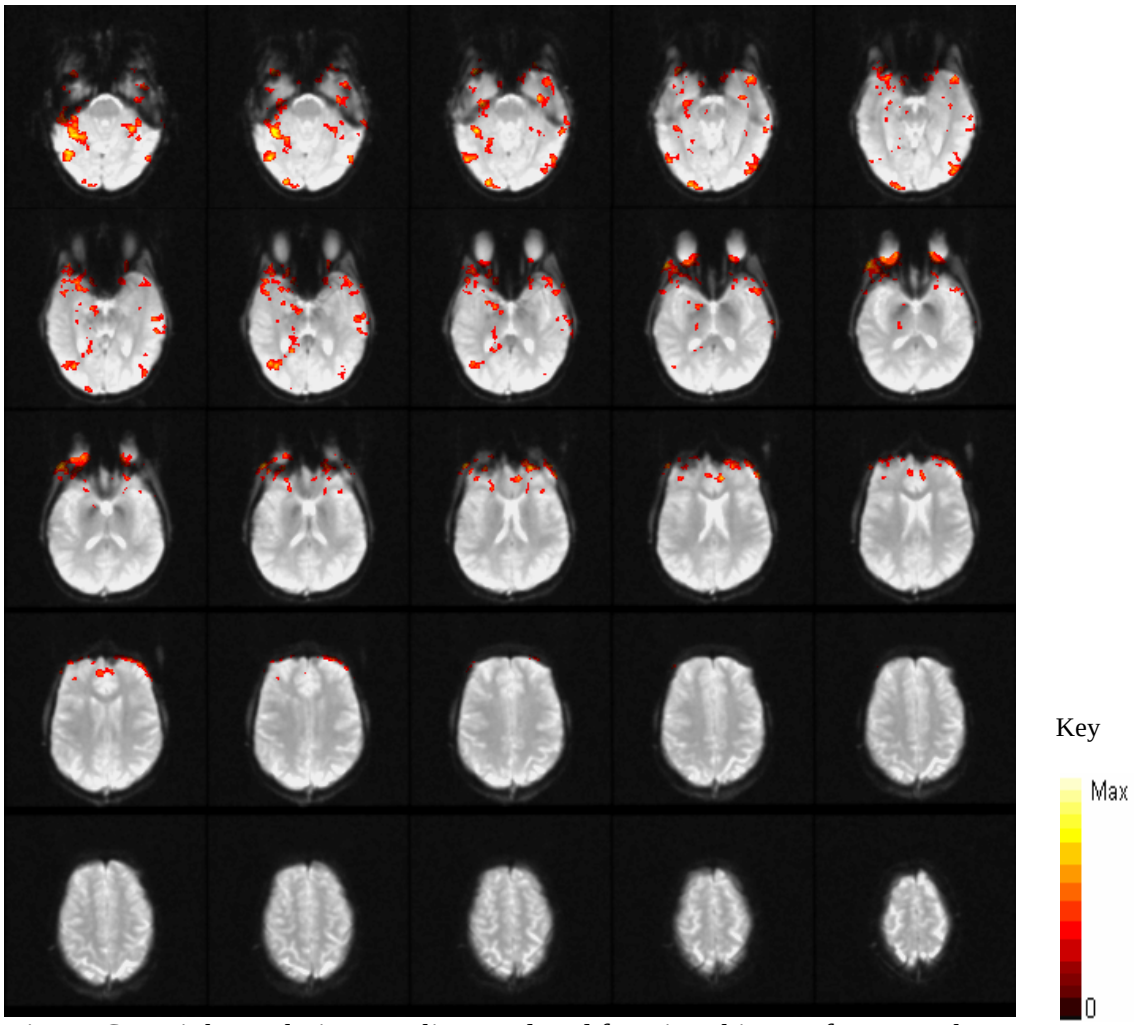

Figure G3. High resolution 25-slice rendered functional image for control group participant c4 during the fMRI Famous Faces task.

fMRI Famous Faces Task Control Group Participant c5

Table G4

fMRI Famous Faces Task Cluster Analysis for Control Group Participant c5

					Talairach Coordinates			
Laterali zation	Level 1 location	level 2 location	No. of voxels	Brodmann's Area	*X*	*y*	*z*	Z Value
Left	Frontal Lobe	Middle Frontal Gyrus	220	10	-45	61.4	8.73	4.25
	Parietal Lobe	Inferior Parietal Lobule	204	40	-46.3	-27	24	5.76
	Occipital Lobe	Middle Occipital Gyrus	864	18	-14.8	-105	21.2	7.36
	Cerebell um	Posterior Lobe, Declive	190		-35	-58	-19	4.93
Right	Frontal Lobe	Precentral Gyrus	125	4	35.4	-16	54.8	4.51
	Tempora l Lobe	Fusiform Gyrus	463	37	37.4	-58	-12	7.6
	Occipital Lobe	Middle Occipital Gyrus	308	18	13	-104	20.9	7.37

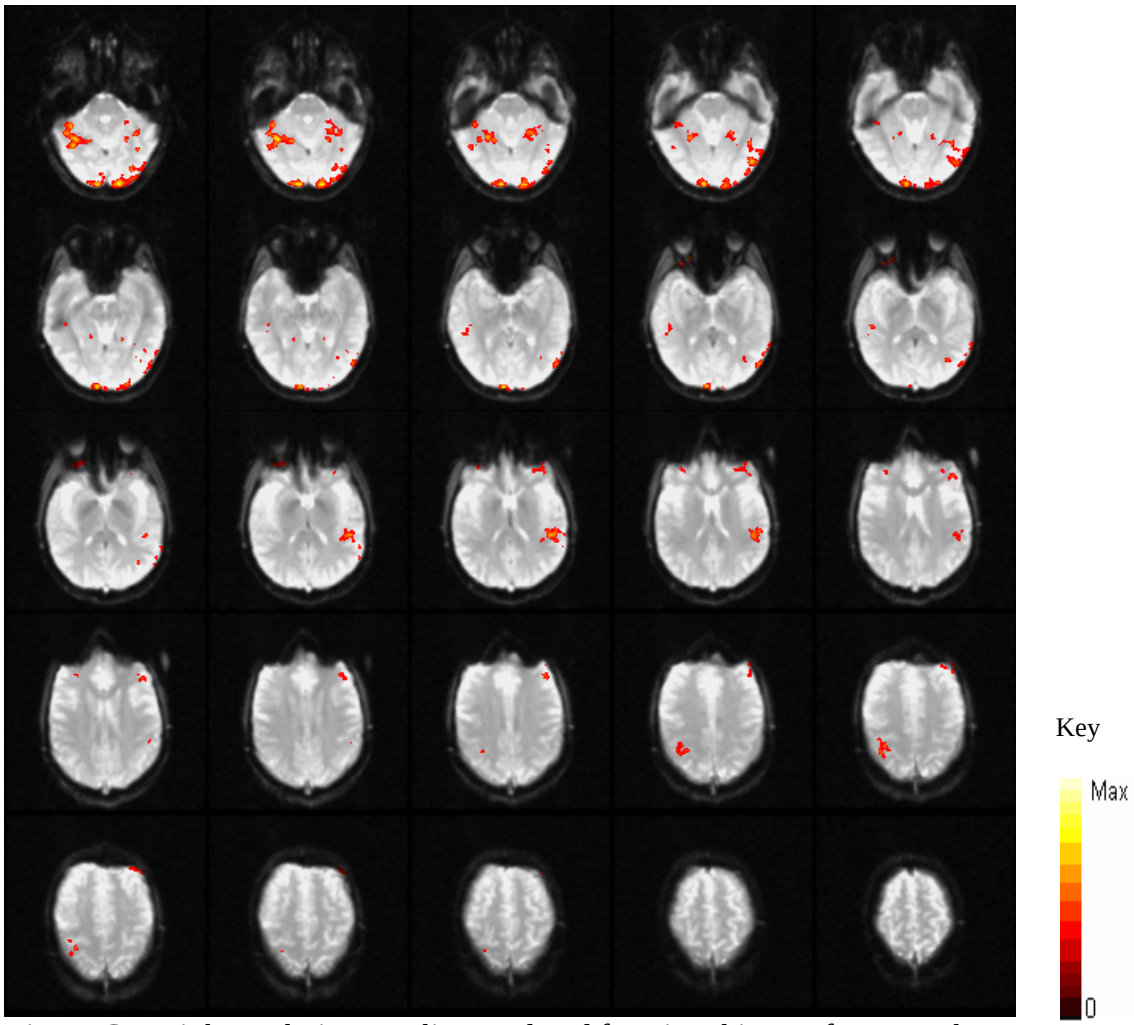

Figure G4. High resolution 25-slice rendered functional image for control group participant c5 during the fMRI Famous Faces task.

fMRI Famous Faces Task Control Group Participant c6

Table G5

fMRI Famous Faces Task Cluster Analysis for Control Group Participant c6

					Talairach Coordinates			
Laterali zation	Level 1 location	level 2 location	No. of voxels	Brodmann's Area	*x*	*y*	*z*	Z Value
Left	Frontal Lobe	Middle Frontal Gyrus	112	11	-40.1	38.2	-20	4.88
		Inferior Frontal Gyrus	402	13	37.2	22.3	10.6	5.12
	Occipital Lobe	Cuneus	770	18	-9.02	-103	7.47	9.28
		Middle Temporal Gyrus	139	19	-49.1	-65	15.3	5.48
Right	Frontal Lobe	Middle Frontal Gyrus	297	46	53.1	30.7	18.1	4.84
		Inferior Frontal Gyrus	161	47	32.2	31.2	-8.5	5.26
	Occipital Lobe	Cuneus	2178	18	10	-105	14.2	10

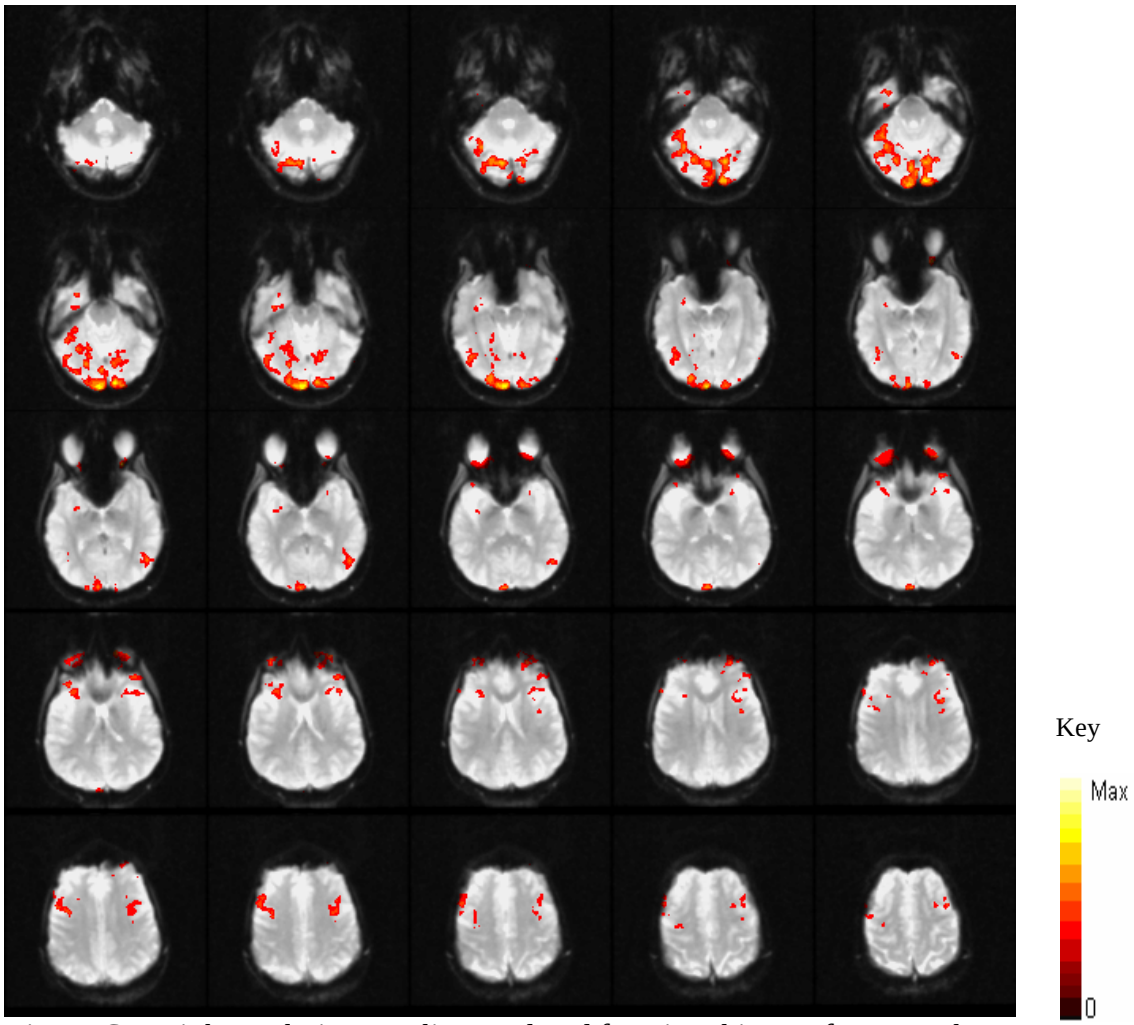

Figure G5. High resolution 25-slice rendered functional image for control group participant c6 during the fMRI Famous Faces task.

fMRI Famous Faces Task Control Group Participant c8

Table G6

fMRI Famous Faces Task Cluster Analysis for Control Group Participant c8

					Talairach Coordinates			
Laterali zation	Level 1 location	level 2 location	No. of voxels	Brodmann's Area	*x*	*y*	*z*	Z Value
Left	Tempora l Lobe	Superior Temporal Gyrus	726	22	-46.1	-3	-43	5.3
		Middle Temporal Gyrus	164	39	-56.6	-67	10.7	4.15
	Occipital Lobe	Cuneus	655	18	-2.68	-94	2.78	7.2
		Fusiform Gyrus	306	19	-40.5	-73	-13	4.94
Right	Frontal Lobe	Superior Frontal Gyrus	3355	10	29.5	65.6	-14	7.19
	Tempora l Lobe	Inferior Temporal Gyrus	134	20	37.6	-5.6	-41	3.49
	Parietal Lobe	Precuneus	142	7	21.4	-49	47.6	4.73
	Occipital Lobe	Middle Occipital Gyrus	469	19	40.5	-66	9.93	5.63
		Fusiform Gyrus	235	19	25.7	-66	-10	4.88

