Review of Functional Magnetic Resonance Imaging Language Mapping in Patients with Epilepsy

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Declaration

I, Matthew Nairn, declare that the Doctor of Psychology (Clinical Neuropsychology) thesis entitled Review of fMRI Language Mapping in Patients with Epilepsy is no more than 40,000 word in length, exclusive of tables, figures, appendices, 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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Abstract

In cases where patients with epilepsy require surgery to help reduce the frequency and severity of their seizures, information about the areas of the brain involved with language function, such as the anterior temporal pole, can be valuable in predicting and minimising language difficulties that may arise after brain surgery. The aim of the project was to first evaluate the current group of functional magnetic resonance imaging (fMRI) language tasks used in the Epilepsy Centre of St Vincent's Hospital Melbourne (SVHM). This group of task included sentence completion, verbal fluency, and picture-naming tasks. Secondly, two new language tasks, reading and semantic decision-making were examined in an attempt to improve upon the existing battery's ability to detect anterior temporal pole activation for patients undergoing anterior temporal lobectomy. Healthy controls and patients with epilepsy performed tasks in the original battery on one of two standard 1.5 tesla MRI scanners (an older Siemen Magnetom or a newer Siemen Avanto). With the older scanner, the sentence completion task was the only original SVHM fMRI language task to show consistent activation. In contrast, with the newer scanner, all four original tasks, along with the new reading and semantic decision tasks, demonstrated consistent language activation when thinner slices covering a larger area were obtained. When used on the newer MRI imager, the new reading, the picture naming, and the sentence completion tasks produce the highest levels of anterior temporal lobe activation. The reading and picture naming tasks tended to show more temporal lobe activation, while the semantic decision and verbal fluency tasks tended to show more frontal lobe activation. Practical and theoretical implications of the research for presurgical fMRI evaluation are discussed.

CHAPTER ONE - INTRODUCTION

Brain surgery is often required for patients who suffer from intractable epilepsy. However, surgery can lead to impairments in language functioning, as the surgery often occurs near language regions. The locations of brain regions important for language functioning need to be identified in individual patients preoperatively, to help surgeons when making decisions about the suitability of surgery and how to best perform the surgery to minimise any possible postoperative language problems. Various methods have been used to identify language areas in the brain, one of which is functional magnetic resonance imaging (fMRI). This chapter includes a review of the types of surgeries performed to treat epilepsy, a review of the current understanding of language functioning in the brain, and a description and comparison of each of the language identification methods, together with an explanation of why the role of fMRI in the presurgical investigation of patients with epilepsy has been meet with enthusiasm. In the second chapter, the utility of a battery of fMRI tasks used by the Epilepsy Centre of St Vincent's Hospital Melbourne (SVHM) in identifying language areas in the temporal lobe, particularly in the anterior temporal lobe, is investigated. In the third chapter, attempts to improve upon this existing battery are presented. Finally, in the last chapter the results are discussed.

Classification of Epilepsy

Epilepsy is a term given to one of the most common serious neurological disorders (Commission of the ILAE, 2007). The overall (age-adjusted) prevalence estimates range from 2 to 50 per 1000 people, but are most commonly reported at around 5 per 1000 and the incidence of epilepsy in developed countries is estimated to be between 25 to 50 per 100,000 people (Hauser, Annegers, & Kurland, 1993). Incidence is very high in neonates and infancy and falls dramatically after the first year of life and then more gradually throughout childhood (Hauser et al., 1993). After reaching a minimum in early adulthood, it then increases during late adulthood to peak again in the elderly (Forsgren, 1990; Hauser et al., 1993). The term epilepsy covers a group of conditions that have epileptic seizures as a common symptom. Epileptic seizures are caused by abnormal electrical discharges from neurons in the brain and are transient, have a sudden unpredictable onset, and are often brief in duration (usually only lasting for a few minutes). The presentation of epilepsy varies with behavioural manifestations that can include motor (e.g., convulsions and rigidity), sensory (e.g., flashing lights, unpleasant odors, vertigo, and pain), psychic (e.g., déjà vu, hallucinations, and fear), or autonomic (e.g., flushing, sweating, and vomiting) disturbances (Jordan, 2007). The behavioural manifestations can occur alone or in combination with others, depending on the origin of the electrical discharge in the brain (Jordan, 2007).

In 1981, the International League Against Epilepsy (ILAE) developed an international classification of epileptic seizures that divides them into three main groups; partial seizures, generalised seizures, or unclassified epileptic seizures (Commission of

the ILAE, 1981). A seizure where the epileptic discharge is localised to an area of the brain is termed a partial seizure. There are three types of partial seizures: (1) simple partial seizures, where consciousness is fully preserved and where the discharge remains localised, (2) complex partial seizures, which are similar to simple partial seizure but involve an impairment of consciousness, and (3) secondary generalized seizures, where the seizure begins partially and then spreads to involve the whole cortex, so that a generalized seizure follows.

Complex partial seizures are the most common type of seizure in the adult population (Ben-Menachem, 2001). Specifically, mesial temporal lobe epilepsy is the most common form of epilepsy in adults and accounts for about 40% of all cases. While it is possible for all areas of the cortex to be an epileptogenic zone, most partial seizures of the extratemporal origin often originate from the frontal lobes (Cascino, 2004).

A generalised seizure is where the epileptic discharge activity does not occur in one localised area of the cortex, but throughout the whole cortex from its beginning. While all generalised seizures vary in severity and duration, there are five main subtypes; (1) absence seizures, which involve a brief arrest of consciousness; (2) myoclonic seizures, which are involuntary movements involving the whole body, or parts such as the arms or head; (3) tonic-clonic seizures, which are the more severe and include stiffening of muscles and possible falling down (tonic stage), and then jerky limb movements (clonic stage); (4) clonic seizures, and (5) tonic and atonic seizures, which occur suddenly and involve a sudden loss of tone in the postural muscles leading to falls (Commission of the ILAE, 1981; 1989).

The causes for epilepsy are varied and can include, congenital disturbances of the

brain (Hauser et al., 1993; Nelson & Ellenberg, 1987), hippocampal sclerosis (Sloviter, 1994), severe head injury (Annegers et al., 1980; Clear & Chadwick, 2000), cerebrovascular disease (Annegers, Rocca, & Hauser, 1996), central nervous system infection (Annegers, Hauser, Beghai, Nicolosi, & Kurland, 1998), neoplasms (Annegers et al., 1996), and dementias (Annegers et al., 1996; Hauser, Morris, Heston, & Anderson, 1986).

Surgeries for Epilepsy

The three main strategies for the treatment of epilepsy include avoiding the triggers that can usually precipitate seizures (e.g., excessive alcohol, lack of sleep, stress, and flashing lights), the use of anti-epileptic medication, and neurosurgery to remove epileptic focus (Elger & Schmidt, 2008). Another recently new strategy involves the intermittent stimulation of the vagal nerve by surgically implanting a small stimulator under the skin in the neck (Schachter & Saper, 1998). Vagal nerve stimulation is usually a treatment used for patients with intractable partial epilepsy who are not suitable for epilepsy surgery (Schachter & Saper, 1998). Its efficacy has been shown to be comparable to anti-epileptic medication (Handforth et al., 1998). In general, approximately 70 to 80% of patients diagnosed with epilepsy become seizure free, with about 50% being able to discontinue their anti-epileptic medication (Sander & Sillanpaa, 1998).

For those who do not adequately respond to medication, and where the seizures significantly impact upon quality of life, brain surgery is considered as a treatment option. Epilepsy surgery as a treatment is not a risk-free undertaking, as it involves

removing the part of the brain where the seizures begin. The surgical approach chosen depends on many considerations, including the risk-benefit balance of the resective surgery. For example, while the removal of the dominant temporal lobe may halt the seizures it may also result in unacceptable memory and language deficits. Also, the presence of a progressive tumor or other inherent risks, such as possible hemorrhaging from an arteriovenous malformation, would be the primary consideration for surgery rather than the seizure disorder.

There are two approaches with the surgical treatment of seizures. The first involves resective surgery, in which the aim of the surgery is the removal of the epileptic focus itself. Examples of resective surgery include an anterior temporal lobectomy (ATL), a selective amygdalo-hippocampectomy (in which only the mesial temporal structures are removed), and the resection of a frontal lobe lesion (Elger & Schmidt, 2008). An ATL is the most commonly performed operation because mesial temporal lobe epilepsy is the most common surgically remediable refractory partial epilepsy (Elger & Schmidt, 2008). It involves the resection of the anterior temporal pole, anterior hippocampus and part of the parahippocampal gyrus (Deblaere et al., 2002) and accounts for nearly 70% of all surgical interventions and render approximately 60% of operated patients seizure free (Engel, 1993). A hemispherectomy, which is the most radical resective procedure, is where most or all of one hemisphere is deactivated due to it being abnormal.

The second approach for the surgical treatment of seizures is to interrupt the pathways of the seizure spread, so isolating the epileptic focus from the rest of the brain (Elger & Schmidt, 2008). Examples of this type of surgery include a callosotomy, where

a section of the corpus callosum is transected. It is used to prevent secondary generalisation of seizures, and to treat intractable generalised seizures, particularly tonic seizures. Another example is a multiple subpial transection. This is a technique that relies upon the theory that seizures spread tangentially through the cerebral cortex, while impulses controlling voluntary movement travel radially. In this operation, multiple cuts are made vertically in the cortex in an effort to isolate the epiliptogenic region from the surrounding cortex.

Outcomes from Epilepsy Surgery

It has been suggested that the prognosis from epilepsy surgery is best for patients who have surgery early in the course of the epilepsy (Meyer, Marsh, Laws, & Sharbrough, 1986; Mihara, Inoue, & Matsuda, 1996). Up to 30% of patients with complex partial epilepsy of temporal lobe origin (TLE) have little or no seizure relief with anticonvulsant therapy (Engel, 1996). Epilepsy surgery in the temporal lobe (i.e., ATL and amydalo-hippocampectomy) results in approximately 60-70% of adult patients becoming seizure free (Polkey, 2000; Sperling, O'Connor, Saykin, & Plummer, 1996; Walczak et al., 1990). The mortality rate is less than 0.5% and the risk of permanent hemiparesisis is less than 1%. Possible morbidities include memory and language problems, and visual field defects. A reliable relationship between verbal memory decline following resections of the left hemisphere has been noted in the epilepsy surgery literature (Hermann, Seidenberg, Schoenfield, & Davies, 1997). In contrast, such a reliable relationship has not been identified for right TLE and non-verbal memory impairments. Non-verbal memory impairments have been observed from both left- and

right-sided TLE (Hermann et al., 1997). Decline in naming ability is the most frequent language deficit after an ATL in the dominant hemisphere (Hermann, Wyler, Somes, & Clement, 1988; Seidenberg et al., 1998; Stanfiniak et al., 1990). While there is often rapid recovery in the early postoperative weeks, persistent naming difficulties have been observed in 25% of left ATL patients studied one year after surgery using a confrontation naming task (Langfitt & Rausch, 1996). Others suggest the incidence of postoperative naming decline is between 39-60% (Bell, Seidenberg, Hermann, & Douville, 2003; Brown et al., 2002; Davies, Bell, & Bush, 1998). Following a language dominant anterior temporal lobectomy, nearly 40% of patients in one study demonstrated a significant decline on a standard neuropsychological naming test postoperatively (Davies et al., 1998). Much of our current understanding of language mapping is based on the extensive work of George Ojemann and colleagues (Ojemann, 1983) with electrical stimulation mapping. The assumption with this technique is that electrical stimulation of a particular area of cortex produces a temporary, reversible lesion, and can be used to predict which functions will be disturbed if the stimulated cortex is to be removed. Most investigations have looked at visual naming (Ojemann, 1979, 1983) because dysnomia is a feature of virtually all aphasic syndromes. It has been reasoned that the use of object naming would enable the identification of cortex with any role in language (Ojemann, 1979). Naming sites have been identified in from the anterior temporal lobe to the posterior temporal cortex (Hamberger, Goodman, Perrine, & Tammy, 2001; Ojemann, 1979). Reading sites have included the inferior and lateral frontal, parietal, and temporal cortex (more anterior and broader than for naming sites) (Ojemann, 1990). Compared to healthy controls, patients with seizure foci in the dominant temporal lobe have been found to have more

associated widespread or atypical distribution of naming and reading areas (Devinsky, Perrine, Llinas, Luciano, & Dogali, 1993). For patients with early left hemisphere damage there is also an increased chance of essential language areas being located in the anterior temporal lobe (Schwartz, Devinsky, Doyle, & Perrine, 1998). These findings suggest that language abilities, particularly naming, are at risk following dominant temporal lobe surgery. The reported predictors of persisting naming difficulties include patients with an older age at onset and the absence of hippocampal sclerosis (Hermann, Davies, Foley, & Bell, 1999). Extra-temporal surgery is performed less frequently and the results are slightly less impressive, with about 56% becoming seizure-free (Elsharkawy et al., 2008).

Identifying Language Areas Prior to Surgery

Information about the cortical organisation of language functioning in the brain is often obtained for patients with intractable epilepsy who are being considered for surgical treatment. Baxendale (2002) suggests two main reasons for the importance of acquiring information on language lateralisation and function for patients with epilepsy. Firstly, the information will help identify if the surgery will occur in the language dominant hemisphere and secondly, knowledge regarding any unusual language representation can be used in planning the surgery and predicting language deficits. Although language processes are predominantly associated with the left cerebral hemisphere in most individuals, this is not always the case. For example, Szaflarski and colleagues (2002) reported that the rate of atypical language lateralisation (i.e., not in the left hemisphere) in normal left handed and ambidextrous individuals was higher than normal right handed

individuals. Further, some research suggests that language lateralisation varies on a continuum from high left lateralisation to high right lateralisation in normal adults (Springer et al., 1999). As with genetic left-handed individuals, atypical language dominance is more commonly encountered with patients with epilepsy. For patients with epilepsy, an early onset of recurrent seizures, an early insult to the left hemisphere, left handedness, and weak right handedness are all predisposing factors associated with a higher incidence of bilateral or right lateralisation (Springer et al., 1999). Information about the location of language regions in the temporal lobe is valuable in minimising postoperative language morbidity and to better predict language deficits post surgery (Sabsevitz et al., 2003).