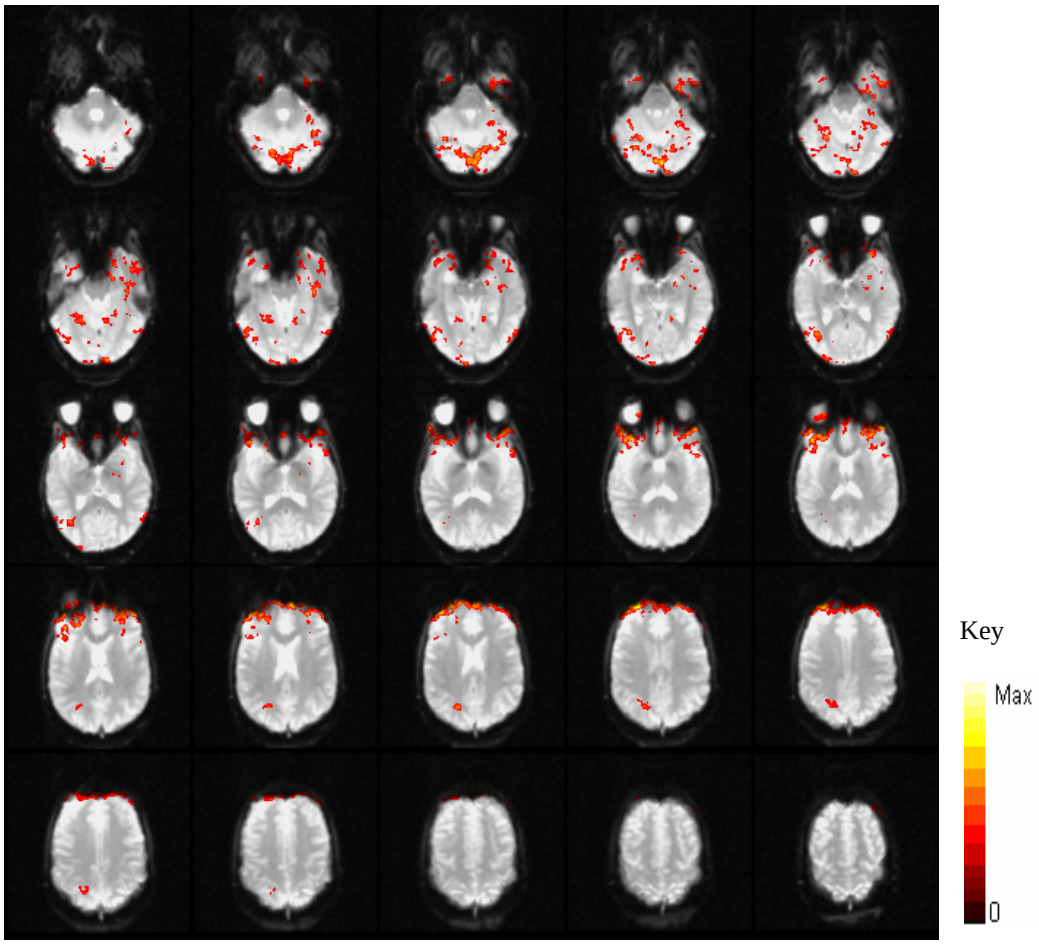

Figure G6. High resolution 25-slice rendered functional image for control group participant c8 during the fMRI Famous Faces task.

fMRI Famous Faces Task Control Group Participant c9

Table G7

fMRI Famous Faces Task Cluster Analysis for Control Group Participant c9

					Talairach Coordinates			
Laterali zation	Level 1 location	level 2 location	No. of voxels	Brodmann's Area	*x*	*y*	*z*	Z Value
Left	Frontal Lobe	Precentral Gyrus	262	6	-45.5	-6	46.9	6.23
		Inferior Frontal Gyrus	2058	45	-51.2	25.5	9.5	7.66
	Limbic lobe	Cingulate Gyrus	596	32	-1.45	13.5	42.3	8.74
	Parietal Lobe	Inferior Parietal Lobule	1805	40	-59.8	-42	22.1	7.22
	Occipital Lobe	Middle Occipital Gyrus	468	19	-40.6	-86	6.72	6.06
		Cuneus	165	7	-21.8	-77	30.6	5.18
Right	Frontal Lobe	Middle Frontal Gyrus	124	10	28.2	44	25.1	3.91
		Inferior Frontal Gyrus	187	47	50.1	17.6	-2.4	4.31
		Sub-gyral white matter	256	47	39.4	31.8	-2	5.76
	Limbic lobe	Uncus	302	28	27.3	2.23	-27	4.33
	Occipital Lobe	Lingual Gyrus	4168	18	8.4	-86	-4.4	9.39

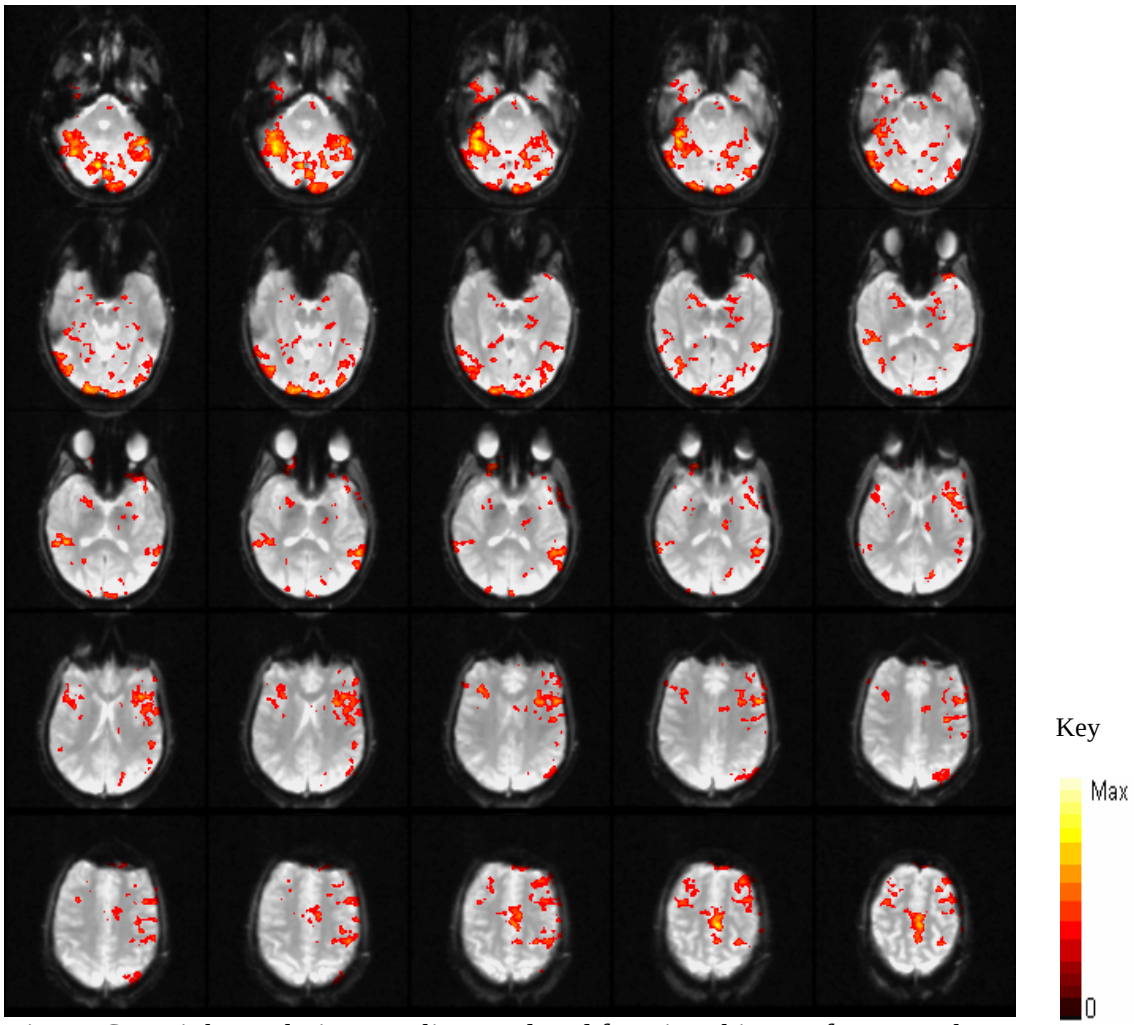

Figure G7. High resolution 25-slice rendered functional image for control group participant c9 during the fMRI Famous Faces task.

fMRI Famous Faces Task Control Group Participant c10

Table G8

fMRI Famous Faces Task Cluster Analysis for Control Group Participant c10

					Talairach Coordinates			
Lateralization	Level 1 location	level 2 location	No. of voxels	Brodmann's Area	*x*	*y*	*z*	Z Value
Left	Temporal Lobe	Middle Temporal Gyrus	148	39	-48.8	-71	15.1	5.61
	Cerebellum	Anterior Lobe, Culmen	833		-41.4	43	-29	5.06
		Anterior Lobe, Culmen	365		-41.5	-41	-20	4.92
Right	Frontal Lobe	Precentral Gyrus	887	6	33.2	-12	68.2	5.86
		Inferior Frontal Gyrus	203	47	36.2	29.4	-20	4.72
	Temporal Lobe	Fusiform Gyrus	285	37	39.8	-53	-17	5.6
	Occipital Lobe	Cuneus	286	18	19.3	-98	22.9	6.07
		Inferior Temporal Gyrus	139	37	49.4	-72	0.37	5.4

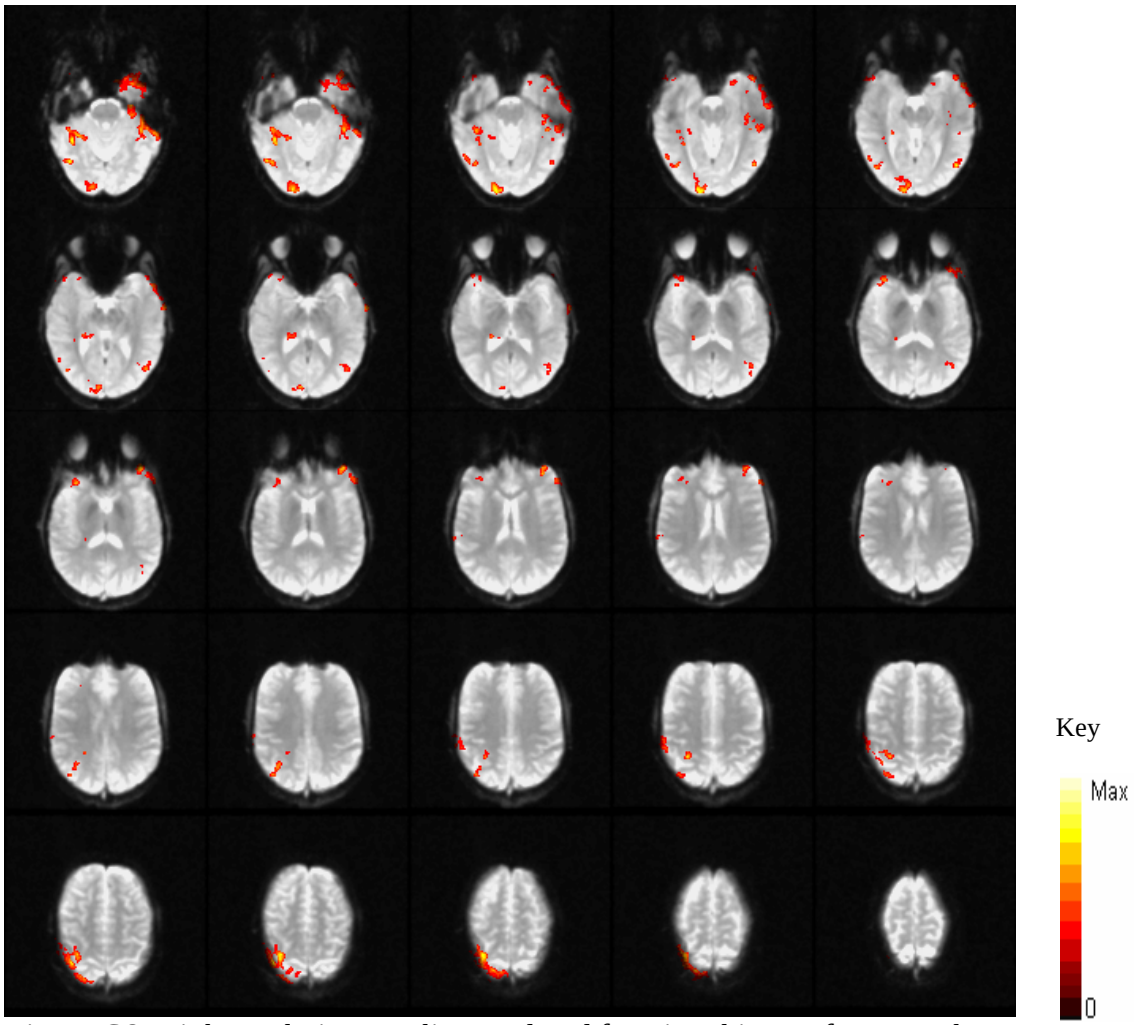

Figure G8. High resolution 25-slice rendered functional image for control group participant c10 during the fMRI Famous Faces task.

APPENDIX H

Patient Group: Individual fMRI Famous Faces Task Results

fMRI Famous Faces Task Patient Group Participant p1

Table H1

fMRI Famous Faces Task Cluster Analysis for Patient Group Participant p1

					Talairach Coordinates			
Laterali zation	Level 1 location	level 2 location	No. of voxels	Brodmann's Area	*x*	*y*	*z*	Z Value
Left	Frontal Lobe	Inferior Frontal Gyrus	8545	44	-58.6	16.5	9.44	7.91
	Temporal Lobe	Middle Temporal Gyrus	237	39	-48.6	-75.2	8.29	5.85
	Limbic lobe	Cingulate Gyrus	487	32	-1.84	28.1	24.3	4.87
Right	Frontal Lobe	Inferior Frontal Gyrus	728	44	61.1	14.1	13.7	6.44
	Temporal Lobe	Transverse Temporal Gyrus	127	42	60.6	-18.7	7.73	6.16
	Limbic lobe	Posterior Cingulate	250	30	5.46	0.763	-59.3	5.46
	Sub cortical	Lentiform Nucleus, Putamen	149		25.4	-7.45	10.4	4.05
	Occipital Lobe	Fusiform Gyrus	484	19	36.6	-68.5	-9.12	7.69

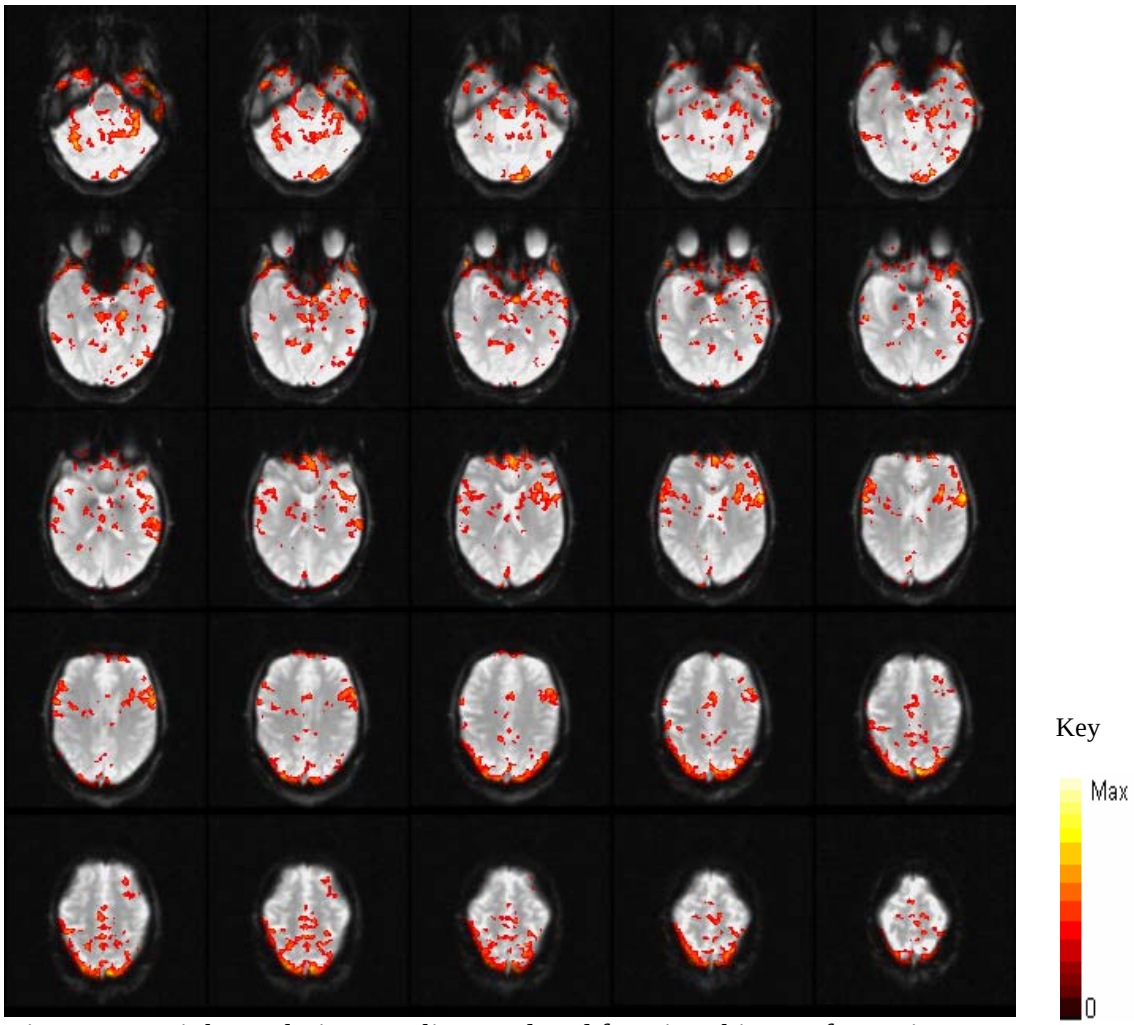

Figure H1. High resolution 25-slice rendered functional image for patient group participant p1 during the fMRI Famous Faces task.

fMRI Famous Faces Task Patient Group Participant p2

Table H2

fMRI Famous Faces Task Cluster Analysis for Patient Group Participant p2

					Talairach Coordinates			
Laterali zation	Level 1 location	level 2 location	No. of voxels	Brodmann's Area	*x*	*y*	*z*	Z Value
Left	Temporal Lobe	Superior Temporal Gyrus	3619	22	-60.5	-50.7	13.9	6.98
	Limbic lobe	Cingulate Gyrus	118	32	-0.06	12.8	40.5	4.38
Right	Frontal Lobe	Precentral Gyrus	336	6	39.7	-5.72	37.7	4.2
		Middle Frontal Gyrus	121	6	26.3	-11.7	57	4.22
	Temporal Lobe	Middle Temporal Gyrus	760	21	54.8	-5.41	-17.9	4.91
			551	21	60.3	-55.4	6.17	5.86
	Parietal Lobe	Postcentra l Gyrus	151	5	28.8	-43.2	63.4	3.95
	Occipital Lobe	Middle Occipital Gyrus	599	21	25.5	-91	10.6	7.21
		Lingual Gyrus	195	17	5.34	-82.5	4.98	7.78

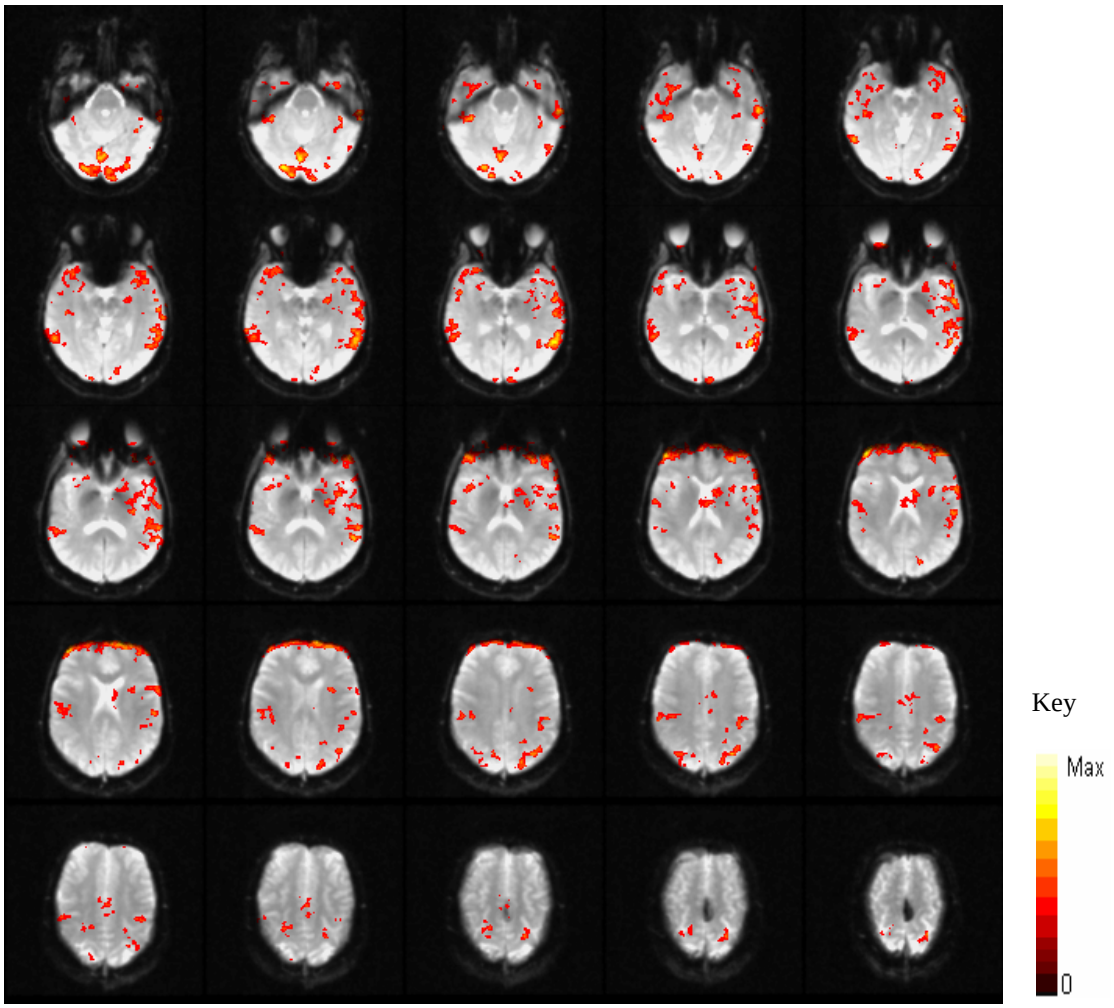

Figure H2. High resolution 25-slice rendered functional image for patient group participant p2 during the fMRI Famous Faces task.

fMRI Famous Faces Task Patient Group Participant p3

Table H3

fMRI Famous Faces Task Cluster Analysis for Patient Group Participant p3

					Talairach Coordinates			
Laterali Zation	Level 1 location	level 2 location	No. of voxels	Brodmann's Area	*X*	*y*	*z*	Z Value
Left	Parietal Lobe	Inferior Parietal Lobule	199	39	-44.9	-65.1	41.3	4.89
Right	Parietal Lobe	Inferior Parietal Lobule	112	39	47.5	-68.8	43.8	5.09

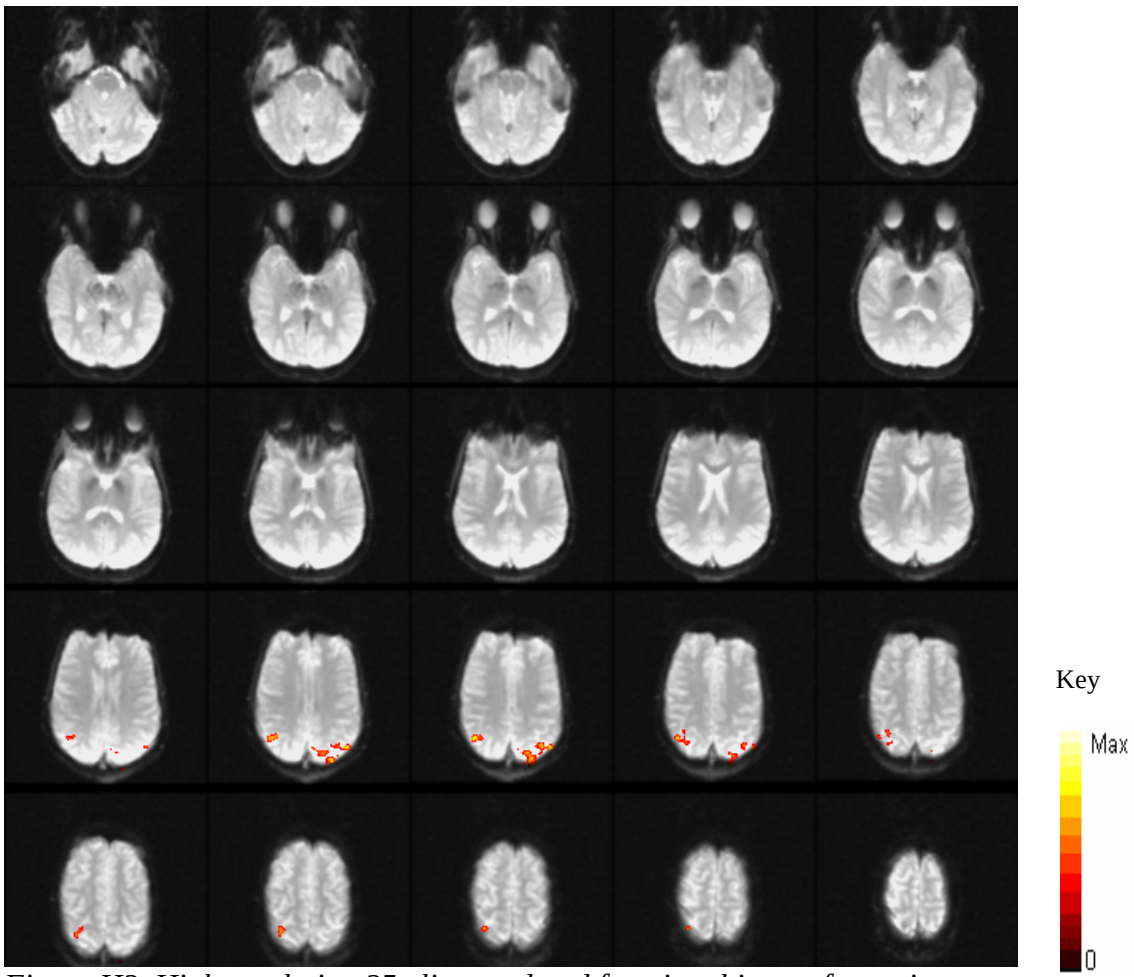

Figure H3. High resolution 25-slice rendered functional image for patient group participant p3 during the fMRI Famous Faces task.

fMRI Famous Faces Task Patient Group Participant p4

Table H4

fMRI Famous Faces Task Cluster Analysis for Patient Group Participant p4

					Talairach Coordinates			
Laterali zation	Level 1 location	level 2 location	No. of voxels	Brodmann's Area	*x*	*y*	*z*	Z Value
Left	Frontal lobe	Medial Frontal Gyrus	1509	11	-4.1	53.5	-13.4	6.48
	Parietal Lobe	Superior Parietal Lobule	193	7	-45.5	-68.5	54.7	4.35
	Occipital Lobe	Cuneus	164	18	-7.07	-97.6	24.4	5.05
Right	Frontal Lobe	Inferior Frontal Gyrus	314	47	35.9	33.5	-20	3.99
			133	45	54.4	37.3	0.267	4.31
	Temporal Lobe	Middle Temporal Gyrus	291	21	60	6.35	-25.6	7.09
		Middle Temporal Gyrus	150	37	53.5	-61.4	6.2	4.25
	Parietal Lobe	Precuneus	604	7	8.44	-58.8	43.4	5.19
		Inferior Parietal Lobule	150	40	66	-27.4	43.2	4.11
	Occipital Lobe	Cuneus	296	18	15.4	-98.1	22.5	8.81

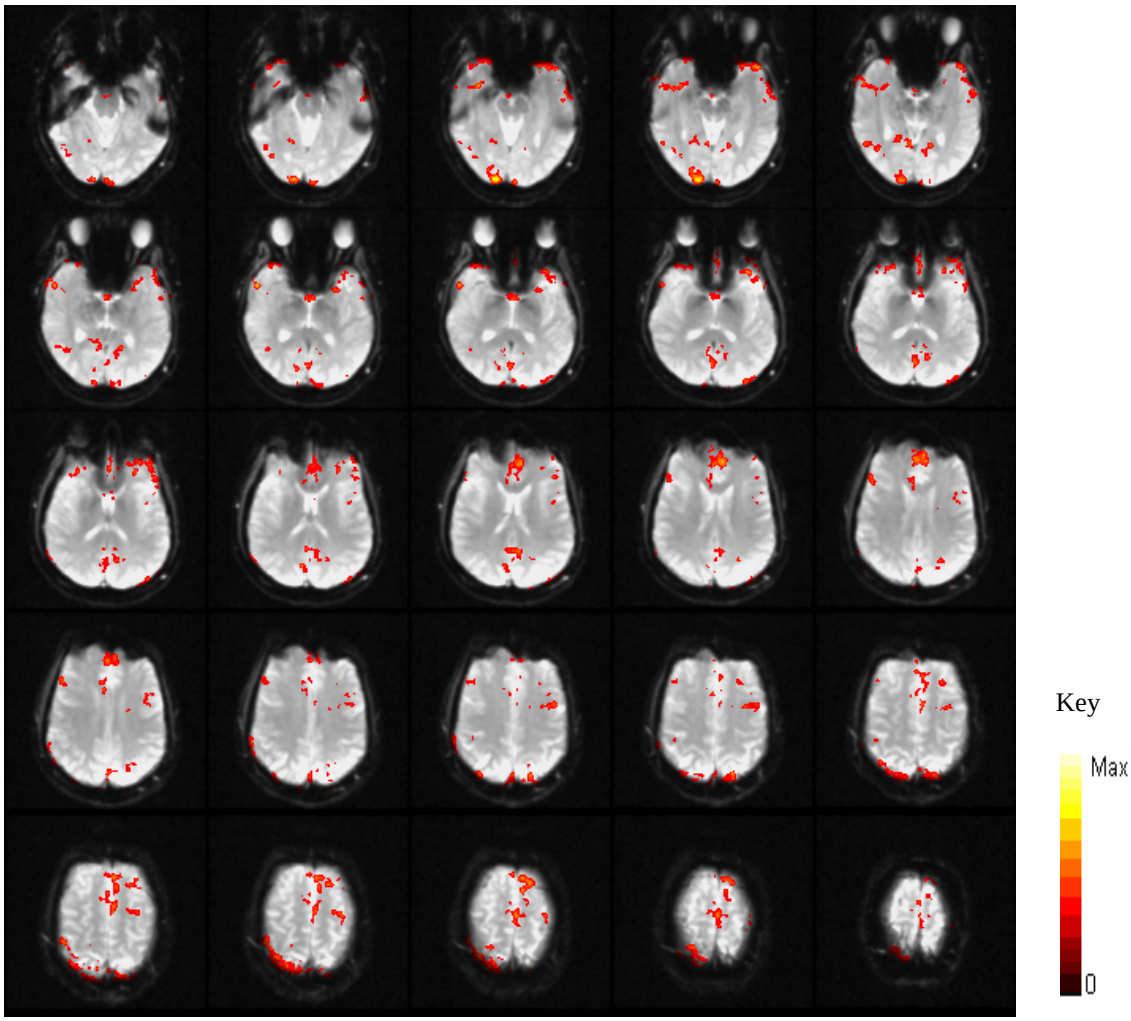

Figure H4. High resolution 25-slice rendered functional image for patient group participant p4 during the fMRI Famous Faces task.