Techniques Used to Locate Language Areas

Functional Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is becoming an increasingly important technique in the presurgical evaluation of patients with epilepsy as it enables the identification of previously invisible pathologies that were once only seen post mortem (Ducan, 2007). In contrast to the use of x-rays with computerised tomography (CT), the MRI process exploits the magnetic properties of organic tissue. Hydrogen is an atom that is sensitive to magnetic forces, (due to the number of protons and neutrons in the nuclei), and can be found in all organic tissue. The protons that form the nucleus of the hydrogen atom are in constant motion, spinning about their principal axis. It is this motion that creates at tiny magnetic field. Normally, the orientation of these protons is randomly

distributed. However, when they are subjected to strong magnetic fields, such as in an MRI scanner, the protons become orientated in the direction parallel to the magnetic force. MRI scanners typically create magnetic fields from 0.5 to 4.0 tesla units and above (the magnetic field of the earth is about 0.001 tesla). In an MRI scanner, once the protons are aligned, radio waves are passed through the magnetised region, and as the protons absorb the energy in these waves, their orientation is disrupted in a predictable direction. When the radio waves are turn off, the absorbed energy is dissipated and the protons rebound back toward the orientation of the magnetic field. This synchronised rebounding produces energy signals that are picked up by MRI detectors surrounding an individual's head. By systematically measuring these signals throughout the three dimensional volume of the head, an image reflecting the distribution of the protons and other magnetic agents in the tissue can be produced. As the density of hydrogen atoms is different in the white and gray matter of the brain a gray-scale picture of the brain can be produced. MRI scanners can typically resolve structures less than one millimeter (Gift, Pera, & Moore, 1989; Villafana, 1988) .

MRI (or even CT) scans cannot be used to diagnose epilepsy, however, they play a major role in identifying potential surgical candidates as the scans can reveal subtle structural abnormalities in patients with intractable epilepsy. As a result, MRI has been responsible for the rapid growth of surgical treatment of epilepsy (Duncan, Shorvon, & Fish, 1995). The use of MRI techniques has revolutionised the investigation and treatment of people with epilepsy (Baxendale, 2002).

An additional benefit of MRI machines comes from their ability to measure changes in blood flow in the brain while an individual is engaged in a cognitive task.

Such a technique is termed functional magnetic resonance imaging (fMRI). Since the 1990s, fMRI has been used with humans to detect regional changes in blood oxygenation resulting from neural activity (Bandettini, Jesmanowicz, Wong, & Hyde, 1992; Belliveau et al., 1991; Kwong et al., 1992). The procedure is essentially identical to the one used in MRI (i.e., using radio waves to make the protons in hydrogen atoms oscillate and then measure the energy emitted as they return to the orientation of the magnetic field). However, with fMRI, imaging is focused on the magnetic properties of haemoglobin rather than hydrogen atoms. When oxygen is carried by haemoglobin in the bloodstream it is absorbed and the haemoglobin then becomes deoxygenated (deoxyhaemoglobin). When the amount of blood being directed to an area increases, the neural tissue in the area does not absorb all the excess oxygen. Increased blood flow to active areas of the brain therefore results in higher concentrations of oxyhaemoglobin relative to deoxyhaemoglobin. As deoxyhaemoglobin is more sensitive, or paramagnetic, than oxygenated haemoglobin the MRI detectors can be used to measure the ratio of oxygenated versus deoxygenated haemoglobin. This ratio is referred to as the blood oxygen level-dependent (BOLD) effect (Ogawa, Lee, Kay, & Tank, 1990). The link between neuronal activity and the BOLD signal has been firmly established through the association of corresponding electrophysiological recordings in non-human primates (Logothetis, Pauls, & Augath, 2001).

Blood flow modulation takes place over a longer time frame than it takes for neural events to occur. While neural events are measured in a scale of milliseconds, the initial rise in oxygenated haemoglobin is not evident for at least a couple of seconds and peaks between 6 to 10 seconds after the neuronal event. This delay suggests that

immediately after a neural region is activated, there should be a small drop in the ratio of oxyhaemoglobin and deoxyhaemoglobin. In fact, the newest generation of MRI scanners, reaching strengths of 4.0 tesla and above, are able to detect this initial drop (Ernst & Henning, 1994; Thompson, Peterson, & Freeman, 2004). The decrease is small, representing no more that 1% of the total haemoglobin signal. The subsequent increase in the oxygenated blood can produce a signal as large as 5%. By continuously measuring the fMRI signal, it is possible to construct a map of the changes in regional blood flow to areas of the brain. By using fMRI technology, the identified changes in the magnetic field can be used to indicate where in the brain and when local increases in blood flow are occurring.

Functional MRI is a technique that can use the BOLD signal change to indicate the neuronal activity associated with the performance of a specific task, thereby allowing for the effects of neural activity on cerebral blood flow to be observed. Functional areas within the brain using fMRI can be localised by comparing regional cerebral blood flow between the performing of a task (or experimental condition) and a resting state (or a baseline condition) (Bookheimer et al., 1997). The differences observed in the fMRI signal between the two conditions can then be used to tease out and identify specific cognitive states not shared between the two. Most clinical fMRI studies have used blocked design paradigms with alternating blocks of task and rest conditions, to maximise sensitivity to detecting activations.

Prior to the use of fMRI to investigate cognitive functioning in patients with epilepsy, the only preoperative methods available to identify language areas of the brain included the intracarotid amobarbital procedure (IAP or Wada test), direct cortical

stimulation of the cerebral cortex, positron emission tomography (PET), and neuropsychological testing. Following is a description of each of these additional procedures (as compared with fMRI) together with an explanation of why the role of fMRI in the presurgical investigation of patients with epilepsy has been meet with enthusiasm.

Intracarotid Amobarbital Procedure

The IAP was first conducted by Wada in 1948 (Wada, 1949, cited in Wada, 1997), and has been used to determine language lateralisation (i.e., assessing language hemisphere dominance) (Loring, Meador, Lee, & King, 1992)and in predicting preoperative-to-postoperative memory changes after an ATL (Davis, Bell, Bush, & Wyler, 1998; Loring et al., 1995; Stroup et al., 2003). Specifically, memory capacities of the no affected hemisphere are evaluated to identify if a patient would be at risk for postoperative global amnesia (Scoville & Milner, 1957). The IAP procedure involves the patient being injected with sodium amytal (barbiturate) into a single internal carotid artery via a catheter in the femoral artery; thus transiently anaesthetising a major part of one hemisphere of the brain for approximately 10 minutes. Several tests of language and memory functioning are then performed to test these abilities in the non-anaesthetised hemisphere (Baxendale, 2002). The procedure is then repeated with the other hemisphere of the brain. Language tests often include verbal fluency, comprehension, naming, repetition and reading (Kloppel & Buchnel, 2005). Assessments of language dominance between brain hemispheres come from clinical observations of a patient's response, which can include speech arrest, dysphasic responses, comprehension, and reading

abilities. The testing of memory can vary. It typically requires the patient to recall (either during the IAP or after the sodium amytal has worn off) stimuli that was previously presented during the IAP (Kloppel & Buchnel, 2005).

The IAP has been popular and useful, particularly for determining language laterality and predicting risk for memory decline following ATL. However, the popularity of the Wada test has declined over the past 15 years. In 1993, as reported from a survey of epilepsy surgery centers, it was extremely rare for an IAP not to be preformed on prospective TLE surgery patients (Rausch et al., 1993). From a more recent survey of centers it was reported that one third of respondents never or very rarely (in less than 5% of cases) employed the IAP procedure on prospective TLE surgery patients (Baxendale, Thompson, & Duncan, 2008). The relative contribution of the test results in predicting memory outcome may not be beneficial enough to justify the risks and cost inherent in the procedure. It is an invasive procedure with possible risk of thromboembolic complications. The rate of neurological complications with older patients has been reported to be 1.3%, with 0.5% of these being permanent (Willinsky, Taylor, & TerBrugge, 2003). With the exception of predicting memory for visual information after a delay, Lineweaver and colleagues (2006) suggest that the results from the Wada procedure do not significantly improve prediction above other noninvasive procedures, such as neuropsychological testing and MRI (Lineweaver et al., 2006). Additionally, the examination needs to be short, not lasting longer than three to five minutes, and individual vascular anatomy needs to be taken into account when interpreting language and memory with an IAP. For example, blood perfusion to the other hemisphere has been noted in over 30% of cases (Simkins-Bullock, 2000). Lastly, there is variability in the

administration of the Wada. Since Wada first described the procedure in 1949 various standardised protocols have been developed with differences between protocols in timing, dose, rate of the injection and methods used to assess language and memory abilities (Baxendale, 2002).

Despite the above-mentioned limitations of the IAP, the primary limitation in using the Wada procedure is that it only provides part of the information required to predict and avoid postoperative language deficits. The additional information needed is the location of the language areas in the brain. As discussed before, such areas can be widely distributed both within and between the hemispheres (Springer et al., 1999). Therefore whilst, at best, the IAP may provide information on language laterality, this is too broad and does not provide detailed information about the localisation of specific language skills (Baxendale, 2002).

Electrical Stimulation Mapping

An estimated 5 to 10% of epilepsy patients who undergo surgery have language areas anterior to the rolandic cortex (Schwartz et al., 1998). Such specific language skills in these patients can be studied preoperatively using subdural grid stimulation or intraoperatively with electrical stimulation mapping (Ojemann, 1983). Although direct cortical stimulation or the implantation of a subdural grid can be used to localise areas of the cortex involved in language (Ojemann, Ojemann, Lettich, & Berger, 1989) it is an invasive and risky procedure.

Positron Emission Tomography

Positron emission tomography (PET) is a similar technique to fMRI in that it measures changes in blood flow due to neuronal activity (Ter-Pogossian, Phelps, & Hoffman, 1975). In PET, a radioactive element, or isotope, is introduced into the blood stream. Owing to their unstable state, these isotopes rapidly decay by emitting a positron from their atomic nucleus. When a positron collides with an electron, two photons, or gamma rays are created. These gamma rays move away from the collision site in opposite directions and can pass through all types of tissue (Ter-Pogossian et al., 1975). The PET scanner detects these gamma rays and can determine where, in a three-dimensional volume of the head, the collisions took place. An image can then be constructed identifying areas containing more radiation, thus indicating where there are increases in blood flow. In a typical PET experiment, the injection is administered at least twice, once during a control condition and again during an experimental condition. The results are usually reported in terms of a change in regional cerebral blood flow between the two conditions (Bookheimer et al., 1997; Poeppel, 1996; Warburton et al., 1996).

Neuropsychology Assessments

Standardised neuropsychological tests are often conducted with patients with epilepsy as part of a preoperative and postoperative workup. The preoperative assessment can provide cerebral lateralising and localising information to help patients and their doctors make decisions regarding surgery. The postoperative assessment can be compared with the preoperative assessment in order to identify changes in cognition and

mood.

Hermann, Seidenberg, Schoenfild, and Davies (1997) investigated the neuropsychological features of TLE using a battery of neuropsychological tests administered preoperatively to a group of patients with TLE (based on histopathological examination). They reported that TLE was associated with considerable generalised cognitive impairment, independent of attention, concentration and executive functioning. Specifically, impairments were noted with intellectual functioning, reading, language, and visuospatial ability.

Postoperatively, it has been reported that patients with left TLE, where there is no evidence of MRI hippocampal atrophy or underlying hippocampal sclerosis, compared to patients with TLE who do exhibit hippocampal sclerosis, show significant declines on verbal memory, confrontation naming, and overall verbal abilities (Seidenberg et al., 1998).

Comparison of Functional MRI with other Techniques

Cortical stimulation, IAP, and even PET have significant limitations in that they are invasive, are attached to risk and do not lend themselves to being repeated. The development of noninvasive techniques such as fMRI, to lateralise and localise language areas represent a significant advance in the care and management of patients with intractable epilepsy. Recently, the clinical application of fMRI has been investigated as a replacement for the invasive procedures currently used to lateralise and localise language (Powell & Duncan, 2005). The benefits of the fMRI technique is that it is noninvasive, cheaper than the IAP procedure, not constrained by the procedural and methodological

limitations of the IAP procedure, allows for language localisation below the cortical surface, and has excellent spatial resolution (Cabeza & Nyberg, 2000).

Compared to PET, fMRI is a more practical option as MRI scanners are present in almost all hospitals in technologically advanced countries and, with modest hardware modifications, most of them can be used for functional imaging. In contrast, PET scanners are present in only a handful of major medical facilities and require a large technical staff to run the scanner and the cyclotron used to produce the radioactive tracers. A methodological advantage of fMRI is its spatial resolution. In general, fMRI is more sensitive than PET due to its superior signal-to-noise ratio (Sadato et al., 1998). Some fMRI scanners are currently able to resolve volumetric areas of around 3 mm^3. Another methodological advantage is that fMRI has much better temporal resolution than PET. Another problem with PET is it is constrained by the decay rate of the radioactive agent. As fMRI does not involve the injection of radioactive tracers, the same individual can be tested multiple times in a single session for longer periods. The localisation process is also improved with fMRI because high-resolution anatomical images are obtained during the same session as when the functional scanning occurs. With PET, anatomical precision is compromised by the need to average across individuals. Also with PET, accurate localisation requires a PET scan to be registered with a higher resolution structural MRI scan from the same participant (i.e., aligned with a structural MRI scan via anatomical markers). This process introduces error.

There are disadvantages to using fMRI protocols. These include continuous loud noise, and the requirement for the patient to restrict motion (particularly jaw motion) during the language assessments in order to avoid movement artefact. FMRI (and PET)

have lower temporal resolution in comparison with techniques such as cortical stimulation. While fMRI can operate quickly, it still lacks synchrony between changes in the neuronal activity and changes in the measured blood flow. However, this is not such as issue with the current project as good spatial (rather than temporal) localisation is the main goal.

Although there is good spatial resolution with fMRI, the anatomical localisation is coarse compared to the scale of the microcircuitry of language (Cabeza & Nyberg, 2000). Even if the metabolic activity in a particular area correlates with an experimental variation, inferences still need to be made about the area's functional contribution. Correlation does not imply causation. For example, an area may be activated during a task, but not play a critical role in the task's performance. The area may simply be "listening" to other brain areas that are providing the critical computations for the task (Kloppel & Buchnel, 2005). However, these limitations they do not outweigh the many advantages to using fMRI techniques in investigating language functioning in patients with epilepsy.

Location of Language Areas in Healthy Individuals

Broca's and Wernicke's Areas

As previously mentioned, the degree of cerebral dominance for language differs between individuals, but the left hemisphere dominates language processing in the majority of cases. Anatomically, the two most commonly identified speech areas in the brain are Broca's and Wernicke's areas (Binder, Frost, Hammeke, & Cox, 1997). Broca's

area is thought to be involved in planning and executing speech. It is located in the opercular and triangular sections of the inferior frontal gyrus of the frontal lobe of the cortex. The exact funtion of Broca's area is still under debate, however (Bartels & Wallesch, 2003). For example, Bavelier et al (1997) suggest this area is associated with syntactic processing and with verbal short-term memory. Broca's area comprises Brodmann area (BA) 44, and some researchers also include BA 45 (Duffau, 2003; Ojemann et al., 1989). It is part of the the precentral association cortex, which is located between the cortical motor strip and the prefrontal cortex. The more anterior part of Broca's area is the pars triangularis, which is thought to support the interpretation of various modes of stimuli and the programming of verbal conducts. The more posterior part is the pars opercularis, which is thought to support the management of only one kind of stimulus, and the coordination of the speech organs for the actual production of language, given its favorable position close to motor-related areas. Another frontal lobe area involved in language production, specifically with the initiation of speech acts, is the left supplementary motor area at the medial aspect of the frontal lobe (Bartels & Wallesch, 2003). Functionally, this area is part of the anterior cingulum.

Broca's area is connected to Wernicke's area by a neural pathway called the arcuate fasciculus. Wernicke's area is located in the left posterior third section of the superior temporal gyrus (posterior part of BA 22), near the auditory cortex, surrounding the posterior end of the sylvian fissure, and the supramarginal gyrus. Wernicke's area is a region of the brain particularly known to be involved in the understanding and comprehension of spoken language, or receptive language ability (Binder et al., 1997). However, there is debate about which aspects of speech processing it is responsible for.

Some authors have suggested it is involved with auditory or phonological processing and with short-term memory, as the area has been reported to activate during a task requiring phonological processing of visually presented stimuli (Petersen & Fiez, 1993). Another suggested role of Wernicke's area is as the lexicon for written and spoken words, and thus being part of a neural network making up the semantic system (Bavelier et al., 1997).

The core of Wernicke's area is the planum temporale, which is larger in the left hemisphere in about 75% of normal people (Steinmetz, 1996). Wernicke's area also includes the temporal lobe association cortex. This area integrates auditory, visual, and even somatonsensory information and is interconnected with the temporal limbic cortex and the amygdalohippocampal system (Bartels & Wallesch, 2003). Wernicke's area is also connected to the primary auditory cortex for comprehension of the spoken word.

In addition to the traditional language areas (Broca's and Wernicke's areas), the angular gyrus is also thought to play an important role in language functioning. However, it is not always viewed as a separate area and is often included as part of Wernicke's area. Its role is thought to involve the comprehension of written word processing (Bartels & Wallesch, 2003).

While traditional models of language organisation have consisted of Broca's area, Wernicke's area, and their communicating pathways, research over time has confirmed that the language system is considerably more complex (Bookheimer, 2007).

Anterior Temporal Lobe Language Areas

Results from electrical stimulation studies and subdural electrode implants have indicated that language-activated cortical regions are not only found in the classic language areas, but also along the anterior and middle parts of the temporal lobe in the left hemisphere (Ojemann, 1991). In addition to this, electrical stimulation and subdural electrode implant research suggests that language-relevant cortical regions can be extremely patchy and focal. For example, Ojemann (1991; 1989) has described a localised area as small as 5 mm on the temporal lobe where naming is disrupted by electrical stimulation. Similar findings with subdural implants have been reported whereby the signal observed at two adjacent electrode sites (which is separated by only a few millimeters), reveal different functions in the underlying cortex (Nobre, Alison, & McCarthy, 1994). Furthermore, the distribution of these patches of focal language sites varies between subjects (Ojemann, 1991). Together these findings suggest that the overall cortical organisation of language is in small nonadjacent focal spots distributed throughout the left hemisphere, rather than in a few large cortically well circumscribed language centers (Bavelier et al., 1997). The implication of these findings is that language areas, particularly those in the anterior portion of the temporal lobe, need to be identified in individual cases where surgery is planned in this area to help in predicting and preventing possible postsurgery impairments.

While Broca's and Wernicke's areas are not typically resected during epilepsy surgery, the anterior area of the temporal lobe is, particularly with the standard ATL procedure. Given this area has been implicated in language processing, an understanding of the anterior temporal lobe role is important if surgery is planned in this area. Evidence

of the role of the anterior temporal lobe in language functioning comes from patients with damage to the left anterior temporal pole, which has lead to verbal memory and verbal learning difficulties. Such patients have been shown to have poor recall of stories with intact comprehension and working memory ability (Frisk & Milner, 1990). This is expected, as deep medial structures in the temporal and limbic lobe are known to be involved in mediating the formation of memory. From a review of the literature, Bavelier and colleagues (1997) identified two other possible language-related functions of the middle and anterior parts of the superior and middle temporal lobe, namely, semantic processing and syntactic analysis. They also suggest that the middle portion of the temporal lobe mediates semantic processing and the anterior portion mediates the syntactic analysis of sentence-type material (i.e., where there are conceptual relationships between the words presented). Price (2000) also supports the involvement of these areas in reading and comprehending sentences.

Anterior Frontal Lobe Language Areas

In addition to the Broca's area, the prefrontal cortex (e.g., the dorsolateral prefrontal cortex) is another region that is thought to be involved in language functioning. Electrical stimulation and PET studies have identified language areas in the middle and superior frontal gyrus, in addition to Broca's area (Ojemann, 1992; Petersen, Fox, Posner, Mintun, & Raichle, 1988). Damage to this area can affect language and may result in transient language difficulties in generating words (Bookheimer, 2007). The suggested role of the dorsolateral prefrontal cortex could be either as the locus of semantic processing, or as a modulator of activity within related structures (such as Wernicke's

area) during semantic processing (Bavelier et al., 1997). The functions of areas within the inferior frontal gyrus have been reported to range from syntax to phonology and also include higher order semantic operations (Bookheimer, 2002).

Right Hemisphere Language Areas

In general, traditional evidence on the involvement of the right hemisphere in language comes from two sources. Firstly, it has been observed that damage to the right hemisphere in some patients' leads to language disturbance. While this is an uncommon occurrence, it has been attributed to patients having crossed lateralisation of function, associated with left-handedness (Code, 1987). Secondly, evidence of right hemisphere involvement with language also comes from patient recovery of language function after a brain lesion in the left hemisphere. It has been argued that recovery of language function is either due to the right hemisphere taking over some of the impaired functions or due to right-hemisphere language capabilities being released from inhibition from the dominant left hemisphere (Code, 1987).

While the areas of cortex involved with language processing are predominately in the left hemisphere, some studies have suggested a participation of the right superior temporal gyrus (Mazoyer et al., 1993). As the same area on the left could be specialised for lexical processing, the right superior temporal gyrus could be related to the lexical capacities of the right hemisphere (Bavelier et al., 1997).

Limitations in Identifying Language Areas

Bavelier and colleagues (1997) have highlighted two limitations to our understanding of the neural basis of language. Firstly, the localisation of anatomical areas is very coarse compared to the scale of the micro-circuitry that actually computes language. The second limitation comes from the type of paradigm or task used. Traditionally, language has been tested with simple tasks such as listening, speaking, repeating or naming. However, over time the number of different types of tasks has grown, with some tasks attempting to identify and isolate specific subcomponents of language processing (e.g., purely phonetic tasks). Most of these tasks are highly unnatural and may encourage participants to rely on strategies that are only remotely related to those at play during natural language processing. A number of authors have argued for the use of tasks that are cognitively natural for the skills being studied (Bavelier et al., 1997; Doemonet, Wise, & Frackowiak, 1993; Poeppel, 1996).

Nature of the Current Research

The present study was comprised of two parts. The first part involves the evaluation of a collection of fMRI language tasks that have been used in the Epilepsy Centre of SVHM since 1998 on two different 1.5 tesla MRI machines, the older Siemen Magnetom and the newer Siemens Avanto. The language tasks were chosen and designed to provide important information in identifying the language areas of the brain involved in reading (a sentence completion task), decision-making (sentence completion and picture-naming tasks), generating words (letter fluency and category fluency tasks), and

covertly naming pictures. Each of the tasks was assumed to involve different, but overlapping, aspects of language processing and therefore would allow for the mapping of frontal and temporal language areas, particularly in the anterior temporal cortex. These tasks have been used with epilepsy patients requiring surgery, where information about the areas of the brain involved with language could be valuable in minimising language difficulties that may arise after brain surgery and to better predict language difficulties after surgery. The analysis of the results of the existing SVHM fMRI battery was conducted to evaluate its utility in detecting language function in controls and epilepsy presurgical patients (see chapter two). The second part of the study was intended to improve upon the SVHM battery of fMRI language tasks by developing, piloting, and testing two new tasks sensitive to anterior temporal pole language function, namely, a semantic decision-making task and a reading task (see chapter three).

The aim of the study was to evaluate the original battery of fMRI language tasks used at SVHM and to improve upon it in an attempt to consistently identify temporal lobe language sites, particularly anteriorly, near where resection for TLE surgery occurs. The identification of other important language sites, such as Broca's and Wernicke's areas, for example, are included for completeness but were not the focus of the study.
The study focused on language mapping with fMRI and its clinical application, rather than primarily focusing on language theory.

CHAPTER TWO – EVALUATION OF ORIGINAL FMRI LANGUAGE BATTERY

Introduction

In studies where patients have undergone both fMRI language tasks and the IAP (e.g., Bahn et al., 1997; Benbadis et al., 1998; Benson et al., 1999; Binder, Swanson, Hammeke, & Morris, 1996; Carpentier et al., 2001; Desmond, Sum, Wagner, & Demb, 1995; Hertz-Pannier, Gaillard, Mott, & Cuednod, 1997; Lehericy et al., 2000; Sabbah, Chassoux, & Leveque, 2003; Springer et al., 1999; Yetkin et al., 1998), most have reported impressive concordance rates (near 100%) between the two techniques in determining language lateralisation despite using different IAP protocols and fMRI paradigms. Several of these studies have demonstrated that verbal fluency tasks (Benson et al., 1999; Lehericy et al., 2000; Worthington et al., 1997), and semantic decision tasks (Binder et al., 1996; Desmond et al., 1995; Springer et al., 1999) can be used to identify language lateralisation in neurologically normal participants and patients with epilepsy using fMRI. Verbal fluency tasks require participants to think of as many words as they can that conform to a particular rule, whereas semantic decision tasks require participants to make decisions based on semantic information presented. Authors of these fMRI and IAP studies have suggested that future research should focus on developing fMRI techniques that reliably elicit such language related activation, because fMRI could replace the IAP test.

As mentioned earlier, in addition to lateralisation, information about localisation is needed to help limit language deficits post surgery by informing the surgeon about an individual's cortical language representation. This chapter reports on an investigation into

the utility of the existing SVHM fMRI battery in detecting language function in controls and epilepsy presurgical patients. Following is a review of the language paradigms used in the SVHM language battery to localise and lateralise language functions in the brain. These tasks include verbal fluency, picture naming, semantic decision-making, and reading tasks.

Verbal Fluency Tasks

Verbal fluency tasks involve the quick generation of as many words as possible that conform to a particular rule, for example, reciting only words that start with a given letter of the alphabet (letter fluency), reciting only words from a particular category (category fluency), or generating verbs in response to a given noun (verb generation). Verbal fluency tasks are among the most commonly used tasks in fMRI language batteries. They have been found to produce activation predominantly in frontal regions, including Broca's area, with some less consistent activation in the temporal lobes (Deblaere et al., 2002; Herholz et al., 1996; Hertz-Pannier et al., 1997; Lehericy et al., 2000; Spreer et al., 2001; van der Kallen et al., 1998; Yetkin et al., 1998).

Verb generation tasks. The first published study to investigate areas of brain activation during a language task in normal controls used a verb generation task with PET (Petersen et al., 1988). Many researchers have since suggested verb generation tasks can be used to reliably predict language dominance because they require semantic processing (Binder, Rao, Hammeke, & Frost, 1995; Desmond et al., 1995; Petersen et al., 1988).

When the lateralising ability of a verb generation task (as determined from IAP and electrocortical stimulation mapping) was compared with picture naming and single

word reading tasks with fMRI in normals, Benson and colleagues (1999) found the verb generation task to be the most reliably lateralising. A similar finding was reported by Deblaere and colleagues (2002). From a group of tasks (i.e., reading, picture naming, and letter fluency) they found the most reliable single participant language lateralisation came from the letter fluency task.

While the verb generation task paradigm has produced multiple reliably lateralised foci of activation that extends from the occipital to the frontal lobes, the strongest and most reliable activation from this task has been seen in the triangular, orbital, and opercular parts part of the left inferior frontal cortex (BA 44, 45, 46 and 47) (Herholz et al., 1996; Lehericy et al., 2000). Differences in the relative intensity of activation in any of these inferior frontal areas can differ between studies. For example, Herholz et al. reported the strongest activation in BA 45 for the verb generation task, whereas Lehericy et al. reported the strongest activation in BA 47. However, these difference may be attributable to variations in task design (Warburton et al., 1996). While not activated as consistently as the frontal areas, the superior temporal gyrus, parts of the middle temporal gyrus, and the paracingulate gyrus have also been reported to activate from this task (Herholz et al., 1996). Of particular interest is the activation in the left superior part of the anterior temporal pole, demonstrating the possible participation of this area in verb generation.

Letter fluency task. Similar to the verb generation task, the main areas of activation with the letter fluency task have been in the left prefrontal cortex (BA 44, 45, 46, and 47) (e.g., Cuenod et al., 1995; Herholz et al., 1996). The letter fluency task has also been found to activate the frontal association, premotor (BA 6), and dorsolateral

prefrontal cortex. A letter fluency task is the first task in the SVHM language battery.