fMRI Famous Faces Task Patient Group Participant p5

Table H5

fMRI Famous Faces Task Cluster Analysis for Patient Group Participant p5

					Talairach Coordinates			
Laterali zation	Level 1 location	level 2 location	No. of voxels	Brodmann's Area	*x*	*y*	*z*	Z Value
Left	Frontal Lobe	Precentral Gyrus	566	4	-25.4	-21.1	54.7	6.44
		Middle Frontal Gyrus	216	46	-37.9	30.3	22.8	4.69
		Medial Frontal Gyrus	312	6	-0.14	-12.6	49.5	5.6
			125	8	-8.44	26.3	40.7	5.37
	Limbic lobe	Posterior Cingulate	335	30	-21.4	-60.9	7.46	6.33
	Sub cortical	Thalamus, Anterior Nucleus	498		-5.79	-0.51	7.77	5.2
	Cerebellu m	Posterior Lobe, Declive	206		-29.6	-56.6	-14.7	5.81
		Anterior Lobe, Culmen	149		-2.96	-47.1	2.98	3.87
Right	Frontal Lobe	Precentral Gyrus	204	4	34.4	-21.3	61.4	5.44
		Superior Frontal Gyrus	134	11	22.3	52.4	-19.3	5.2
		Inferior Frontal Gyrus	2597	9	56.9	21.1	22.7	5.34
	Sub cortical	Thalamus	363		13.4	-32.1	21.2	5.77
	Parietal Lobe	Supramargin al Gyrus	120	40	46	-43.6	35	4.04
		Paracentral Lobule	436	4	1.59	-39.3	68.4	6.31
		Postcentral Gyrus	171	5	36.9	-41.5	61.6	4.58
		Inferior Parietal Lobule	146	40	55.7	-30.5	26	4.69
	Occipital Lobe	Middle Occipital Gyrus	332	19	43.1	-74.8	5.05	5.94

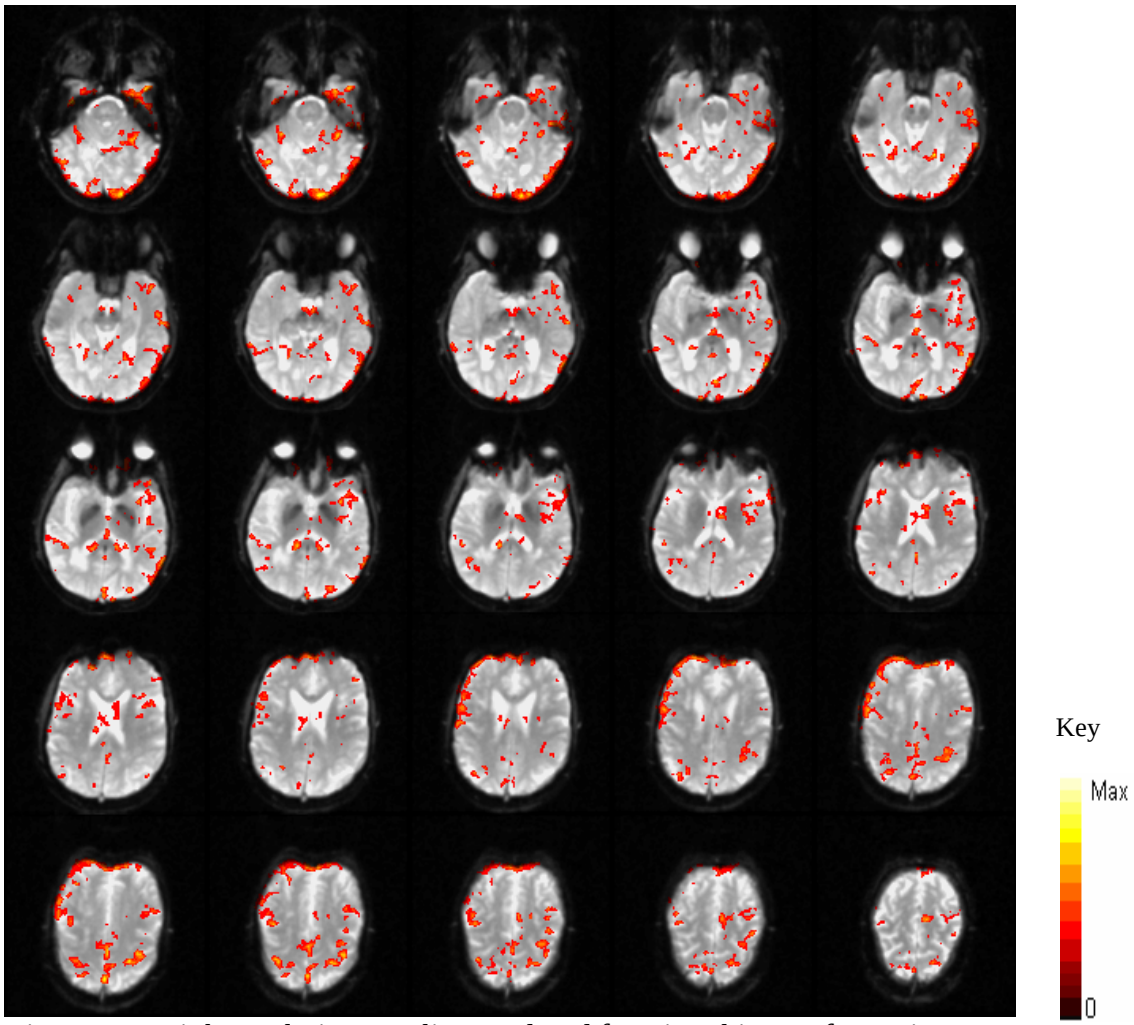

Figure H5. High resolution 25-slice rendered functional image for patient group participant p5 during the fMRI Famous Faces task.

fMRI Famous Faces Task Patient Group Participant p6

Table H6

fMRI Famous Faces Task Cluster Analysis for Patient Group Participant p6

					Talairach Coordinates			
Laterali Zation	Level 1 location	level 2 location	No. of voxels	Brodmann's Area	*x*	*y*	*Z*	Z Value
Left	Frontal Lobe	Precentral Gyrus	1131	44	-54.2	8.32	5.03	7.27
		Superior Frontal Gyrus	2253	6	-12.3	-1.8	72.4	8.06
	Temporal Lobe	Superior Temporal Gyrus	154	13	-47.7	-44.2	18.8	4.7
	Limbic lobe	Parahippocampal Gyrus	235	36	-19.5	-39.1	-6.57	4.89
	Parietal Lobe	Inferior Parietal Lobule	847	40	-51.1	-55.9	45.7	6.86
	Occipital Lobe	Middle Occipital Gyrus	371	19	-53.9	-67.7	6.67	5.11
Right	Frontal Lobe	Middle Frontal Gyrus	110	6	26.8	-7.3	44	4.73
	Sub cortical	Thalamus	298		10.7	-9.75	19.2	6.46
	Cerebellum	Posterior Lobe, Pyramis	3696		37.4	-71.7	-33.3	6.93

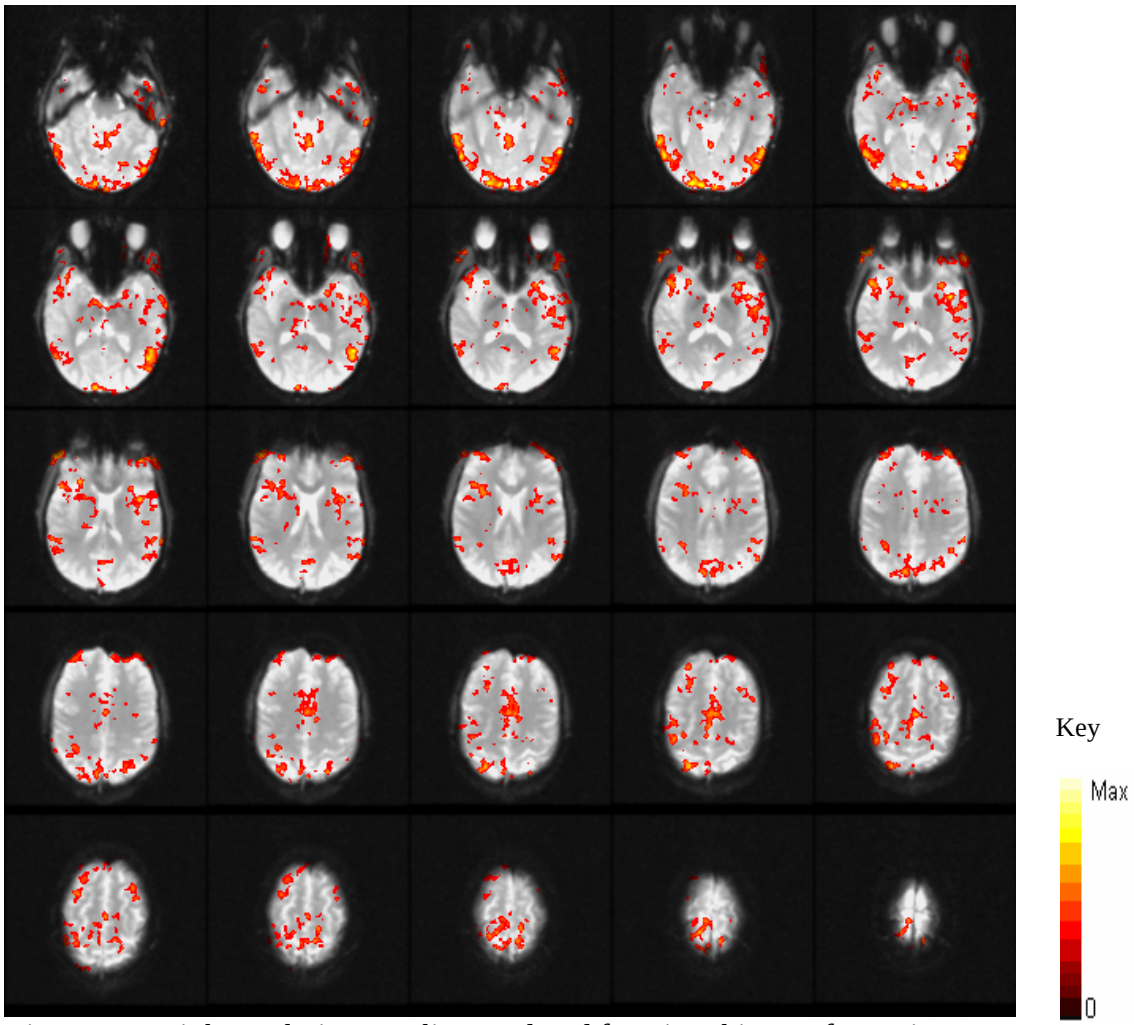

Figure H6. High resolution 25-slice rendered functional image for patient group participant p6 during the fMRI Famous Faces task.

APPENDIX I

Control Group: Individual Results for the fMRI Sentence Reading Task

fMRI Sentence Reading Task Control Group Participant c1

Table I1

fMRI Sentence Reading Task Cluster Analysis for Control Group Participant c1

Laterali zation	Level 1 location	level 2 location	No. of voxels	Brodmann's Area	Talairach Coordinates *x*	*y*	*z*	Z Value
Left	Frontal Lobe	Paracentral Lobule	352	6	-13.2	-22	47.9	4.39
		Sub-gyral gray matter	534	8	-18.8	22	42.5	4.38
	Limbic Lobe	Anterior Cingulate	1656	32	-11.2	30.5	-1.8	5.28
	Temporal Lobe	Middle Temporal Gyrus	158	21	-53.2	-14.5	-13.7	3.99
Right	Frontal Lobe	Medial Frontal Gyrus	209	10	17.7	56.4	6.86	4.79
	Sub-lobar	Insula	176	13	40	-4.3	21.4	4.38
	Occipital Lobe	Lingual Gyrus	930	18	0.563	-71.1	-2.59	6.21

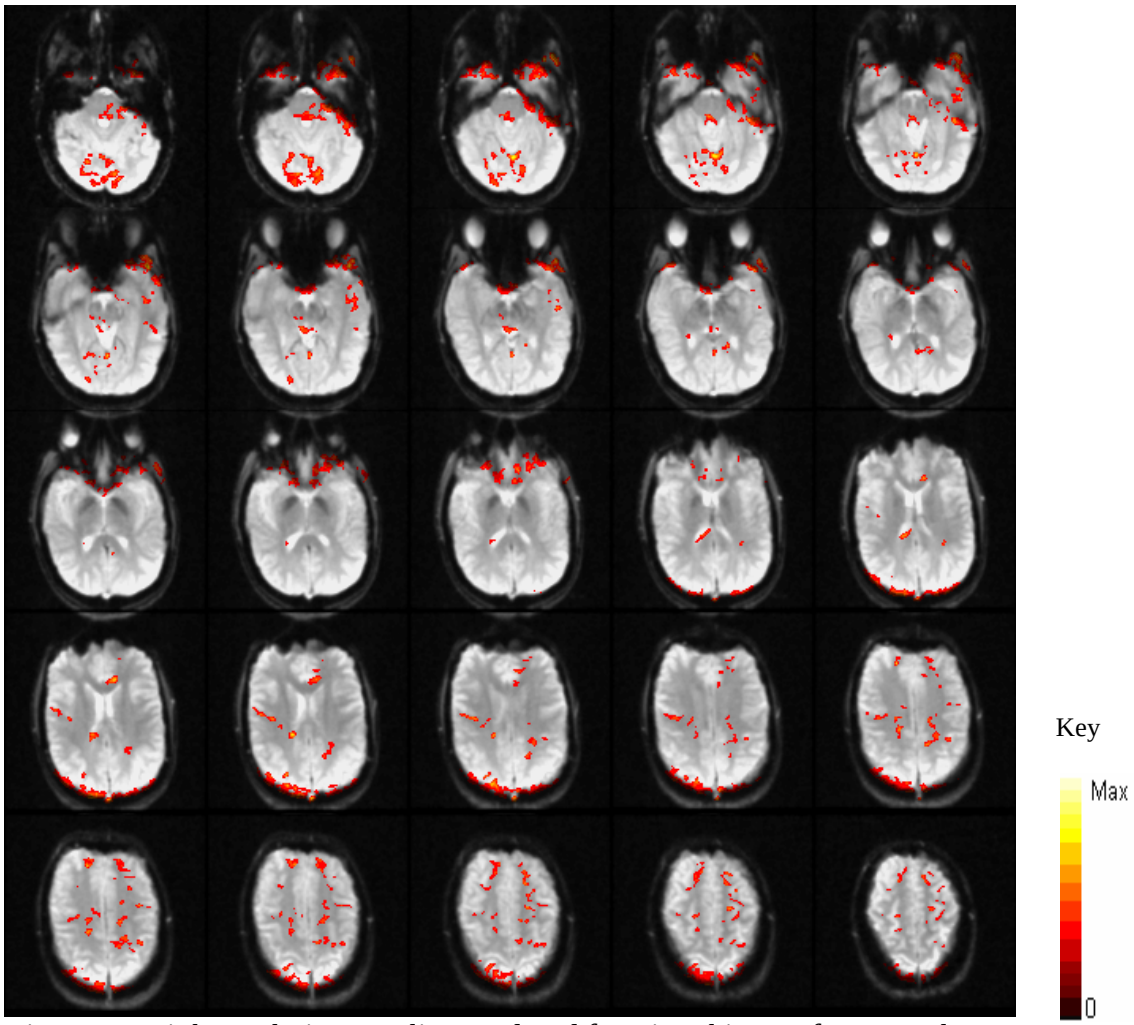

Figure I1. High resolution 25-slice rendered functional image for control group participant c1 during the fMRI Sentence Reading task.