Category fluency task. The second task in the SVHM language battery is a category fluency task. As with the letter fluency and verb generation tasks, when patients generate items from a category, there is similar specific activation in the left frontal lobe (Hertz-Pannier et al., 1997; Lehericy et al., 2000; Pihlajamaki et al., 2000; Spitzer, Kwong, Kennedy, Rosen, & Belliveau, 1995). Specifically, left frontal lobe activation has been shown in the inferior and middle frontal areas (BA 9, 44, 45, 46, and 47), the premotor cortex (BA 6), and the supplementary motor and cingulate areas. Other consistently reported areas of activation have been in the premotor cortex (posterior part of the middle frontal gyrus and the adjacent precentral sulcus), the dorsolateral prefrontal cortex, the inferior frontal sulcus, and the anterior part of the insula. The activation in the dorsolateral prefrontal cortex is expected given its possible role with semantic processing. In regards to non--frontal activation, activation has been reported near Wernicke's area, the left medial temporal lobe, the retrosplenial cortices, and left superior parietal lobule (Hertz-Pannier et al., 1997; Lehericy et al., 2000; Paulesu et al., 1997; Pihlajamaki et al., 2000; Spitzer et al., 1995). In Pihlajamaki et al.'s (2000) study, consistent left medial temporal lobe activation was observed from a category fluency task, either in the hippocampus or in the posterior parahippocampal gyrus.

Comparison between category and letter fluency tasks. While letter and category fluency tasks rely on some common cognitive processes and therefore activate similar areas in the brain, research has suggested that there are some differences between the tasks (Paulesu et al., 1997; Rende, Ramsberger, & Miyake, 2002). Paulesu et al. (1997) compared fMRI activation from participants who silently generated words from letters

and category cues. Compared with the resting state, both verbal fluency tasks showed common activation in the anterior triangular portion of the left prefrontal cortex and the left thalamic nucleus. The unique areas of activation for the letter fluency task were in the left posterior opercular portion of the left inferior frontal lobe (Broca's area) and in the premotor and supplementary motor areas. For the category fluency task, unique activation was identified in the left retrosplenial cortex (Paulesu et al., 1997). Consistent with these results, but in another more recent fMRI study, bilateral retreosplenial cortex activation has been report from a category fluency task (Pihlajamaki et al., 2000). From a working memory perspective, Rende et al. (2002) found that the letter fluency task relied more on systems involved in the temporary storage and processing of speech-based phonological information than the category fluency task. In contrast, they found the category fluency task relied more on systems involved in the temporary storage and processing of visual and spatial information than the letter fluency task. They suggest this is because the category fluency task participants tended to implement visualisation strategies when generating words. Such differences between the tasks may translate to unique fMRI activations.

While there is support for differences in fMRI activation between category and letter fluency tasks, for the purposes of the current research, the most important difference would be consistent temporal lobe activation, as the identification of language sites in the temporal lobes is important when planning epilepsy surgery in the temporal lobe. It has been suggested that the medial temporal lobe is required for the process of retrieval by category (Pihlajamaki et al., 2000). The cortical representation of semantic information is thought to be spatially localised (at least in part) in the temporal lobes, as

impairments with specific semantic categories have occurred in brain-damaged patients (Spitzer et al., 1995). Specifically, patients with damage to part of temporal lobe have been shown to exhibit selective impairments with specific semantic categories and not others. These findings suggest that category specific information is stored in the temporal lobes (Spitzer et al., 1995).

The accessing of semantic information from a category fluency task is expected to activate temporal regions as a result of the access to this information. While both category and letter fluency tasks are expected to consistently identify frontal and temporal language regions (see Hypothesis 1, page 39), a category fluency task is expected to exhibit more consistent activation in the temporal lobes (see Hypothesis 2, page 39), as the processing and accessing of semantic knowledge is essential, compared to a letter fluency task, which only requires orthographic and phonemic knowledge. A comparison between these two tasks, which are used in the current SVHM fMRI language battery, was planned to investigate what, if any, differences there are between these two types of verbal fluency tasks.

A consistent finding between studies using verbal fluency tasks is the activation of frontal areas that allows for reliable determination of lateralisation of language. Although verbal fluency tasks have been shown to be effective in determining the lateralisation of language and the localisation of frontal language areas, it appears they are less effective in localising temporal lobe areas involved in language (with the possible exception of the category fluency task). The identification of temporal lobe language areas is critical in the planning of individual surgical resections for patients with epilepsy, particularly those with TLE, as the temporal lobe is resected and there is the possibility of

this leading to impairments with language functioning.

Picture Naming Tasks

The third task in the SVHM battery is a picture naming task. Picture naming tasks are commonly used during the IAP. Benson et al. (1999), Deblaere et al. (2002) and Spitzer et al. (1995) have attempted to identify brain areas that are utilised during naming tasks. In these studies, the naming task required the covert or overt naming of pictures of objects. Although there was variability in the reported activation sites, possibly due to different test protocols, activation was identified in the left superior and medial temporal (fusiform, posterior parahippocampal and hippocampal gyri) and frontal areas (BA 9, 45, and 47). Some studies that have used a picture naming task (both covert and overt naming) have reported bilateral activation (Benson et al., 1999), and others left lateralised activation (Spitzer et al., 1995). An explanation for the bilateral activation could be the involvement of bilateral memory-encoding processes (Deblaere et al., 2002).

As mentioned earlier, confrontational naming appears to be at risk from surgery to the temporal lobe as electrical stimulation on the temporal lobe can disrupt confrontation naming (Ojemann, 1991; Ojemann et al., 1989), and ATL surgery for TLE can lead to impairments in confrontation naming (Seidenberg et al., 1998). Therefore areas of the temporal lobe involved in confrontation naming are important to identify in a presurgical fMRI language battery. From a picture-naming task used in the current SVHM fMRI language battery, consistent activation in the frontal and temporal lobe, including the anterior temporal lobe, was expected (see Hypotheses 1 & 3, page 39).

Semantic Decision Tasks

The fourth task in the SVHM language battery is a semantic decision task that requires sentence reading. With this task, the participant is presented with an incomplete sentence and is required to make a decision regarding which of two presented words is missing from the sentence. As the task also required reading of sentences, the task used in the SVHM battery is a combination of two types of tasks (i.e., semantic decision task and a reading task). Semantic decision tasks will be discussed first followed by reading tasks.

Like verbal fluency tasks, semantic decision tasks are another popular group of tasks that have been employed to identify language areas. These tasks have been shown to activate both the frontal and temporal lobes (Binder et al., 1997; Booth et al., 2002; Carpentier et al., 2001; Deblaere et al., 2002; Spreer et al., 2001). An example of such a task was where participants heard names of animals and were required to decide if the animals were found in the United States of America and used by humans (Binder et al.,1995; Binder et al., 1996; Springer et al., 1999). The control condition was a tone decision task where participants heard a series of tones and were asked to decide whether the last two tones presented were high-pitched. Activation from this task was reported in the prefrontal cortex (middle, inferior and superior frontal gyrus), mid-anterior cingulate gyrus, posterior cingulate gyrus, anterior superior temporal sulcus, middle temporal and posterior inferior temporal gyri, mid-fusiform and parahippocampal gyri, anterior hippocampus, angular gyrus, and thalamus. Sabsevitz and colleagues (2003) preoperatively employed the same blocked semantic decision task to determine language lateralisation. They found that language lateralisation in the left hemisphere predicted naming decline in patients undergoing a left ATL. Lateralised temporal lobe activation

was reported to be the best predictor of outcome.

Another example of a semantic decision task is one used by Deblaere (2002), which had an experimental condition where participants decided if a particular animal was a mammal. The control condition required the participant to decide if the letter "a" was present in a string of vowels. The authors reported activation in the prefrontal region (BA 8, 45 and 47), the anterior cingulate, and the middle and inferior temporal gyrus (BA 20 and 21). Although semantic decision tasks are not used as frequently as verbal fluency tasks, they have been shown to consistently activate language areas in both the frontal and temporal lobes, and some activation has been reported in the anterior temporal lobe (Deblaere et al., 2002; Sabsevitz et al., 2003).

Reading Tasks

Many researchers have shown the importance of a reading-based paradigm for temporal lobe activation in individual participants (Bavelier et al., 1997; Brockway, 2000; Deblaere et al., 2002; Gaillard et al., 2002; Gao, Jiang, Lu, & Shen, 2001; Thickbroom, Byrnes, Blacker, Morris, & Mastaglia, 2003). Many of these studies identified activated areas in the frontal and temporal lobe that are involved in reading and comprehending sentences. However, of particular interest is the reported activation within the middle temporal gyrus and the anterior temporal pole. It is therefore likely that a reading paradigm enables the localisation of language function in the anterior temporal pole and middle temporal gyrus, areas typically resected during epilepsy surgery.

While the sentence completion task is arguably both a reading and semantic decision task, both types of task have been shown to activate the anterior temporal lobe,

in addition to other temporal and frontal areas of the cortex. Thus, consistent activation in the frontal and temporal lobes, particularly in the anterior temporal lobe, was expected from the SVHM sentence completion task (see Hypothesis 1 & 3, page 39).

Batteries of fMRI Language Tasks

A number of studies that have sought to identify relevant language areas in epilepsy patients have used a battery of multiple fMRI language tasks (Benson et al., 1999; Deblaere et al., 2002; Gaillard, Balsamo, & Xu, 2004; Rutten, Ramsey, van Rijen, Noordmans, & van Veelen, 2002). Deblaere et al. (2002) claimed to be the first to report on a protocol designed to address aspects of lateralisation and localisation of brain regions normally resected during surgery for TLE. They suggest the overlap of the results of the different language tests is an advantage of using a battery of tasks. The use of verb generation, sentence completion, and picture naming tasks together were shown to have high sensitivity for detecting critical language sites, as validated by electrical stimulation maps. Sensitivity was reported to be higher when the results for the tasks were combined, compared to any individual task results. It has been suggested that resections can safely occur, without using electrical stimulation mapping, in areas of the brain where no significant fMRI activity occurs for the language battery (Powell & Duncan, 2005).

A battery of language tasks should test both expressive language and comprehension. Given the most reliable single participant language lateralisation often comes from the verbal fluency and semantic decision tasks, their inclusion in such a battery is desirable. These tasks are likely to activate most parts of the language system,

particularly in the frontal cortex, especially when material is presented visually and inner speech is involved.

Naming and reading abilities are the language skills most at risk following surgery in the dominant temporal lobe (Baxendale, 2002; Powell & Duncan, 2005). Sabsevitz et al. (2003) report that 25 to 60% of patients who undergo such surgery develop difficulties in remembering names or recalling words needed for oral or written language (dysnomia). Lehericy et al. (2000) found that although fMRI covert repetition tasks were not strongly lateralising, they were useful in the detection of language sites in and around Wernicke's area. These findings give support to the notion that certain language tasks may be more useful in identifying specific areas in and around the temporal lobe needed for language. Therefore, while naming and reading tasks may not lateralise language function as clearly as verbal fluency and semantic decision tasks, they may provide important clinical data for individual patients in identifying the regions that are important for these tasks (Benson et al., 1999). While the inclusion of verbal fluency and semantic decision tasks has been established in the literature, the review of research evidence given above suggests that naming and reading tasks should also be included in a battery as they may provide more important clinical data in identifying language regions that are at risk in TLE patients (e.g., anterior temporal lobe).

Aims of Research

The analysis of the results of the existing SVHM fMRI battery was conducted to evaluate its utility in detecting language function in controls and epilepsy presurgical patients. The utility of a task was defined as when the task consistently showed

significant language activation in single cases, for both healthy right–handed controls and patients with epilepsy. The verbal fluency, picture-naming, and sentence completion tasks were expected to show significant activation in the frontal and temporal lobes (see Hypothesis 1, page 39). In addition, the category fluency task was expected to consistently identify more temporal lobe language areas (see Hypothesis 2, page 39). Lastly, consistent activation in the anterior temporal lobe was expected from the picture naming task and the sentence completion task because it resembles both a semantic decision task and reading task, both of which, as mentioned earlier, have shown to activate the anterior temporal lobe in other studies (see Hypothesis 1 & 3, page 39). After all of the control and some of patient data were obtained, a new MRI scanner was installed at SVHM. Data from patients who underwent the same SVHM language battery was obtained on the new MRI scanner with different acquisition parameters (which included more slices over a larger cortical area). The hypotheses were expected to hold for the healthy controls, the patients who underwent the battery on the old MRI scanner, and patients who underwent the battery on the new MRI scanner.

An ATL is the most common surgical procedure for epilepsy with known language deficits resulting, whereas non-ATL procedures for epilepsy are often done for a heterogeneous variety of lesions in a wide range of cerebral areas. Therefore, while frontal lobe language areas are important in frontal lobe surgery the current research has focused more on identifying language function in the temporal lobe, specifically the anterior temporal lobe.

Hypotheses

(1) Both verbal fluency tasks (letter and category), the picture-naming task, and sentence completion task were expected to show consistent significant activation in the frontal and temporal lobes across patients and controls.

(2) The category fluency task was expected to consistently activate more language areas in the temporal lobe than the phonemic verbal fluency task for patients and controls.

(3) The sentence completion task and the picture-naming task were expected to show consistent activation in the anterior temporal lobe for patients and controls.