fMRI Sentence Reading Task Control Group Participant c2

Table I2

fMRI Sentence Reading Task Cluster Analysis for Control Group Participant c2

Laterali zation	Level 1 location	level 2 location	No. of voxels	Brodmann's Area	Talairach Coordinates *x*	*y*	*z*	Z Value
Left	Frontal Lobe	Superior Frontal Gyrus	764	11	-3.33	56.8	-26.7	5.78
			213	10	-15.8	70.9	13.7	4.76
			157	8	-4.99	27.7	51.9	4.95
		Inferior Frontal Gyrus	871	45	-46.8	22.2	12.3	6.5
	Temporal Lobe	Middle Temporal Gyrus	299	22	-50.4	-40.2	-1.02	6.3
			190	21	-53.7	-1.82	-22.3	5.73
			156	39	-47.4	-70.1	20.4	4.61
		Inferior Temporal Gyrus	117	20	-42.6	-15.5	-34	4.54
	Limbic Lobe	Uncus	194	36	-16	-2.06	-32.2	4.31
Right	Frontal Lobe	Precentral Gyrus	428	6	55.2	-1.12	43.1	6.34
		Inferior Frontal Gyrus	144	45	51.9	30.2	1.8	5.85
	Temporal Lobe	Fusiform Gyrus	125	37	36	-44	-14.4	4.68

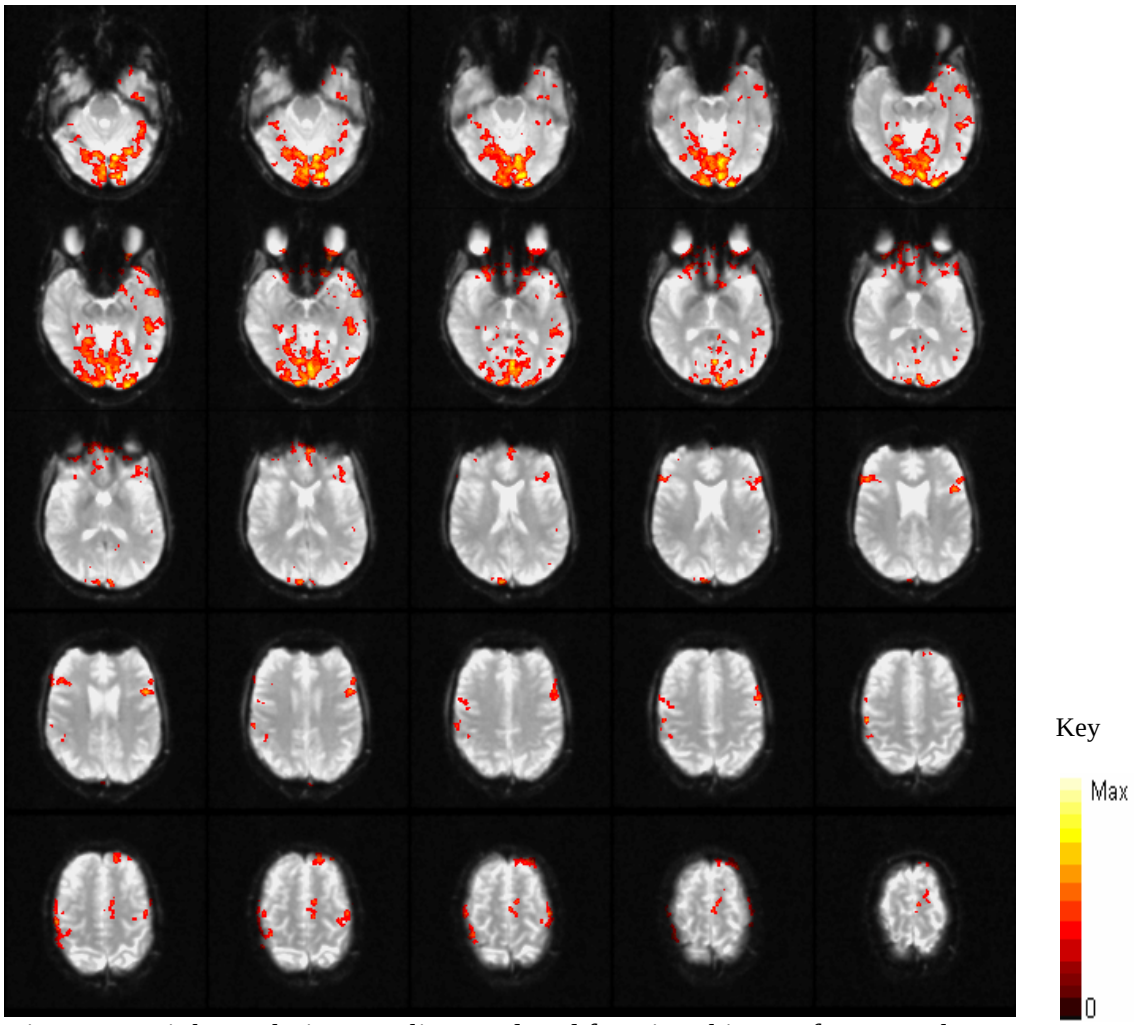

Figure I2. High resolution 25-slice rendered functional image for control group participant c2 during the fMRI Sentence Reading task.

fMRI Sentence Reading Task Control Group Participant c3

Table I3

fMRI Sentence Reading Task Cluster Analysis for Control Group Participant c3

Laterali Zation	Level 1 location	level 2 location	No. of voxels	Brodmann's Area	Talairach Coordinates *x*	*y*	*z*	Z Value
Left	Frontal Lobe	Inferior Frontal Gyrus	143	46	-48.5	31.2	7.74	4.79
		Subcallosal Gyrus	143	34	-7.69	2.33	-16.7	5.24
	Temporal Lobe	Middle Temporal Gyrus	2916	22	-56	-34.3	-1.56	6.82
	Parietal Lobe	Superior Parietal Lobule	268	7	-34.6	-47.6	67.4	4.49
Right	Frontal Lobe	Precentral Gyrus	136	4	43.2	-17.1	59.4	4.74
		Inferior Frontal Gyrus	127	45	48.4	22.6	16	5.03
	Temporal Lobe	Middle Temporal Gyrus	372	21	49.3	-28.9	-4.13	7.28
	Occipital Lobe	Cuneus	2678	18	2.74	-97.7	9.13	7.44
		Middle Occipital Gyrus	149	19	42.7	-80.9	3.9	5.03
	Cerebellum	Anterior Lobe, Culmen	119		15.9	-37.5	-10.8	4.81

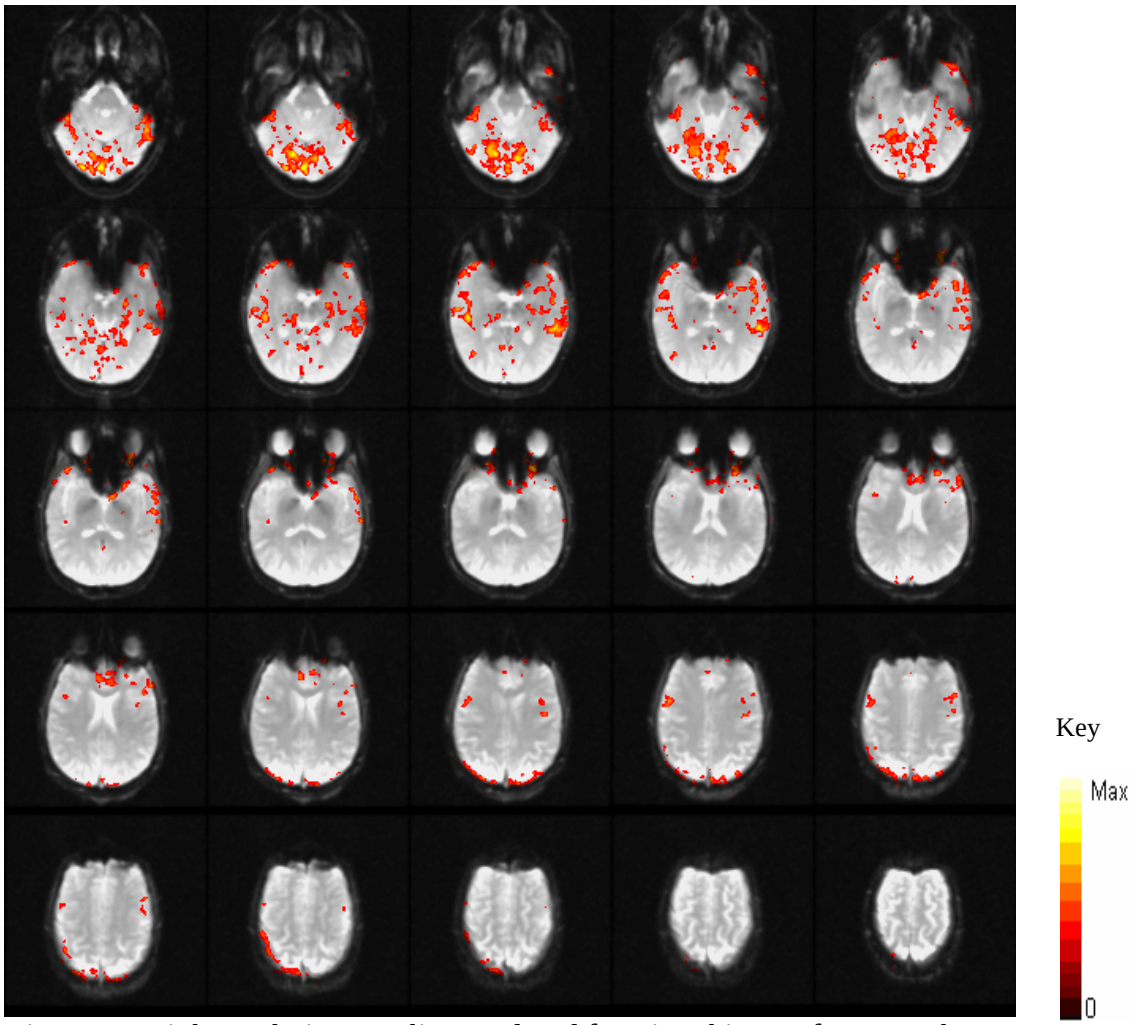

Figure I3. High resolution 25-slice rendered functional image for control group participant c3 during the fMRI Sentence Reading task.

fMRI Sentence Reading Task Control Group Participant c5

Table I4

fMRI Sentence Reading Task Cluster Analysis for Control Group Participant c5

					Talairach Coordinates			
Laterali Zation	Level 1 location	level 2 location	No. of voxels	Brodmann's Area	*x*	*y*	*z*	Z Value
Left	Temporal Lobe	Middle Temporal Gyrus	330	22	-63	-41.2	3.01	5.23
			164	21	-62	-3.63	-2.15	4.79
			155	39	-32.6	-52.3	27.2	4.24
	Occipital Lobe	Middle Occipital Gyrus	1589	18	-16.9	-100	18.1	7.22
Right	Parietal Lobe	Postcentral Gyrus	499	2	65.5	-24.2	44.9	4.74

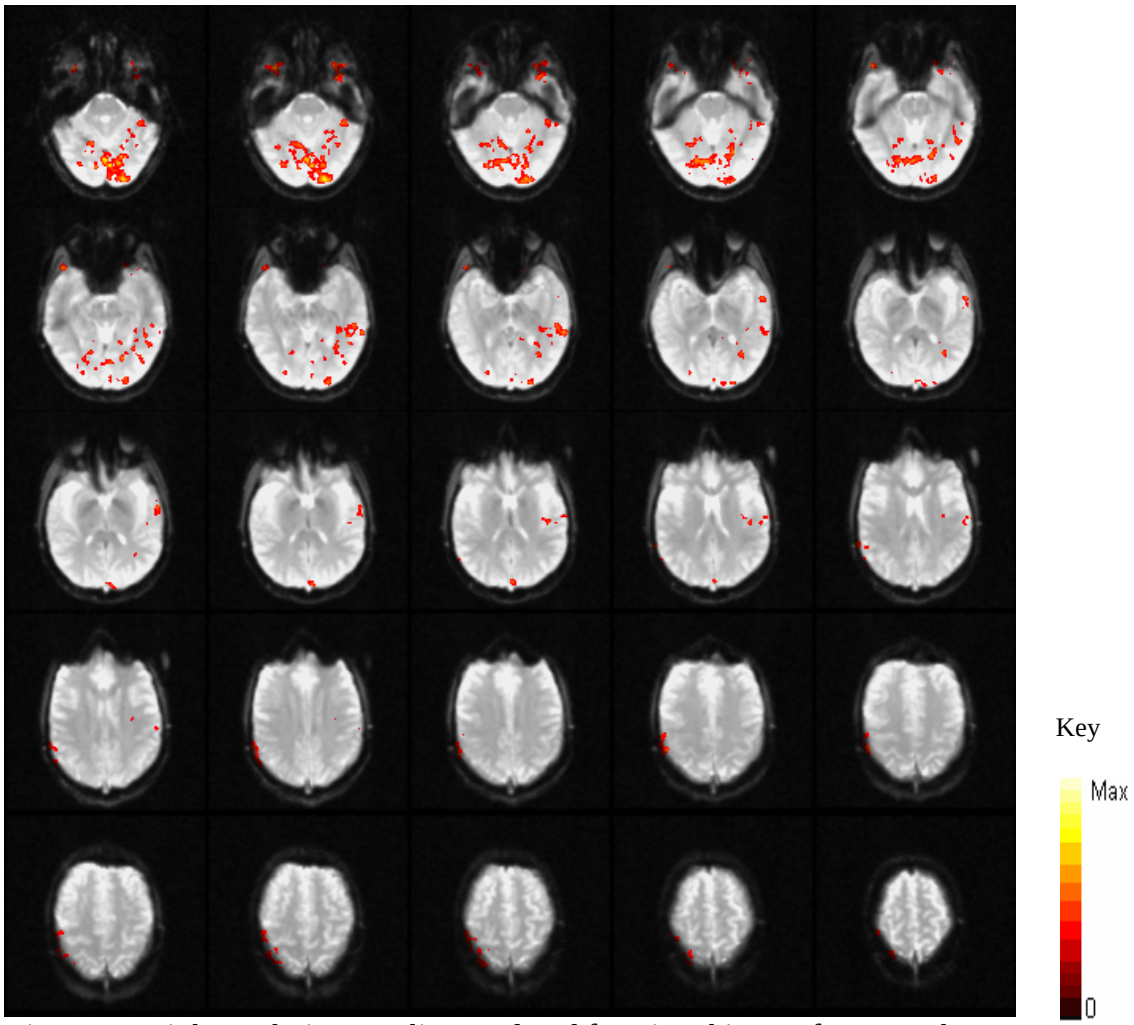

Figure I4. High resolution 25-slice rendered functional image for control group participant c5 during the fMRI Sentence Reading task.