Method

Participants

In the original SVHM fMRI data set, functional MRI data was obtained from 20 healthy volunteers who were English speaking, right-handed male (n = 8) and female (n = 12) participants with a mean age of 32.0 years (SD = 12.7 years; range 20 - 65 years). Participants in this control group (or group C) were recruited from family and friends of staff members from the Victoria Epilepsy Centre (VEC) at SVHM. All normal control participants were right-handed and screened to rule out a history of neurological or psychiatric disorders, head trauma, substance abuse, and other serious medical conditions. Also, data from 12 patients (4 male; 8 female) was obtained from one right TLE and 11 left TLE patients admitted to SVHM for presurgical evaluation using the original fMRI language battery with the old MRI scanner. These 12 patients constituted the first patient group (or group A). The mean age for patient group A was 34.3 years (SD = 12.5 years; range 18 - 57 years). In Table 1 the seizure type and pathology location for each patient in group A are provided along with histological and surgical outcome data, where possible. In addition, data from six patients (3 male; 3 female) was obtained from four patients with left TLE, one patient with left frontal lobe epilepsy, and one with generalised seizures, who were admitted to SVHM for presurgical evaluation using the original fMRI language battery with the new MRI scanner. The mean age for this second group of patients (or group B) was 43.8 years (SD = 8.34 years; range 32 - 55 years). In Table 2 the seizure type and pathology location for each patient in group B are provided along with histological and surgical outcome data, where possible. Previous research has

demonstrated that small sample sizes (n = 5 - 10) are adequate for fMRI activation using tasks similar to the ones used in the current study, as described below (Tsukiura et al., 2002). The data from the normal controls (group C) and epilepsy patients (both groups A & B) constituted the original data sample. Informed consent was obtained from all participants.

Materials

Functional MRI Image Acquisition

The fMRI studies for both the participants in groups C and A were performed at SVHM on a SVHM 1.5 Tesla Siemens Magnetom Vision MRI scanner with echo-planar imaging (EPI) capabilities. For patients in group B, fMRI studies were also performed at SVHM, but on the newer Siemens Avanto 1.5 Tesla MRI scanner with EPI capabilities, because the hospital had upgraded their MRI scanner.

Table 1

Details of patients in group A.

Patient	Seizure Type & Pathology Location	Overlapping Activation	Brief Histology	Outcomes
A1	Large (5 cm) mass lesion (anaplastic oligoastrocytoma) in the left fronto-temporal region.	Overlapping bilateral anterior temporal pole activation	N/A	Left temporal craniotomy
A2	Epileptogenic focus in the medial aspect of the left temporal lobe While an MRI of the brain showed no definite evidence of mesial temporal sclerosis; the posterior aspect of the left hippocampus was reported to be of suspicious appearance.	Overlapping activation in the right frontal gyrus (BA 11), and right anterior temporal lobe (BA 21).	N/A	Left TLE surgery was recommended to help control seizures.
A3	A large mass lesion in the left temporal pole (most likely representing an anaplastic astrocytoma). The lesion extended into the frontal lobe	Overlapping activation in the left frontal lobe (BA 6, 9).	Glioblastoma Multiforma.	Excision of temporal lobe lesion. After surgery, the patient experienced unsteadiness and blurred vision.
A4	Medically refractory epilepsy secondary to a lesion in the posterior left temporal lobe with a maximal diameter of over 2 cms. MRI showed a heterogeneous area of signal abnormality in the posterior aspect of the left temporal lobe. It was felt most likely that was representative of a low-grade astrocytoma, ganglioglioma or dysembryoplastic neuroepithelial tumor (DNET).	No	N/A	N/A
A5	Medically refractory epilepsy secondary to a 6 mm ovoid intra-axial lesion in the anterior region of the left temporal lobe. The MRI showed it had a hypointense rim, consistent with haemosiderin, and was reported to be compatible with a cavernous haemangioma.	No	N/A	N/A
A6	Intractable left TLE, as confirmed by PET and scalp EEG recordings. There were no reported visible abnormalities on MRI.	No	N/A	Underwent a left temporal lobectomy and experienced a reduction in frequency and severity of seizures and development of word finding difficulties.

Table 3 (continued)

Patient	Seizure Type & Pathology Location	Overlapping Activation	Brief Histology	Outcomes
A7	Suffered life-long focal epileptic seizures. Previously had a resection of the anterior aspect of the left temporal lobe for cortical dysplasia in the left temporal pole. Five years later, patient was continuing to have seizures. Brain MRI was reported to show an area of gliosis adjacent to the surgical defect in the temporal pole on the left, particularly laterally, which had been a longstanding finding after the previous surgery. There was also moderate atrophy of the head of the hippocampus and mild atrophy of the amygdala.	Overlapping activation in the right parahippocampal gyrus (BA 19, 36)	N/A	N/A
A8	Medically refractory epilepsy secondary to a glioblastoma multiform in the left temporal lobe.	No	N/A	N/A
A9	Intractable TLE, localised to the left temporal pole with scalp EEG, and PET. Deep white matter changes in the temporal pole were noted on the MRI.	Overlapping activation in the left inferior frontal lobe (BA 9)	N/A	N/A
A10	Complex partial seizures since the age of 12 years. The seizures often began with speech arrest, and then progressed to staring and non-responsiveness, which lasted for one to two minutes. Seizure frequency averaged about four per week over many years, with secondarily generalised seizures occurring about three to six times per year. Long-standing mild speech difficulties, consisting primarily of naming difficulties. MRI scans identified a lesion in the left temporal lobe (5 cm in diameter).	No	Glioblastoma Multiforma.	Immediately after resection of temporal lobe lesion, it was reported that the patient had difficulty in following verbal commands.
A11	History of seizures due to a 2 cm medial temporal lobe lesion on the left. Based on a brain MRI, the lesion was thought to represent either a developing cerebral abscess or a left temporal lobe neoplasm.	Overlapping activation in the left and right frontal gyrus (BA 10/32).	N/A	Resection of left temporal lesion was planned.
A12	Suffered intractable complex partial seizures of right temporal lobe onset. MRI brain scans showed no visible evidence of mesial temporal sclerosis, but some subtle signal changes in the deep white matter of the anterior temporal pole.	No	N/A	N/A

Note: N/A, not available.

Table 2

Details of patients in group B.

Patient	Seizure Type & Pathology Location	Overlapping Activation	Brief Histology	Outcomes
B1	Long-term refractory left TLE. A brain MRI revealed a small white lesion, possibly related to prior trauma. An interictal SPECT showed minimal reduction in perfusion in the temporal lobes and an EEG investigation confirmed a left temporal epileptic focus.	Overlapping activation was noted in the left frontal lobe near Broca's area, and near Wernicke's area.	From specimens taken from surgery the pathologist suggested perivascular rarefaction of parenchyma in subcortical white matter with some pigmented macrophages, there was no evidence of tumour or glioneuronal dysplasia.	The patient underwent a left temporal lobectomy and an anterior temporal lobectomy. Post surgery, there were reported problems with balance and increased headaches.
B2	Refractory complex partial seizures. An ictal and interictal SPECT suggested an ictal focus in the posterior aspect of the left frontal lobe. A brain MRI showed a white matter band of hyperintensity in the left inferior frontal gyrus.	Overlapping bilateral activation was noted in the frontal lobes near Broca's area, and in the temporal lobe, particularly in the left.	Specimens taken from surgery included normal white matter, cortical dysplasia with abnormal architecture of cortex with loss of neuronal lamination, abnormal neurons and dense subpial gliosis, and a vascular malformation composed of capillaries and dilated thin-walled vessels.	The patient underwent a partial left frontal lobectomy, where parts of the left middle and inferior frontal gyri were resected.
B3	The patient had suffered from a haemorrhage in the left parietal lobe presumed to be due to a cavernous haemangioma in the left post central gyrus centered in the subcortical matter. The patient experienced tonic-clonic seizures.	Overlapping activation was noted in the left hemisphere near Broca's area, and bilateral activation near in the temporal lobe, particularly in the left.	N/A	Post surgery, minor sensory disturbances of tingling in the right index finger and face were reported.
B4	Left TLE. From MRI, a deep mesial temporal lobe 8mm cavernous haemangioma in the floor of the left mesial temporal ventricle was noted.	Overlapping activation in the left frontal lobe (BA 47)	Specimens taken from surgery showed features of cavernous haemangioma with thrombosis in some cavernous channels, focal old haemorrhage, and chronic inflammation.	Left temporal cavenoma resected. Post surgically, seizures were noted to have reduced, and the patient was reported to be doing well.
B5	Left TLE. EEG, MRI and PET studies supported left temporal lobe seizures and hippocampal sclerosis.	Overlapping activation in the frontal lobe and right anterior temporal lobe.	N/A	Scheduled to have a left temporal lobectomy including mesial temporal structures and cortex close to language
B6	Left TLE.	Overlapping activation near Brocas's area and the precentral gyrus (BA 6) in left.	N/A	N/A

Note: N/A, not available.

Stimuli and Instructions for Original fMRI Activation Tasks

Patients with epilepsy (groups A & B) scheduled for surgery and normal controls (group C) were studied using fMRI to locate and map language areas in the brain. The stimuli for the tasks were presented visually by video projection into the MRI chamber using the software application Microsoft PowerPoint (MicrosoftCorporation, 2000) on a laptop computer connected to a liquid crystal display (LCD) data projector located in the MRI control room. The visual stimuli were back-projected in a reversed mirror image through the observation window between the MRI control and scanner rooms onto a temporary screen mounted on the end of the MRI sliding bed. The participants were able to see the visual stimuli through a mirror on the head coil. The stimuli were presented visually rather than aurally to make the task easier for the patient to understand in the noisy MRI environment. The visual material was as large and simple as practicable so as to minimise difficulty seeing it. A two-button magnet-safe response unit was used in the picture naming and sentence completion tasks, as these tasks required the making of a decision. The response unit did not allow for the recording of responses and only served as a way for the participant to give a response. Participant responses were not recorded due to the high cost of a functional button suitable for use within an MRI. The participants were requested to hold the response unit and press the left or right button with either their index or middle finger, according to the response required by the visually presented information. All participants were requested not to speak or move their head during the tasks in an effort to reduce motion artifact.

Each of the original fMRI tasks was presented in a block design with the target and control conditions being presented for 45 seconds at a time (15 functional images,

TR = 3,000 msec). The target condition was presented first followed by the control condition, with each condition being repeated three times. Each task therefore lasted for a total of 270 seconds, resulting in a time series with 90 sets of functional images. The instructions for each of the four tasks were given verbally and then presented visually on the screen for the patient to read before starting the task. The four tasks used were letter fluency, category fluency, picture naming, and sentence completion. The first two tasks were based on fMRI verbal fluency studies using letter fluency (Hinke et al., 1993; Schlosser et al., 1998) and category fluency (Spitzer et al., 1995). The original tasks are now described in the order in which they were presented.

Letter fluency task. The patient was shown a letter of the alphabet for 45 seconds and was asked to think of as many words as possible beginning with that letter. High frequency letters were used (e.g., H, D, etc.). The letters F, A, and S were not used as they are commonly used in a similar task that is part of the preoperative neuropsychological assessment. The control block lasted 45 seconds and consisted of the presentation of a single Japanese character every three seconds. For the control task participants were asked to look at the characters and to concentrate on breathing evenly. Japanese characters were used because it was thought that patients with medically intractable epilepsy suffering from mental and psychical deficits would not encounter difficulties with such a task. The Japanese characters were selected as being visual stimuli that had no semantic meaning to the participants. The instructions for the task, presented on the display and explained to the patient before the task began were "When a letter is displayed, think of words beginning with that letter. When the Japanese characters are displayed, look a them and concentrate on breathing evenly."

Category fluency task. The category fluency task was similar to the letter fluency task except that instead of the presentation of letters, the name of a category was displayed and the participant was asked to think of as many words as possible from the category (e.g., animals, groceries, etc.). The control condition involved the presentation of a string of six random Japanese characters presented every three seconds for a total of 45 seconds. The instructions, presented on the display and explained to the patient before the task began were "When a category is displayed, think of as many examples as you can. When the Japanese characters are displayed, look at them, and concentrate on breathing evenly."

Picture naming task. The picture-naming task involved presenting a picture of an object along with two capital letters. Each object was displayed for one EPI acquisition cycle (approximately 3 seconds). The object was presented in the middle of the screen along with one letter being presented in the lower left of the screen and another letter in the lower right. One of the letters was the first letter of the name of the pictured object and the other was not. The participant was instructed the press the left button on the response unit if the object displayed started with the left letter, or the right button if the object started with the right letter. In the control condition, a row of six Japanese characters were presented in the top of the display along with another two Japanese characters in the lower left and right of the display for three seconds. Participants were required to press the left or right button depending on whether the Japanese character displayed in the left or right matched one of the characters in the string of characters. The instructions, presented on the display and explained to the patient before the task began, were "Press the LEFT button if the object displayed starts with the LEFT letter. Press the

RIGHT button if the object starts with the RIGHT letter. One symbol from each group is repeated at the bottom of the screen. Press the button which corresponds to this symbol. Press any button if you can't decide."

Sentence completion task. In the sentence completion task the patient was presented with a short sentence with one of the words missing (e.g., He slept in ..... noon). Two words were presented below the sentence (e.g., until, from), one in the lower left and one in the lower right of the display. One of these words was appropriate in completing the sentence, while the other was not. The patient was instructed to press the left or right button on the two-button response unit depending on whether the appropriate word that best completed the sentence was displayed on the left or right. Each sentence was presented for three seconds. The control condition was the same as described for the picture-naming task. The instructions, presented on the display and explained to the patient before the task began, were "When a sentence is displayed, choose the word that goes in the space, and press the corresponding button. When you see Japanese characters, choose the bottom character, which is also in the displayed group, and press the corresponding button. Press any button if you can't decide." (see Appendix B for examples of stimuli and instructions).

Data Processing Software

Available software packages to analyse fMRI data include Statistical Parametric Map (SPM, Wellcome Department of Imaging Science, Functional Imaging Laboratory, London, UK), Analysis of Functional Neuroimages (AFNI) from the Medical College of Wisconsin (Cox, 1996), and the Functional Magnetic Resonance Imaging of the Brain

(FMRIB) Software Library (FSL), released by the Oxford Centre for the FMRIB. FSL is a comprehensive library of functional and structural brain image analysis tools that have powerful research statistical facilities (Smith et al., 2004). It is designed to run on PC, Macintosh, Sun, or Silicon Graphics hardware with either of the Linux, MacOS X, Windows XP, Solaris, or IRIX operating systems. The software package is reported to be capable of running on computers with at least 512MB of RAM. FSL is a good choice for statistical analysis of fMRI data as the software is free, user friendly and relatively easy to use, usable on a wide range of available computer systems, has good free support and tutorials, and has been received well and widely used. During the course of the project an updated version of FSL was released, however, upon reviewing the changes and additions, the use of version 3.2 was continued, as it was decided there was no strong reason to change to the newer version.

Procedures

Ethics approval for the use of archival fMRI data in the present study was obtained from the Victoria University and SVHM Human Research Ethics Committees (see Appendix D). All participants had given informed consent for their participation in the fMRI protocol at the time of scanning. All of the participants were given the standard Medical Imaging MRI information sheet (see Appendix G) and were interviewed and prepared by the MRI unit staff.

All participants initially underwent an anatomical T1 MRI volume of the head, followed by the fMRI language tasks. The test operator entered the MRI chamber at the beginning of each task to verbally explain the language tasks. All participants lay in the supine position with their head held in place with foam to prevent movement. A vitamin E tablet was taped to the right of each participant's head so that left-right orientation of the scans was not confused during data analysis.

Data Acquisitions for the Four Original Language Tasks

Scanning of participants in groups C and A occurred on the older Siemens Magnetom MRI. Initially, a high-resolution 3D T1-weighted image of the entire brain was obtained from participants to allow for anatomical referencing of fMRI data. The imaging parameters for the normal participants were repetition time (TR) = 9700 ms, echo time (TE) = 4000 ms, pixel matrix = 256 x 256. For the normal controls, 2 mm slices, a field of view (FOV) of 240 mm, and 128 slices per volume. For the patients, 1 mm slices, a field of view (FOV) of 250 mm, and 256 slices per volume. Another partial

head T1 anatomical volume image consisting of 10 oblique axial slices of 5 mm was also obtained (TR = 350 ms, TE = 15 ms, slice spacing = 1.5 mm, pixel matrix = 128 x 128, and FOV = 230 mm). This scan covered the same region of interest (ROI) as the fMRI scans, particularly temporal and frontal lobe areas of the brain, and was used for the referencing of the fMRI data. For functional imaging, a standard Siemens echoplanar fMRI sequence was used. The images were obtained while the original normal participants and patients in group A performed the four language tasks. For each of the language tasks, 90 volumes were collected, one every three seconds (TR = 3000) and each volume consisted of 10 axial slices of 5 mm (TE= 118, slice spacing = 1.5 mm, 128 x 128 and FOV = 230 mm).

Scanning of all the patients in group B on the newer Siemens Avanto also involved obtaining a high-resolution 3D T1-weighted anatomical reference image of the entire brain, a partial head T1 anatomical volume image consisting of 25 slices for the referencing of the fMRI data, and the fMRI data. The main differences between the data acquisition for the patients in group B, compared to group A, was with the acquisition parameters (which are detailed below), and that the partial head T1 anatomical volume and fMRI data volumes consisted of 25 slices (group B), rather than 10 (group A), and covered a larger portion of the temporal and frontal lobes.

The imaging parameters for the high-resolution 3D T1-weighted anatomic reference image were TR = 2,130 ms, TE = 2.93 ms, flip angle of 15°, voxel size = .9375 mm^2 x 1 mm, pixel matrix = 256 x 256, and 256 interleaved slices per volume. The partial head T1 anatomical volume image consisted of 25 slices (TR = 579 ms, TE = 12 ms, flip angle = 70°, voxel size = .859375 mm^2 x 3 mm, slice spacing = 3.75mm, pixel matrix = 192 x

256). This scan covered the same areas of the brain as the fMRI scans would, particularly temporal and frontal lobe areas, and was used for the referencing of the fMRI data. For functional imaging, a gradient-echo, T2 - weighted echoplanar sequence was used. The images were obtained while patients performed the language tasks. For each of the language tasks, 90 volumes were collected, one every three seconds (TR = 3000) and each volume consisted of 25 slices (TE = 51, flip angle = 90°, voxel size = 1.71875 mm^2 x 3 mm, slice spacing = 3.75 mm, pixel matrix = 640 x 640). The time required to completed both the language tasks and obtain the MRI scans took up to 30 minutes.

Preparation of Original Data

The utility of the four original tasks (letter fluency, category fluency, picture naming, and sentence completion) to consistently identify the location of areas of the brain important for specific language abilities in single cases, whether healthy controls or patients with epilepsy, was established by comparing brain activity between the target condition and its control.

The Original MRI data was initially acquired in the Digital Imaging and Communications in Medicine (DICOM) format (Bidgood & Horii, 1996), a commonly used format for the storage of medical images. The acquired data were organised into the following computer files; scouts for localisation of the temporal lobe, the anatomical T1 MRI head volume (128 or 256 files where each file was a two dimensional (2D) scan), the T1 fMRI ROI set based on the template (10 or 25 2D scans). There were also files for each of the language tasks: scouts for the fMRI, and the fMRI data for each task (900 scans for each task; 90 volumes each consisting of 10 or 25 scans). This data was

converted to the Analyze file format (a format used by the Analyze program, an image processing program written by the Biomedical Imaging Resource at the Mayo Foundation) with a free software package named MRIcro (Rorden, 2005) in order to use the data with FSL. For each language task, the 900 2D image files were stacked together to produce 90 3D fMRI image files for each task. In turn these were converted into a single 4D format file (3D + time) before being analysed, as the FSL analysis program requires fMRI data to be in a 4D Analyse or NIFTI (a similar but more recent format than Analyse) format. In addition, the 10-slice (or 25 slice) T1 ROI structural images were also converted into a 3D Analyse volume (with MRIcro) and non-brain parts were removed (with the Brain Extraction Tool version 1.1 (BET), part of the FSL software library) to allow for the registration of the fMRI data to a higher resolution image.

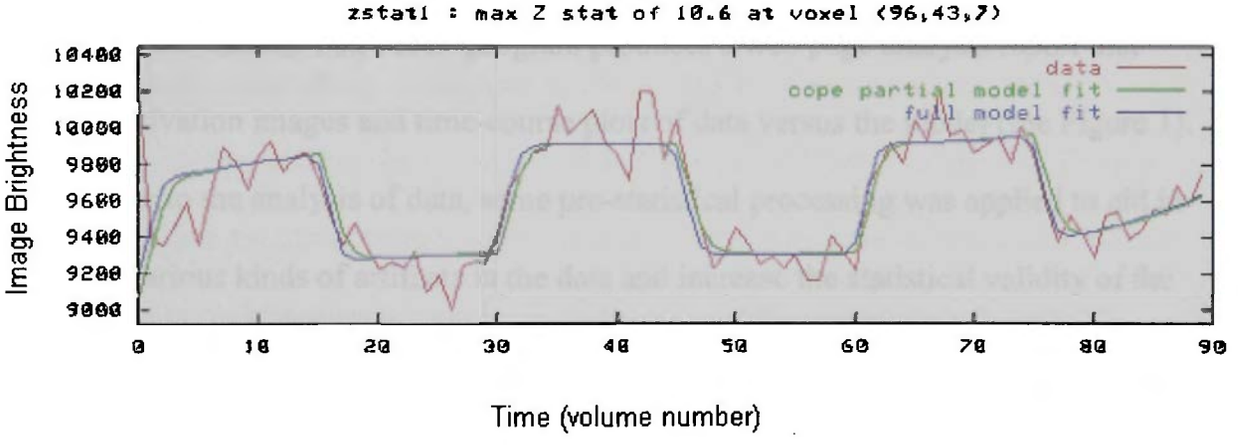


Figure 1. An example of a time-course plot of the fMRI data at a voxel (96, 43, 7) over time (volumes) versus the model.

Analysis of Original Data

FMRI Expert Analysis Tool (FEAT) (version 5.43), part of FSL, was the analysis software tool used to analyse the MRI data (Jenkinson, Bannister, Bady, & Smith, 2002; Jenkinson & Smith, 2001; Smith, 2002; Woolrich, Ripley, Brady, & Smith, 2001; Worsley, Evans, Marrett, & Neelin, 1992). It is a program that can be used for high quality model-based fMRI data analysis. It has an easy-to-use graphical user interface and uses general linear modeling, also known as multiple regression, for the data modeling. With FEAT, the user describes an experimental design from which a model is created that should fit the data (i.e., alternation between brain activation during the active part of the task and no activation during the control part of the task for a voxel or cluster of voxels). It is assumed that when the data fit the model, the brain has activated in response to the stimuli. The FEAT program produces a web page analysis report that includes activation images and time-course plots of data versus the model (see Figure 1).

Prior to the analysis of data, some pre-statistical processing was applied to aid in removing various kinds of artifacts in the data and increase the statistical validity of the results (Smith, 2004). Brain volumes within each fMRI run were motion-corrected using MCFLIRT (Jenkinson et al., 2002). Movement of the participant in the scanner leads to misalignments between volumes. Motion correction involves transforming each volume (using rotation and translation) so that the image of the brain is aligned with that of every other volume (Smith, 2004). Using BET (Smith, 2002), non-brain parts of scans (e.g., skull) were removed from the fMRI data. Spatial smoothing of each volume was applied using a Gaussian-weighted kernal of 5mm at full-width half-maximum (FWHM). This is a step now performed by most researchers and attempts to combine individual voxel

responses into cohesive units, with the intention of reducing noise without reducing valid activation (Smith, 2004). Mean-based intensity normalisation of all volumes by the same factor occurred so that all volumes had the same mean intensity. This can help in reducing the effect of global changes in intensity over time. As a final step in the preprocessing of the data, high frequency noise was reduced with high pass temporal filtering (Gaussian-weighted LSF straight line fitting, with sigma = 45.0s, as recommended in the FEAT manual for the current experimental design). Time series statistical analysis was carried out using FMRIB's Improved Linear model (FILM) with local autocorrelation correction (Woolrich et al., 2001). Z (Gaussianised T/F) statistic images were thresholded using clusters determined by $Z > 2.3$ and a (corrected for multiple comparisons) cluster significance threshold of $p = 0.05$ (Worsley et al., 1992).

After the analysis of the functional data, it was registered to the anatomical image using FMRIB's Linear Image Registration Tool (FLIRT) (Jenkinson et al., 2002; Jenkinson & Smith, 2001). The low-resolution fMRI images were registered (aligned) to a high-resolution structural image, so that activation could be viewed in the context of a good quality brain image and thereby aid in the interpretation of the activations. In addition, as MRI scans vary between individuals, due to differences in slice orientation and brain features (i.e., brain size and shape), it is also generally useful to register scans to a standard template. A template is an average of many brains all registered into a common coordinate system (Smith, 2004). FSL (and other similar fMRI software processing software such as SPM5) use the Montreal Neurological Institute (MNI) 152 brain template, which is based on the average of 152 MRI brain scans of healthy young adults. In this case, the registration process involves the translating, rotating, scaling, and

warping of a brain to roughly match a standard template image. This allows for multi-subject analyses, comparisons between individuals, and the uniform labeling of activation areas. Using FLIRT, functional images were first registered to the high-resolution structural T1- weighted EPI volume after non-brain structures had been removed. Secondly, the high-resolution structural T1-weighted EPI volume was registered to the MNI 152 template. Lastly, the two transformations were combined into a third, which took the low-resolution fMRI data (and the statistic images derived from the analysis) into standard space.

With the original data obtained on the old Siemen Magnetom MRI scanner (participants in groups A and C), the best registration of the low-resolution fMRI data to the high-resolution image (as judged from visual inspection) was achieved by using rigid 2D body movement. The high-resolution image was registered to the MNI template with 12 degree-of-freedom (DOF) and a full search (as the orientation of data was inverted from the template).

Higher-level intra- and inter-group statistics were carried out using mixed effects higher-level modeling and implemented in FLAME (FMRIB's Local Analysis of Mixed Effects). Prior to the higher-level group statistic being carried out the individual data sets were registered into standard space using FLIRT. Second-level mixed effects were then carried out using the first-level statistic maps to test for differences in activation between two tasks or for finding the group average activation for a task. The resulting statistic maps were thresholded using clusters formed by $Z > 2.3$ and then tested with $p < 0.05$. Across participant averaging was undertaken with the control data for the purpose of comparing it with previous imaging studies that have averaged participant activations.

Group averaging of activations was not undertaken with the patient data, given the heterogeneous nature of the sample (i.e., differing types of epilepsy and pathology sites) and because the utility of the language battery needed to be investigated on an individual cases by case basis.

Difficulties in the Interpretation of fMRI Data

An issue related to the interpretation of fMRI data comes from the use of the templates and brain atlases. Like a template, an atlas is also based on a common co-ordinate system, however, it contains more information about the brain at each voxel (e.g., information about tissue type or location in terms of brain anatomy) (Smith, 2004). The majority of functional imaging studies report positions of identified activations in terms of Broadmann cytoarchitectonic areas (BAs). Estimating areas of activation in terms of BA labels often requires the use of the Talairach and Tournoux atlas of 1988 (Talairach & Tournoux, 1988). The Talairach atlas was made from photographs of sagital slices of a brain from a 60-year-old female. The coordinate system defines an origin at the anterior commissure and x, y, and z planes. There are a couple problems with interpreting activations in terms of BA from the Talairach atlas. Firstly, the brain used in the Talairach atlas did not have cytoarchitectonic analysis, so the authors estimated the BA labels by eye, through a comparison of the Talairach brain surface with Brodmann's published data (Brett, Christoff, Cusack, & Lancaster, 2001). Roland et al. (1997) reported that sulci are not generally valid landmarks of the microstructural organisation of the cortex, and as such there can only be approximate correspondence between sulcal landmarks or stereotaxic space and cytoarchitecture. Therefore the BA estimates from the

Talairach atlas are not based on cytoarchitectonic data from the individual brain. Although with their limitations, stereotaxtic coordinates and major brain landmarks are the best way of localising activation as the registration process smoothes brain images, greatly reducing detail of sulci and gyri, and the cytoarchitecture cannot be directly examined in living humans (Rorden & Brett, 2006). Despite there being a few limitations with estimating the position of activation in terms of BAs, Talairach remains the standard for their estimation (Rorden & Brett, 2006).