fMRI Sentence Reading Task Control Group Participant c6

Table I5

fMRI Sentence Reading Task Cluster Analysis for Control Group Participant c6

					Talairach Coordinates			
Laterali Zation	Level 1 location	level 2 location	No. of voxels	Brodmann's Area	*x*	*y*	*z*	Z Value
Left	Frontal Lobe	Inferior Frontal Gyrus	190	47	-56.1	23.6	-11.7	4.93
	Temporal Lobe	Inferior Temporal Gyrus	181	20	-50.7	-5.59	-20.1	6.41
	Sub-lobar	Insula	171	13	-38.6	17.8	18	4.4
	Occipital Lobe	Cuneus	3329	17	-9.81	-89.5	9.91	8.11
Right	Frontal Lobe	Middle Frontal Gyrus	1772	46	48.7	45	14.1	6.33
		Medial Frontal Gyrus	104	11	2.54	56.2	-14.3	5.42

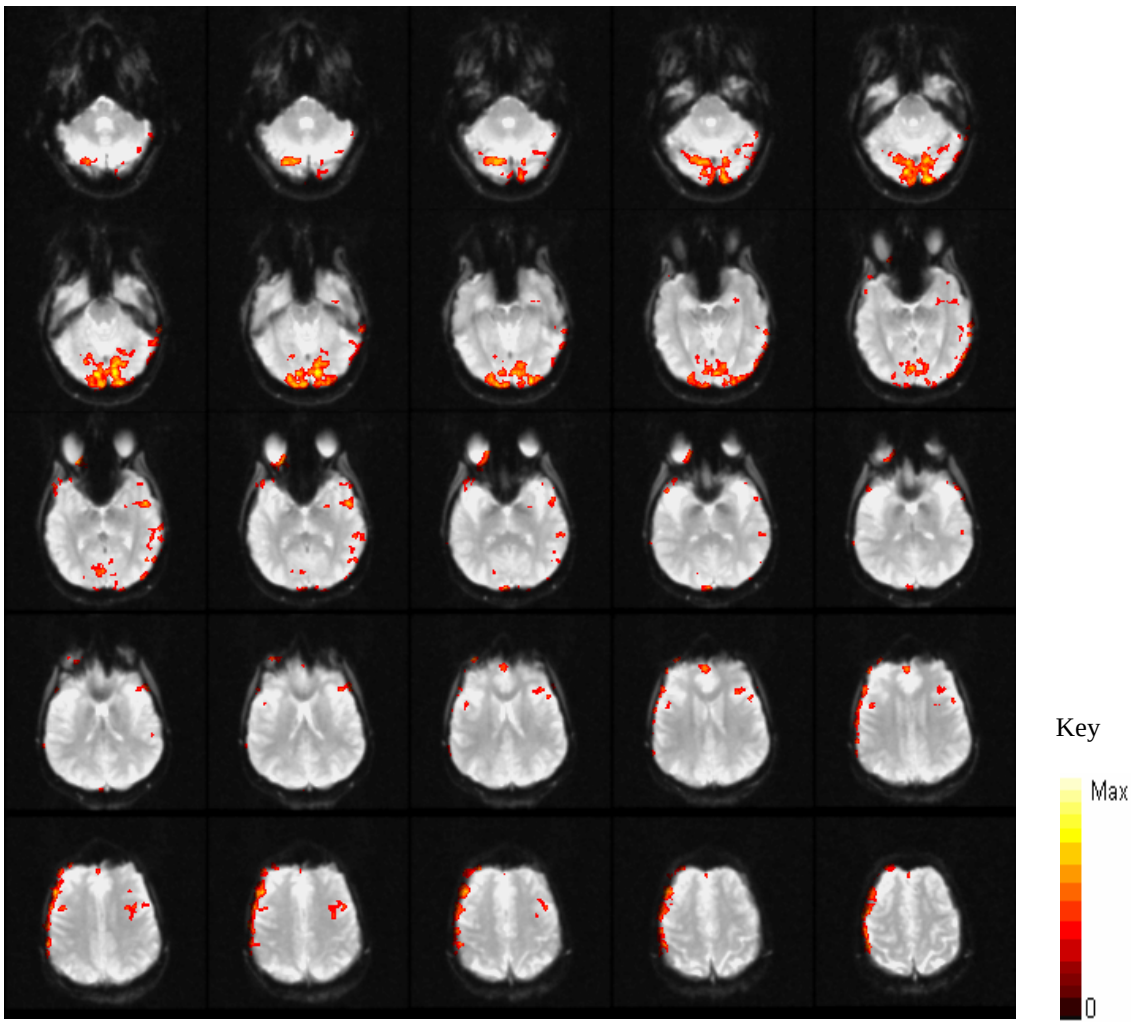

Figure I5. High resolution 25-slice rendered functional image for control group participant c6 during the fMRI Sentence Reading task.

fMRI Sentence Reading Task Control Group Participant c7

Table I6

fMRI Sentence Reading Task Cluster Analysis for Control Group Participant c7

					Talairach Coordinates			
Lateralization	Level 1 location	level 2 location	No. of voxels	Brodmann's Area	*x*	*y*	*z*	Z Value
Left	Frontal Lobe	Superior Frontal Gyrus	107	8	-2.2	21	50.1	5.6
		Middle Frontal Gyrus	143	6	-39.1	3.09	40.3	3.92
		Inferior Frontal Gyrus	302	47	-17.9	16.7	-17.7	5.43
	Temporal Lobe	Middle Temporal Gyrus	2629	21	-66.8	-33.5	1.16	8.22
	Sub-lobar	Hypothalamus	120		-5.05	-5.64	-11.7	4.81
	Parietal Lobe	Precuneus	102	7	-26.2	-77.4	56.6	4.11
Right	Frontal Lobe	Inferior Frontal Gyrus	246	46	55.2	37.6	7.5	5.17
			102	9	41.8	10.9	26.6	4.79
			106	47	23.3	16.6	-21.6	4.3
		Rectal Gyrus	110	11	1.02	47.8	-29.1	4.16
	Occipital Lobe	Cuneus	2845	19	16	-96.8	29	10.6

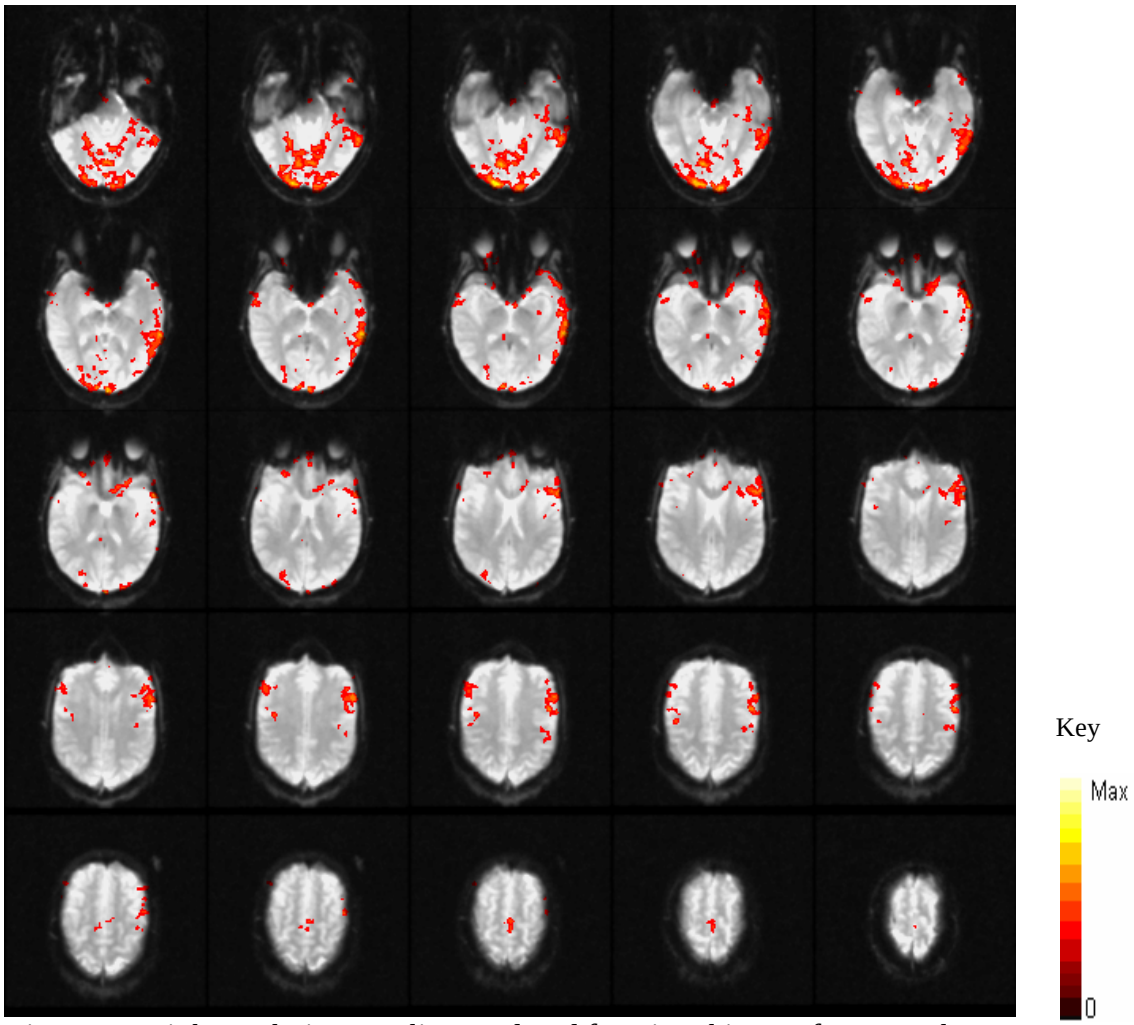

Figure I6. High resolution 25-slice rendered functional image for control group participant c7 during the fMRI Sentence Reading task.

fMRI Sentence Reading Task Control Group Participant c8

Table I7

fMRI Sentence Reading Task Cluster Analysis for Control Group Participant c8

					Talairach Coordinates			
Lateralization	Level 1 location	level 2 location	No. of voxels	Brodmann's Area	*x*	*y*	*z*	Z Value
Left	Frontal Lobe	Superior Frontal Gyrus	188	11	-21.4	65.6	-21.9	4.33
	Temporal Lobe	Superior Temporal Gyrus	173	22	-57	1.38	-3.28	5.27
		Middle Temporal Gyrus	185	21	-57.2	-24.4	-8.87	5.12
	Occipital Lobe	Lingual Gyrus	2141	18	-16.1	-81.5	-3.59	6.4
Right	Frontal Lobe	Superior Frontal Gyrus	193	10	16	70	-10.9	4.15
		Middle Frontal Gyrus	330	11	33.2	34.2	-16.7	4.84
		Medial Frontal Gyrus	130	10	11	55.3	3.04	5.2
	Temporal Lobe	Inferior Temporal Gyrus	310	21	62.5	-14.7	-15.6	6.03
			128	20	46.1	-15.6	-29.7	4.25
	Cerebellum	Posterior Lobe, Declive	343		31.5	-86.7	-18.5	3.87

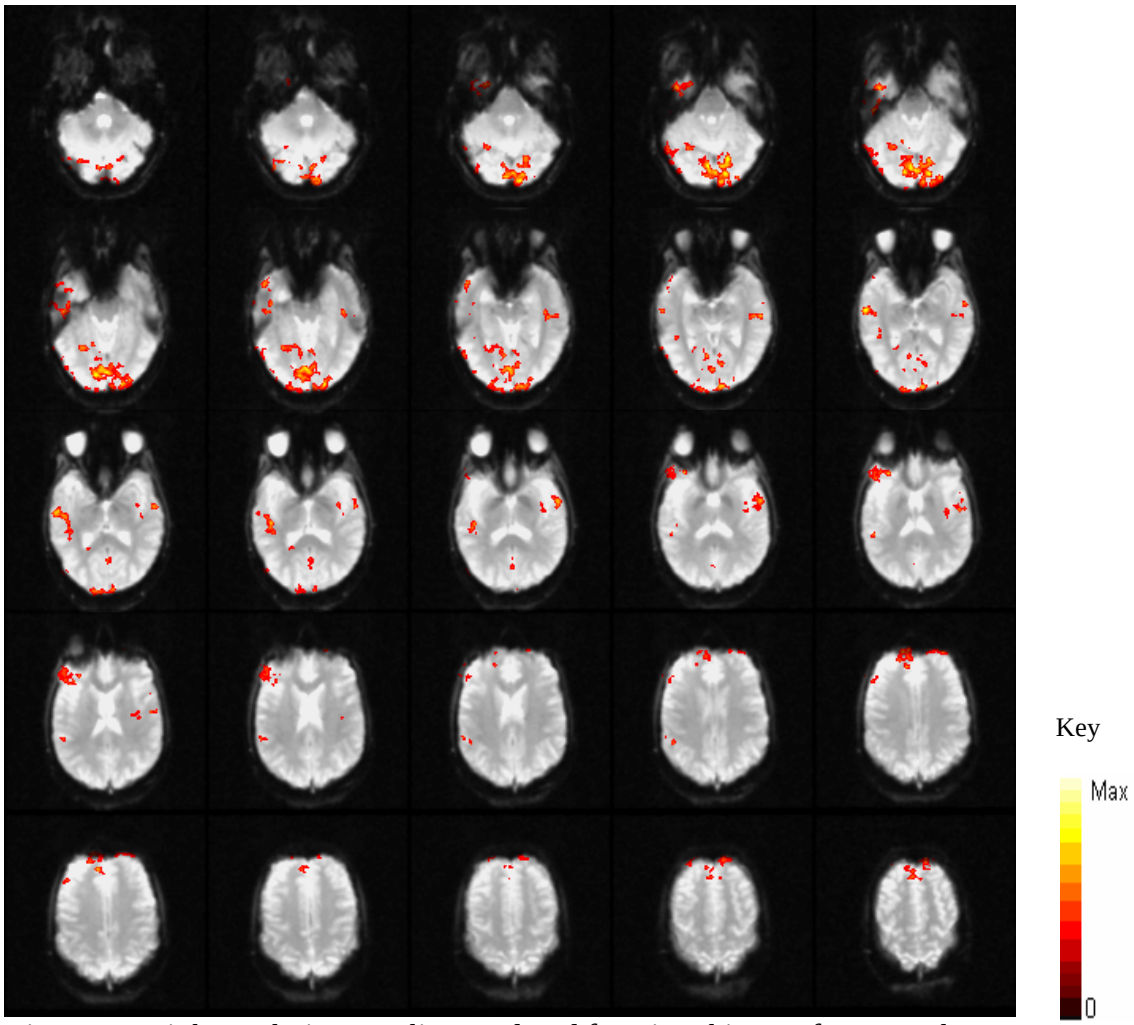

Figure I7. High resolution 25-slice rendered functional image for control group participant c8 during the fMRI Sentence Reading task.