Another problem with using the Talairach atlas for fMRI activation interpretation is that the brain used by Talairach and Tournoux was never scanned with an MRI. As there is no Talairach template the MNI template is commonly used by many MRI analysis software programs for registration of fMRI activations into a standard brain space. The problem introduced with the MNI template is that although it is based on the Talairach brain, the brain is larger, specifically the temporal lobes extend one cm lower (Brett, Johnsrude, & Owen, 2002). Therefore, the coordinates in the MNI template do not directly refer to the Talairach brain, because of the differences between them. Currently, there is no published estimate of BAs that correspond to the anatomy of the MNI template. Many researchers use coordinates from the MNI template to look up estimated BAs in the Talairach atlas (Brett et al., 2002). Brett, Johnsrude and Owen (2002) report that significant errors can occur, particularly for coordinates in the temporal lobe, if differences between the Talairach atlas and MNI brain are not accounted for. They note other approaches have been to either estimate by eye which areas in the atlas correspond to the coordinate in the MNI template, or to use a transformation for coordinates from the MNI template that matches the brains more closely. An appropriate transformation is

provided by Brett (2006), who suggested the use of a simple non-linear transformation that differs for different brain areas. In the current study, this transformation was used in the labeling of BA's. Upon transforming the coordinates from MNI to Talairach space a Talairach atlas (Fox & Uecker, 2005) was referred to in locating the relevant sulci, gyri, and BA's. While the BA's are presented in the results, both stereotaxic coordinates for the MNI template and, where appropriate, an image will also be presented so that the reader can identify relevant landmarks.

Results

In order to evaluate the hypotheses (see page 39), the results focus on activation in language areas and the frontal and temporal lobes.

Results for Controls (Group C) on Original Language Tasks

Table 3 shows results for the four language tasks for the 20 control participants. The table shows the areas where significant activation was identified in the temporal lobe, including the anterior temporal pole, and the frontal lobe. The results show that the original SVHM language battery was only able to identify anterior language activation in 40.0% of control participants studied with the letter fluency, picture naming, and sentence completion tasks. The sentence completion task was also the only task to consistently demonstrate significant activation in the temporal and frontal language areas of the cortex (90%), compared to the other three tasks, which showed activation in between 31.6% to 50.0% of cases. However, the letter fluency and picture naming tasks identified anterior temporal lobe activation in some participants that was not detected by the sentence completion task. Also, the verbal fluency tasks tended to activate more frontal language areas than temporal language areas: frontal lobe activation was between 36.8 and 50.0% and temporal lobe activation was between 25.0 and 26.3% for the fluency tasks. In comparison, the picture naming and sentence completion tasks tended to provide more activation in the temporal lobe than in the frontal lobe: temporal lobe activation was between 26.3 and 75.0% and frontal lobe activation was between 10.5 and 57.9%).

Table 3

Areas activated by the original tasks in the 20 control participants.

	Frequency	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Letter Fluency																					
Any Activation	52.6% (n=19)																	-			
FL / TL Activation	47.4%																				
FL	36.8%		L			L						L		L		L	L	-	L		
Middle/Posterior TL	21.1%						L					L				B		-			B
Anterior TL	15.8%															B		-	L		L
Other	15.8%						L					L			L			-			
Category Fluency																					
Any Activation	50.0% (n=20)																				
FL / TL Activation	50.0%																				
FL	40.0%	L				L	B			L	L	L			L	B					
Middle/Posterior TL	25.0%				B		L				B	B				B					
Anterior TL	0.0%																				
Other	25.0%						L				L	L			L					L	
Picture Naming																					
Any Activation	36.8% (n=19)								-												
FL / TL Activation	31.6%																				
FL	10.5%						L		-										L		
Middle/Posterior TL	21.1%				B		B		-		R		L								
Anterior TL	15.8%				B		B		-												R
Other	5.3%		R						-												
Sentence Completion																					
Any Activation	95.0% (n=20)																				
FL / TL Activation	90.0%																				
FL	57.9%		B	L		L	L		B	L		L				B	L		L		L
Middle/Posterior TL	78.9%		L		L	L	B	L	L	L	L	B		L	L	B	L	L		L	
Anterior TL	21.1%						B		L			L								L	
Other	26.3%						B					L	L			B				L	

Note. L, left; R, right; B, bilateral; FL, frontal lobe; TL, temporal lobe; -, data was not available.

Letter Fluency Task Results

Only one of the control group participants (C17) did not perform the letter fluency task. The averaged group results for the remaining 19 control participants did not exhibit any significant activation on the task. From Table 3 it can be seen that with the individual results, only 10 of these 19 participants (52.6%) displayed any significant activation as a result of the task. Averaged group results for these 10 participants showed language activation in the left frontal lobe in Broca's area (BA 44, 47; see Figure 2 and Table 4). Individually, seven of the participants (36.6%) exhibited left frontal activation, including Broca's area (BA 6, 9, 10, 32, 45, & 46), and five (26.3%) demonstrated some activation (sometimes bilateral) in the temporal lobes, specifically, BA 20, 21, 22, 39, and medial areas including the insula, papahippocampal gyrus, and thalamus. In three cases (C15, C18, & C20) (15.8%), there was left anterior temporal lobe activation. For two of the participants, temporal activation was accompanied with frontal activation. (See Tables 13 - 32 & Figures 8 – 27 in Appendix H for further details).

Table 4

Letter fluency results for the group of 10 control participants showing activation.

Localisation	Cluster Size	Z	x	y	z
L IFG BA47	430	4.05	40	28	0
L IFG BA44	291	3.64	52	8	22

Note. Local maxima in MNI coordinates. Only the local maxima with highest Z score in each cluster are provided in the table. Cluster size is in voxels. When the cluster encompasses more than one anatomical location, the localization given corresponds to the local maxima with the highest Z score. L, left; IFG, inferior frontal gyrus.

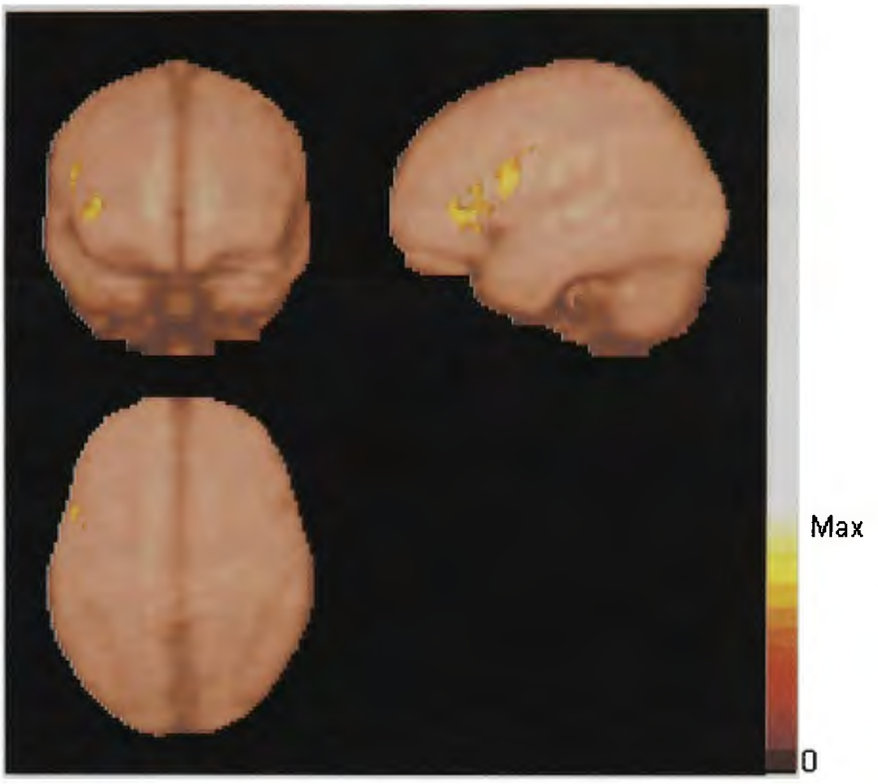


Figure 2. Letter fluency task results for the group of 10 control participants who showed activation overlaid on a 3D anatomical image. Activation is observed in the left frontal lobe in Broca's area (BA 44, 47). (Darker colours correspond to lower *Z* scores).

Category Fluency Task Results

The averaged group results for the 20 control participants who undertook the category fluency task did not exhibit any significant activation. From Table 3 it can be seen that with the individual results, only 10 of these participants (50%) displayed any significant activation as a result of the task. Averaged group results for these 10 participants showed language activation in the left frontal lobe in Broca's area (BA 47) (see Figure 3 and Table 5). Individually, five of the participants (25.0%) demonstrated activation (mostly bilateral) in the temporal lobes (BA 20, 21, 22, 39, 41), some of which was in the medial parts of the lobes. There was no anterior temporal lobe activation. Eight participants (40.0%) exhibited frontal activation in the inferior and middle frontal

gyrus (BA 9). While frontal activation was predominantly in the left hemisphere, two participants showed bilateral activation. The left thalamus was activated in three participants and the left lentiform nucleus in one. (See Tables 13 - 32 & Figures 8 – 27 in Appendix H for further details.)

Table 5

Category fluency results for the group of 10 control participants showing activation.

Localisation	Cluster Size	Z	x	y	z
L IFG BA47	937	4.22	46	22	2

Note. Local maxima in MNI coordinates. Only the local maxima with highest Z score in each cluster are provided in the table. Cluster size is in voxels. When the cluster encompasses more than one anatomical location, the localization given corresponds to the local maxima with the highest Z score. L, left; IFG, inferior frontal gyrus.

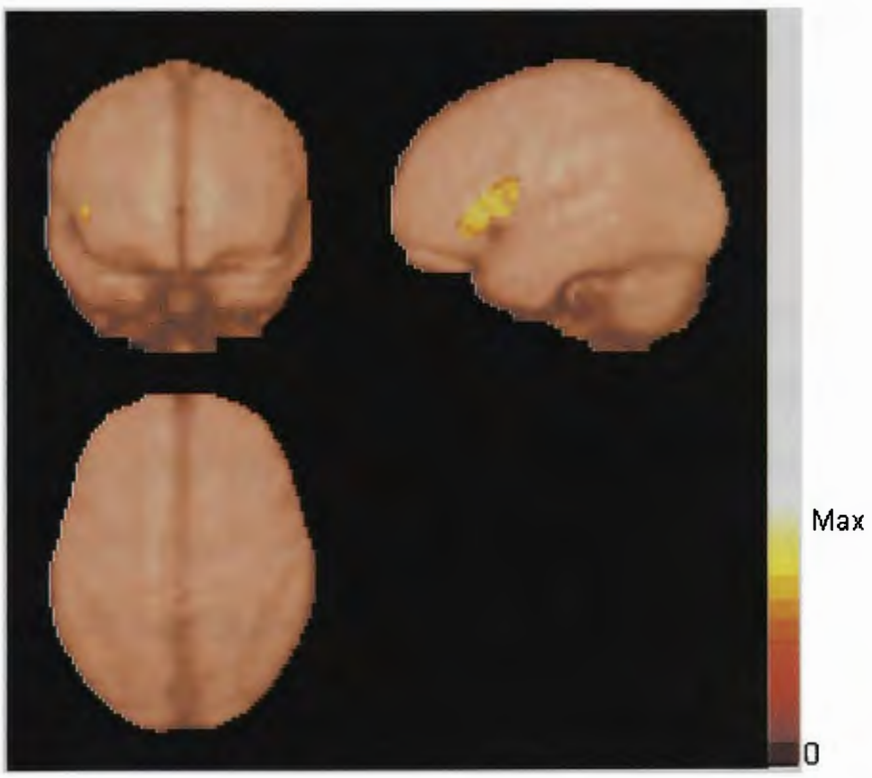


Figure 3. Category fluency for the group of 10 control participants who showed activation overlaid on a 3D anatomical image. Activation is observed in the left frontal lobe in Broca's area (BA 47). (Dark colours correspond to lower Z scores).

Picture Naming Task Results

The averaged group results for the 19 control participants who completed the picture-naming task did not exhibit any significant activation. With the individual results, only seven of the participants (36.8%) displayed any significant activation as a result of the task (see Table 3). Averaged group results for these seven participants showed no significant language activation. Individually, five participants (26.3%) showed activation in the right and left temporal lobes. In three cases (15.8%) the temporal activation was in the temporal poles, bilateral in two cases, right in one. Bilateral activation in the fusiform gyrus was noted in three cases (C4, C6, & C12). Two participants (10.5%) exhibited left frontal activation, and another exhibited right occipital lobe activation. (See Tables 13 - 32 & Figures 8 – 27 in Appendix H for further details.)

Sentence Completion Task Results

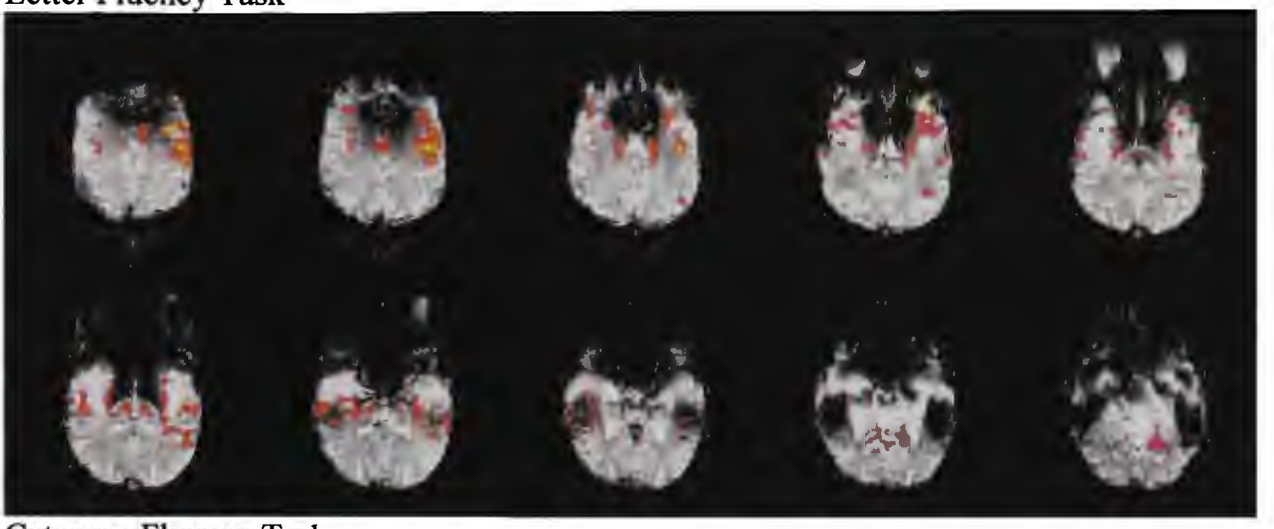
The averaged group results for the 20 control participants who underwent the sentence completion task did not exhibit any significant activation. However, analysis of individual results showed that 19 of the participants (95.0%) displayed significant activation as a result of the task (see Table 3). Temporal lobe activation was noted in 15 of the participants (78.9%), lateralised to the left in 12 cases and near Wernicke's area. Anterior temporal lobe activation was observed in four cases (21.1%), predominantly in the left, but in one case, bilaterally. Eleven participants (57.9%) exhibited left frontal lobe activation (BA 9, 44, 45, 46, &47), with two of these participants exhibiting bilateral frontal activation. Other areas of activation included the precentral gyrus, parietal lobe,

occipital lobes, and thalamus. (See Tables 13 - 32 & Figures 8 – 27 in Appendix H for further details.)