fMRI Sentence Reading Task Control Group Participant c10

Table I8

fMRI Sentence Reading Task Cluster Analysis for Control Group Participant c10

					Talairach Coordinates			
Lateralization	Level 1 location	level 2 location	No. of voxels	Brodmann's Area	*x*	*y*	*z*	Z Value
Left	Frontal Lobe	Superior Frontal Gyrus	249	9	-11.2	56.2	30.6	4.15
		Inferior Frontal Gyrus	182	45	-56.7	32.1	-0.216	4.81
	Limbic Lobe	Posterior Cingulate	182	29	-7.24	-47.9	5.73	5.12
Right	Frontal Lobe	Inferior Frontal Gyrus	176	47	26.6	28	-1.82	4.23
	Parietal Lobe	Postcentral Gyrus	144	43	64.6	-11.8	18.9	4.13
	Occipital Lobe	Cuneus	1549	18	17.6	-102	25	8.42

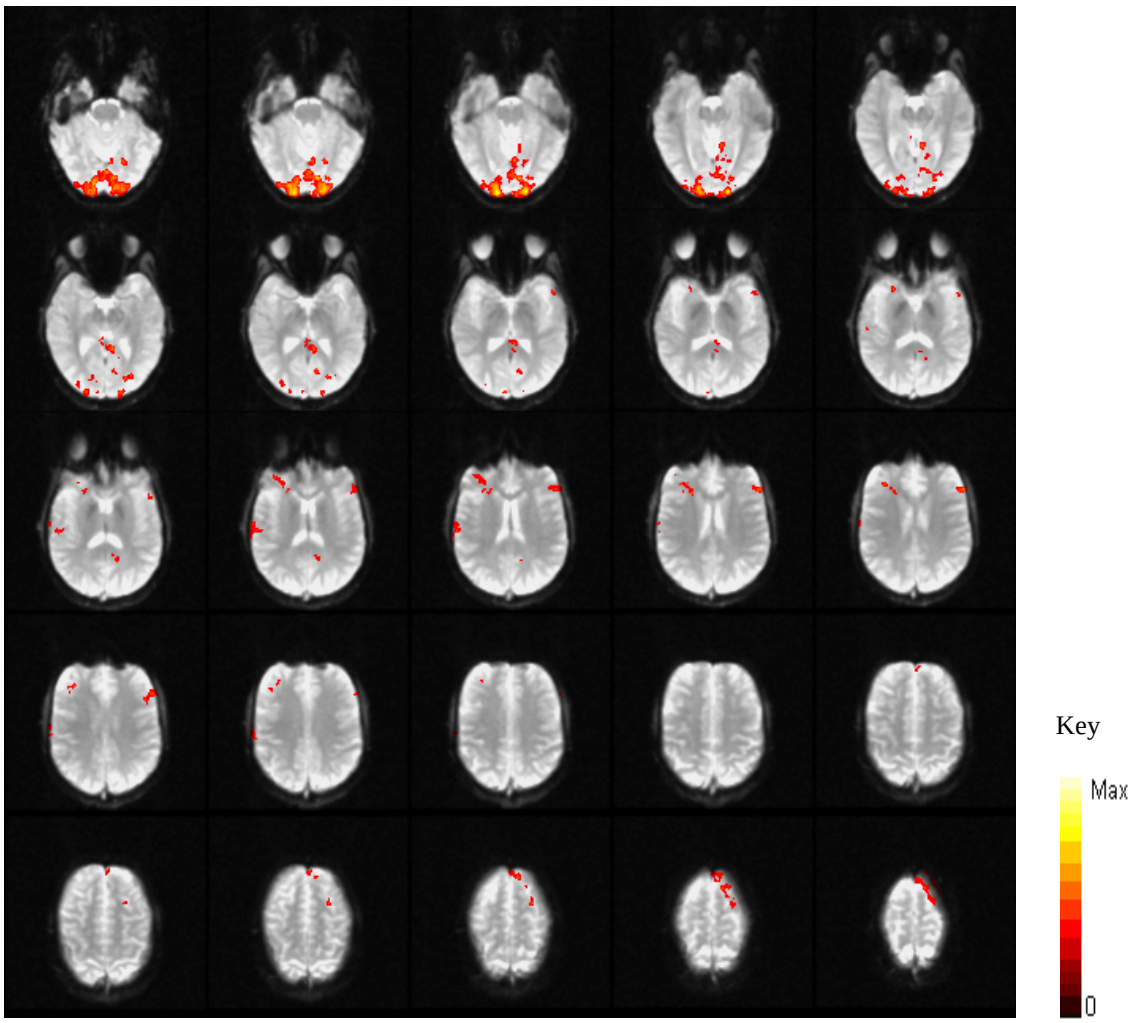

Figure I8. High resolution 25-slice rendered functional image for control group participant c10 during the fMRI Sentence Reading task.

APPENDIX J

Patient Group: Individual fMRI Sentence Reading Task Results

fMRI Sentence Reading Task Patient Group Participant p2

Table J1

fMRI Sentence Reading Task Cluster Analysis for Patient Group Participant p2

Laterali zation	Level 1 location	level 2 location	No. of voxels	Brodmann's Area	Talairach Coordinates *x*	*y*	*z*	Z Value
Left	Frontal Lobe	Precentral Gyrus	1642	6	-62.7	-0.41	18.3	5.42
		Medial Frontal Gyrus	124	32	-5.02	10.4	46.1	5.31
	Occipital Lobe	Middle Occipital Gyrus	172	18	-27.8	-93.6	8.36	7.12
	Parietal Lobe	Superior Parietal Lobule	124	7	-22	-72.2	59.1	5.72
Right	Occipital Lobe	Lingual Gyrus	220		0.442	-80.2	-1.19	5.78
	Cerebellum	Anterior Lobe, Culmen	1956		40.6	-37.8	-21.1	5.29

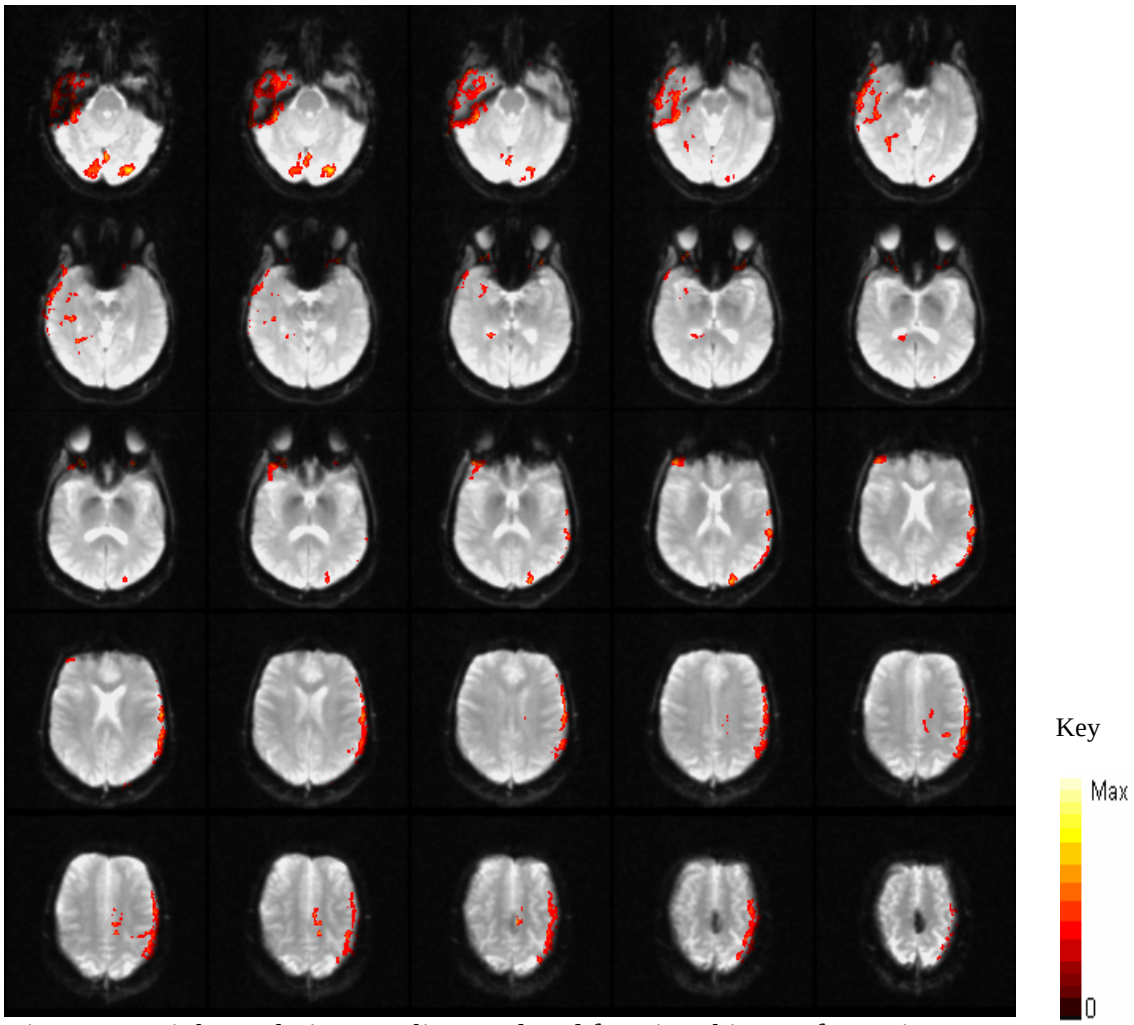

Figure J1. High resolution 25-slice rendered functional image for patient group participant ps2 during the fMRI Sentence Reading task.

fMRI Sentence Reading Task Patient Group Participant p3

Table J2

fMRI Sentence Reading Task Cluster Analysis for Patient Group Participant p3

Laterali zation	Level 1 location	level 2 location	No. of voxels	Brodmann's Area	Talairach Coordinates *x*	*y*	*z*	Z Value
Left	Frontal Lobe	Precentral Gyrus	620	6	-48	-6.7	36.1	5.16
		Inferior Frontal Gyrus	187	47	-43	24.2	-10.1	5.05
	Occipital Lobe	Cuneus	771	18	-5.81	-84.8	12.4	6.19
	Temporal Lobe	Middle Temporal Gyrus	200	21	-65	-11.3	-10.8	5.48
Right	Occipital Lobe	Occipital Gyrus	302	18	17.9	-104	19.7	5.51

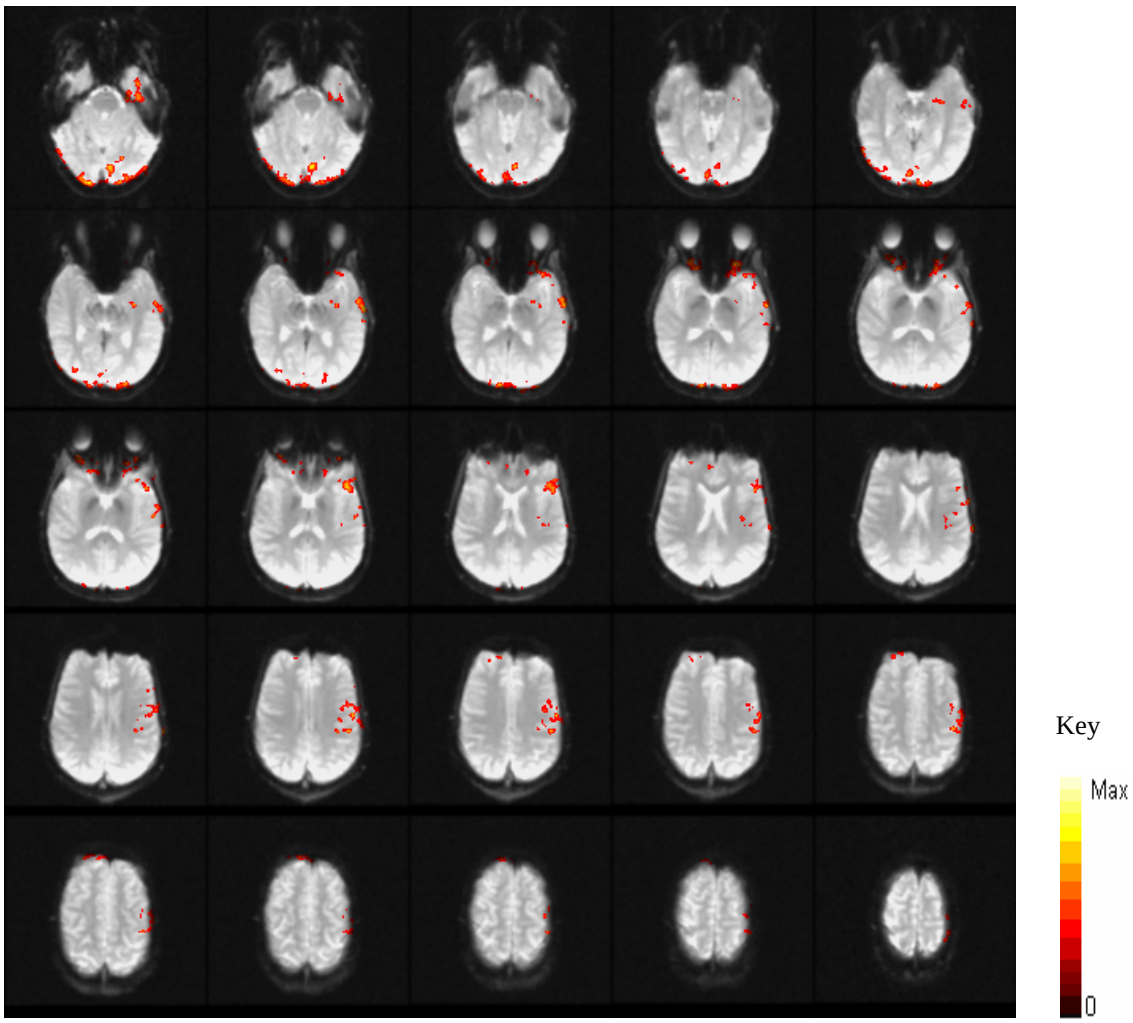

Figure J2. High resolution 25-slice rendered functional image for patient group participant p3 during the fMRI Sentence Reading task.

fMRI Sentence Reading Task Patient Group Participant p4

Table J3

fMRI Sentence Reading Task Cluster Analysis for Patient Group Participant p4

Laterali zation	Level 1 location	level 2 location	No. of voxels	Brodmann's Area	Talairach Coordinates *x*	*y*	*z*	Z Value
Left	Frontal Lobe	Superior Frontal Gyrus	114	9	-10.8	57.6	28.6	6.15
		Frontal Gyrus	765	46	-41.9	31.3	12.8	5.98
		Rectal Gyrus	445	11	-1.17	35	-22.2	5.2
	Temporal Lobe	Superior Temporal Gyrus	408	22	-49.5	-16	-6.04	6.51
		Sub-gyral gray matter	237	37	-50.5	-40.3	-5.28	5.97
	Parietal Lobe	Superior Parietal Lobule	526	7	-34.8	-78.4	47.9	5.24
		Inferior Parietal Lobule	137	40	-32.1	-48.3	38.4	4.41
Right	Frontal Lobe	Precentral Gyrus	203	4	38.8	-28.3	65.5	5.4
		Superior Frontal Gyrus	12	11	32.9	64.2	-23.3	4.01
		Middle Frontal Gyrus	115	46	48.8	43.4	13.8	5.1
	Temporal Lobe	Superior Temporal Gyrus	168	39	58.7	-59.7	19.6	6.79
		Inferior Temporal Gyrus	193	20	57.5	-6.83	-34.1	5.31
	Limbic Lobe	Parahippo campal Gyrus	195	36	31.2	-27.2	-14.3	5.33
	Occipital Lobe	Occipital Gyrus	2243	18	22.6	-94.2	19.4	6.65

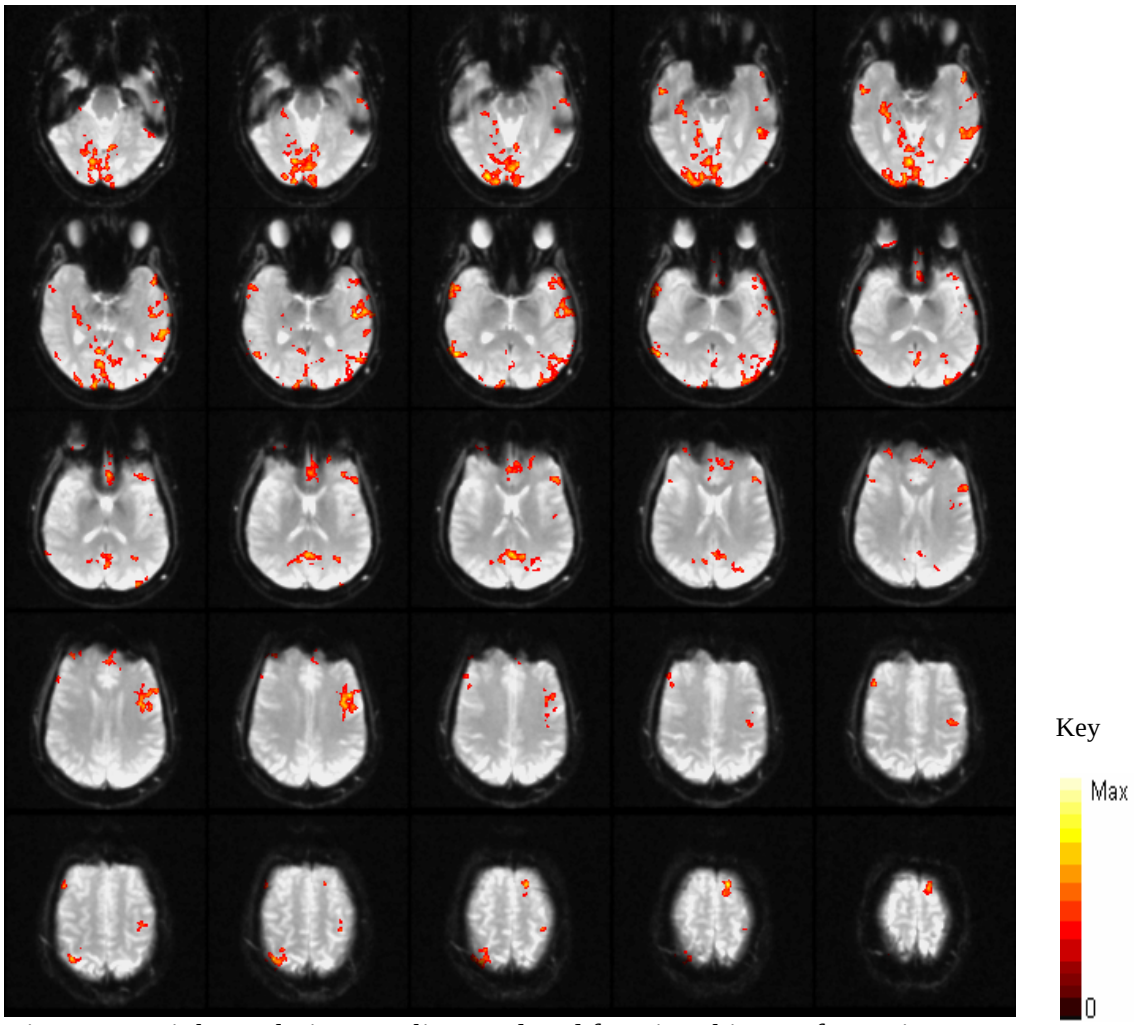

Figure J3. High resolution 25-slice rendered functional image for patient group participant p4 during the fMRI Sentence Reading task.

fMRI Sentence Reading Task Patient Group Participant p5

Table J4

fMRI Sentence Reading Task Cluster Analysis for Patient Group Participant p5

Laterali zation	Level 1 location	level 2 location	No. of voxels	Brodmann's Area	Talairach Coordinates *x*	*y*	*z*	Z Value
Left	Frontal Lobe	Precentral Gyrus	566	4	-25.4	-21.1	54.7	6.44
		Middle Frontal Gyrus	216	46	-37.9	30.3	22.8	4.69
		Medial Frontal Gyrus	312	6	0.143	-12.6	49.5	5.6
			125	8	-8.44	26.3	40.7	5.37
	Limbic Lobe	Posterior Cingulate	335	30	-21.4	-60.9	7.46	6.33
	Sub-lobar	Thalamus, Anterior Nucleus	498		-5.79	-0.51	7.77	5.2
	Cerebellum	Posterior Lobe, Declive	206		-29.6	-56.6	-26	5.81
		Anterior Lobe, Culmen	149		-2.96	-47.1	2.98	3.87
Right	Frontal Lobe	Precentral Gyrus	204	4	34.4	-21.3	61.4	5.44
		Inferior Frontal Gyrus	2597	9	56.9	21.1	22.7	5.34
	Sub-lobar	Thalamus, Pulvinar	363		13.4	-32.1	21.2	5.77
	Parietal Lobe	Supramarginal Gyrus	120	40	46	-43.6	35	4.04
		Paracentral Lobule	436	4	1.59	-39.3	68.4	6.31
			171	5	36.9	-41.5	61.6	4.58
		Postcentral Gyrus	146	40	55.7	-30.5	26	4.69
	Occipital Lobe	Occipital Gyrus	332	19	43.1	-74.8	5.05	5.94
	Cerebellum	Anterior Lobe, Culmen	134		22.3	52.4	-19.3	5.2

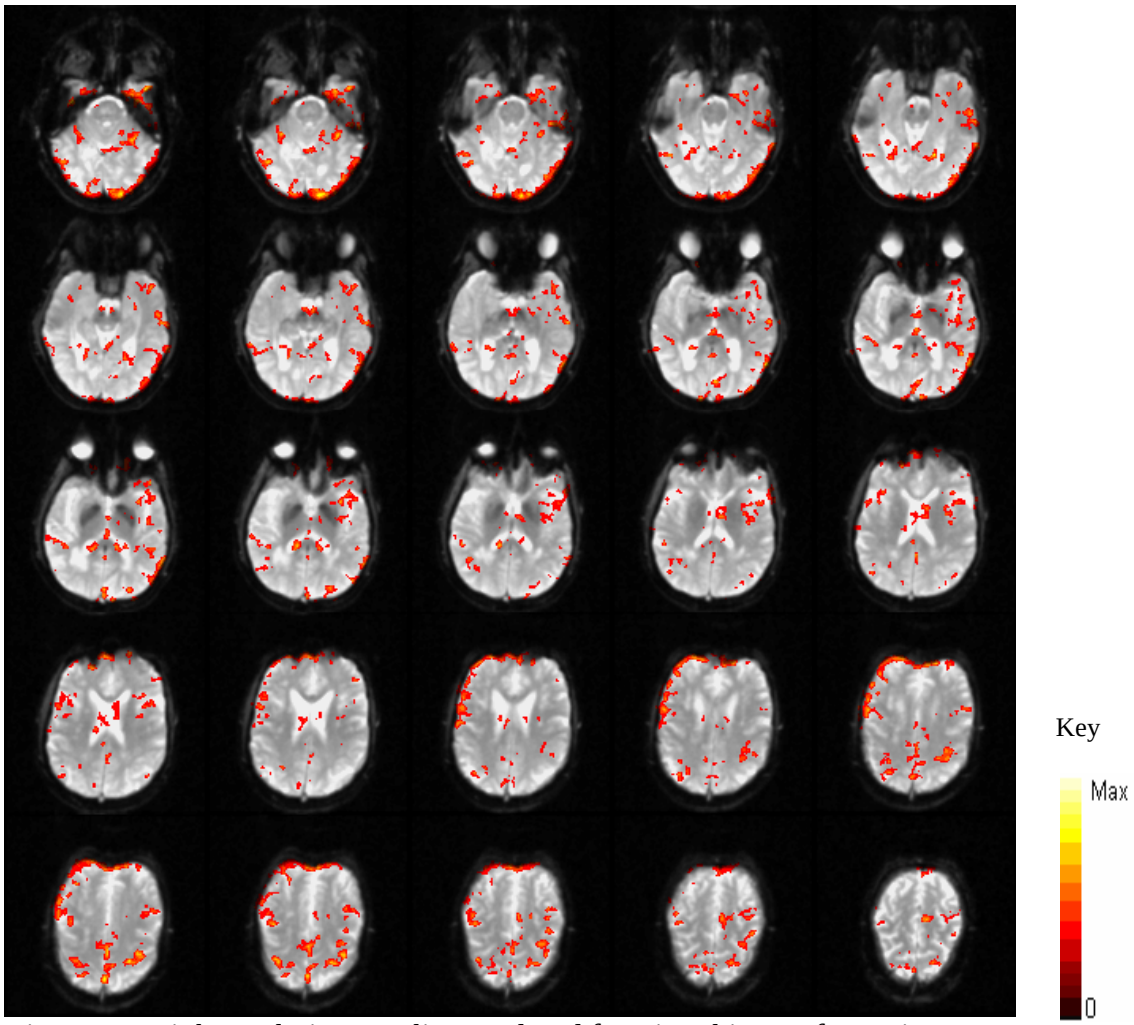

Figure J4. High resolution 25-slice rendered functional image for patient group participant p5 during the fMRI Sentence Reading task.

Table J5

fMRI Sentence Reading Task Cluster Analysis for Patient Group Participant p6

					Talairach Coordinates			
Lateralization	Level 1 location	level 2 location	No. of voxels	Brodmann's Area	*x*	*y*	*z*	Z Value
Left	Frontal Lobe	Inferior Frontal Gyrus	496	47	-47.9	26.1	-10.2	6.1
	Temporal Lobe	Superior Temporal Gyrus	335	22	-56.8	-46.6	14.7	4.76
		Middle Temporal Gyrus	180	21	-61.6	1.72	-8.96	5.17
	Limbic Lobe	Posterior Cingulate	131	30	-16.5	-56	6.36	4.68
	Occipital Lobe	Cuneus	147	19	-7.9	-93.2	38	6.02
Right	Temporal Lobe	Superior Temporal Gyrus	940	38	49.8	21.1	-31	5.66
	Occipital Lobe	Cuneus	1022	19	8.64	-92.1	37.6	8.21

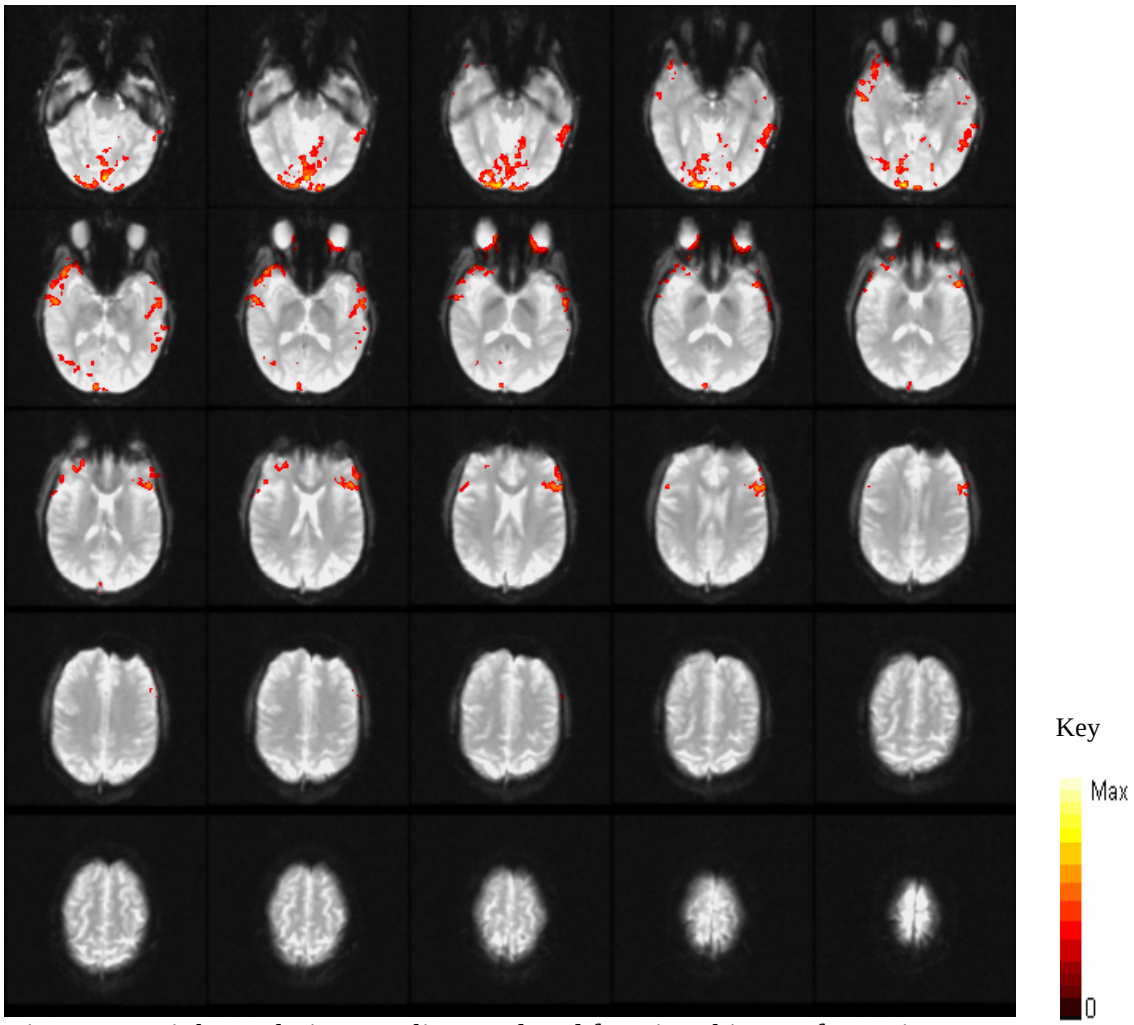

Figure J5. High resolution 25-slice rendered functional image for patient group participant p6 during the fMRI Sentence Reading task.