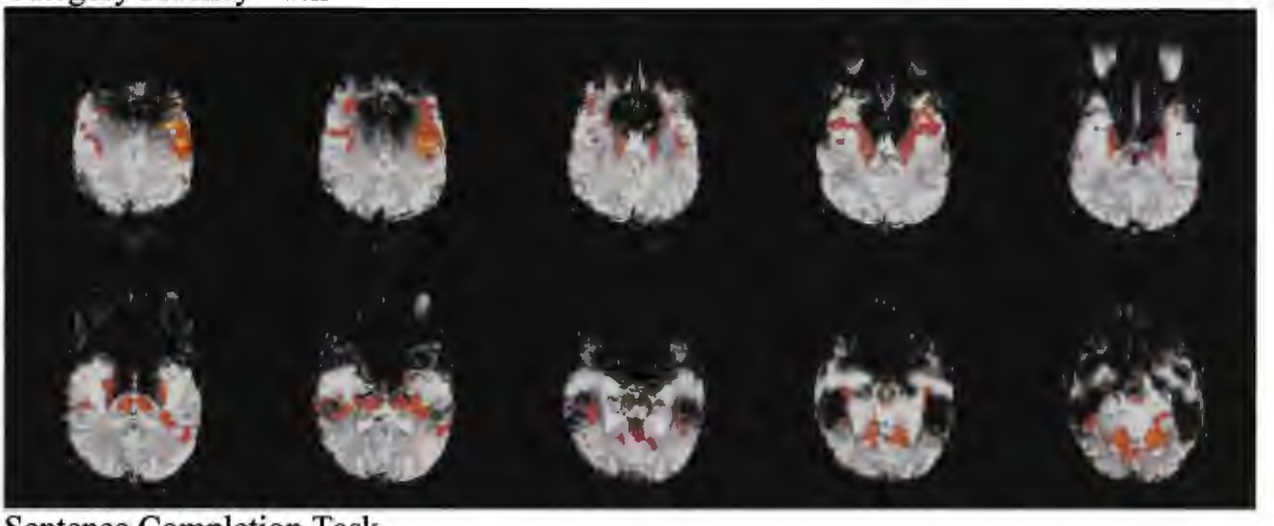
Overlapping Activation Areas between Tasks

None of the tasks showed significant activation for the group of participants analysed as a whole. In total, 15 of the participants (75.0%) showed significant activation on more than one task. Of these 15, nine participants showed overlapping areas of activation on at least two of the four language tasks (see Figure 4 for an example). Seven of these participants showed overlapping activation in the left frontal lobes (C5, C6, C9, C11, C15, C16, & C18). This group of seven normal control participants included four of the five participants who had significant activation with both the letter and category fluency tasks (C5, C6, C11, & C15). Other areas of overlapping activation with the nine participants were in the temporal lobe (C6, C10, C11, & C15), often bilaterally along the temporal lobe and in Wernicke's area on the left, and in the thalamus (C14).

Letter Fluency Task



Category Fluency Task



Sentence Completion Task

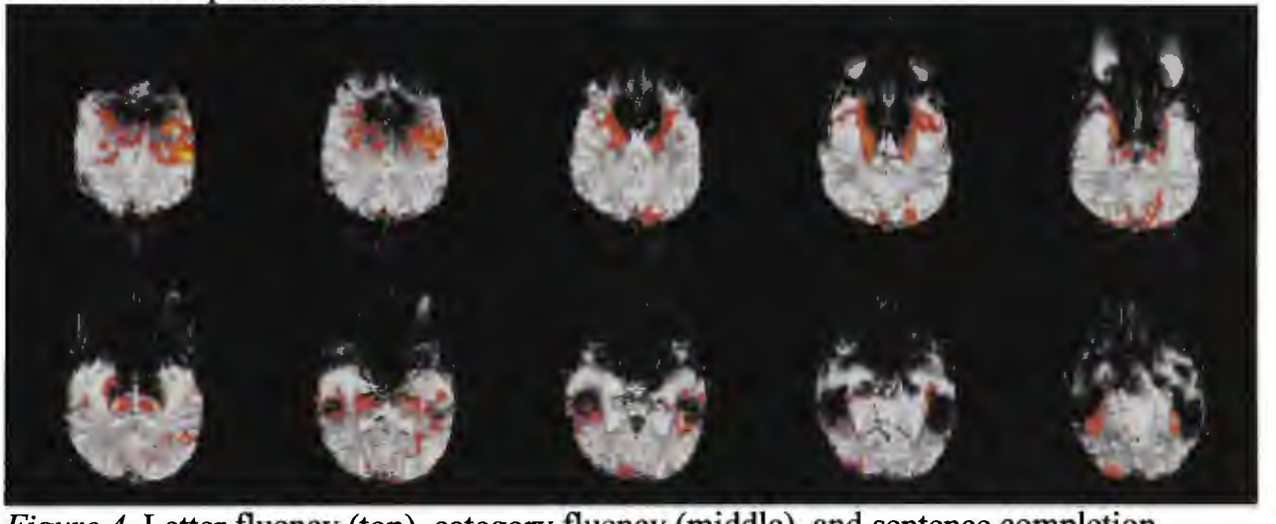


Figure 4. Letter fluency (top), category fluency (middle), and sentence completion (bottom) fMRI activation on axial slices for participant C15. Images are shown in radiological convention: the left hemisphere is displayed on the right side of the image.

Results for Patients with Epilepsy in Group A on Original Language Tasks

Table 6 shows that for the 10 patients in group A who completed the letter fluency task, only three (30.0%) displayed any significant activation in the frontal or temporal lobes. From the 12 patients in group A who completed the category fluency task, only three (16.7%) displayed any significant activation and only two of these showed activation in the temporal or frontal lobes. Only two of the 10 patients in group A who underwent the picture-naming task displayed any significant activation as a result of the task, and this was in the temporal lobe. Ten of the 11 (90.9%) patients in group A displayed significant activation on the task. The sentence completion task resulted in significant anterior temporal lobe activation in 45.5 % of cases, compared to the letter fluency, category fluency, and sentence completion tasks, which showed activation in 10.0%, 8.3%, and 20.0% of cases, respectively.

Table 1 also presents areas of overlapping activation between tasks for patients. Overlapping activation was seen with six patients (50.0%), in the anterior temporal lobe (A1 & A2), frontal lobe (A2, A3, A9, & A11), and hippocampal gyrus (A7). In all of these cases where there were two tasks showing overlapping activation, the sentence completion task was one of the tasks. In cases where participants did not show any activation, no significant overlapping activation was seen with any of the tasks for the patient, or only one task showed activation for the patient. These results suggest that when there were multiple tasks showing activation, overlapping activation in language related areas was observed. (See Figures 28 - 38 & Tables 33 – 44 in Appendix I for further details.)

Table 6

Areas activated by the original tasks in the 12 patients in group A.

	Frequency	A1	A2	A3	A4	A5	A6	A7	A8	A9	A10	A11	A12
Letter Fluency													
Any Activation	30.0% (n=10)												
FL / TL Activation	30.0%												
FL	30.0%		R	L	-					L		-	
Middle/Posterior TL	0.0%				-							-	
Anterior TL	10.0%		R		-							-	
Other	0.0%				-							-	
Category Fluency													
Any Activation	25.0% (n=12)												
FL / TL Activation	16.7%												
FL	16.7%			L								R	
Middle/Posterior TL	8.3%											L	
Anterior TL	8.3%											B	
Other	8.3%							R					
Picture Naming													
Any Activation	20.0% (n=10)												
FL / TL Activation	20.0%												
FL	0.0%			-					-				
Middle/Posterior TL	10.0%			-			L		-				
Anterior TL	20.0%	B		-			B		-				
Other	0.0%			-					-				
Sentence Completion													
Any Activation	90.9% (n=11)												
FL / TL Activation	90.9%												
FL	63.6%	L	R	L		L	-	L		L		B	
Middle/Posterior TL	72.7%	B	R			L	-	B	L	B	L		L
Anterior TL	36.3%	B	B				-	L	L				
Other	63.6%	L	R	L		L	-	B				B	B

Note. L, left; R, right; B, bilateral; FL, frontal lobe; TL, temporal lobe; -, data was not available.

Results for Patients with Epilepsy in Group B on Original Language Tasks

As shown in Table 7, all six patients in group B displayed significant letter fluency task activation in the frontal lobes, and four of these patients (67.7%) showed additional activation in the temporal lobes. Anterior temporal lobe activation was noted in one case (16.7%). From the four patients in group B who completed the category fluency task, all displayed significant activation in the temporal and frontal lobes. Anterior temporal lobe activation was noted in one case (16.7%). Five of the six patients (83.3%) in group B displayed significant activation in the frontal and temporal lobes on the picture-naming task. Anterior temporal lobe activation was noted in four cases (66.7%). All of the patients in group A showed significant activation in the frontal and temporal lobes from the sentence completion task. Anterior temporal lobe activation was noted in four cases (66.7%). The results for each individual patient in group A on the battery of tasks in the SVHM language battery are presented in an attempt to identify how well the battery identifies language areas in the frontal and temporal lobe, specifically in anterior temporal pole, and to present any overlapping activation between tasks (See Figures 39 – 50 & Tables 45 – 50 in Appendix I for further details.)

From Table 2 overlapping activation was seen with all six patients, including the frontal lobe, near Broca's area (all patients), temporal lobe, near Wernicke's area (B1, B2, B3, & B5), anterior temporal lobe (B5), and precentral gyrus (B6). The sentence completion task was often one of the tasks showing the overlapping activation. In some cases all four tasks demonstrated the same areas of overlapping activity (B1, B2, B3, & B6). For both groups of patients it is noted from Tables 1 and 2 that changes in language ability were only recorded in two cases (A6 & A10).

Table 7

Areas activated by the original tasks in the 6 patients in group B.

	Frequency	1	2	3	4	5	6
Letter Fluency							
Any Activation	100.0% (*n*=6)						
FL / TL Activation	100.0%						
FL	100.0%	B	B	L	B	B	B
Middle/Posterior TL	66.7%	B	B		B		B
Anterior TL	16.7%		B				
Other	66.7%	B	B		B		B
Category Fluency							
Any Activation	100.0% (*n*=4)						
FL / TL Activation	100.0%						
FL	100.0%	B	-	-	B	B	B
Middle/Posterior TL	100.0%	L	-	-	R	R	B
Anterior TL	25.0%		-	-			B
Other	75.0%	B	-	-	B	B	
Picture Naming							
Any Activation	100.0% (*n*=6)						
FL / TL Activation	83.3%						
FL	83.3%	B	B		B	B	L
Middle/Posterior TL	66.7%		B		B	R	L
Anterior TL	66.7%		L		L	R	L
Other	83.3%		B	L	B	B	L
Sentence Completion							
Any Activation	100.0% (*n*=6)						
FL / TL Activation	100.0%						
FL	100.0%	B	B	L	B	B	B
Middle/Posterior TL	100.0%	B	B	B	B	R	L
Anterior TL	66.7%	B	B		R	B	
Other	100.0%	B	B	B	B	B	B

Note. L, left; R, right; B, bilateral; FL, frontal lobe; TL, temporal lobe; -, data was not available.

Discussion

Utility of Original SVHM Language Battery in Identifying Language Areas with Healthy Controls

Comparison of Verbal Fluency Tasks

From the first hypothesis, it was expected that the category and letter fluency tasks would consistently show significant activation in the frontal and temporal lobes. The expected frontal and temporal activation was produced in only 47.4% to 50.0% of normal control participants for these two tasks. Therefore, in their present format and as used on the older MRI scanner, the verbal fluency tasks do not consistently activate frontal or temporal language areas of the cortex. Nonetheless, when activation was observed, the left frontal lobe was consistently activated. However, despite the limited number of normal control participants who showed activation for both verbal fluency tasks, significant activation was consistently lateralised to the left hemisphere, and identified more in the left frontal lobe than in the temporal lobes. The strong lateralising ability of the verbal fluency tasks from frontal lobe activation is in keeping with previous research (Deblaere et al., 2002; Herholz et al., 1996; Hertz-Pannier et al., 1997; Lehericy et al., 2000; Spreer et al., 2001; van der Kallen et al., 1998; Yetkin et al., 1998). For both verbal fluency tasks, the left thalamus was also an area of noted activation, consisted with previous research comparing both tasks (Paulesu et al., 1997).

From the second hypothesis, it was expected that, in healthy controls, the category fluency task would activate more language areas in the temporal lobe than the letter verbal fluency task. To aid in the comparison of the two verbal fluency tasks, and to also

allow for the comparison of the current group results with other studies, an analysis of results for group C for each task was undertaken. However, the averaged group results did not show any significant activation due to the lack of consistent activation from the tasks. This gives further support to the finding that the phonemic and verbal fluency tasks, in their present format when used on the older MRI scanner, do not consistently activate frontal and temporal language areas in healthy people.

Not surprisingly, when normal control participants without significant activation were excluded from group analysis, significant averaged group activations were seen. These were near the anterior triangular portion of the left inferior frontal lobe (BA 47) for both tasks, and near the posterior opercular portion of the left inferior frontal gyrus (BA 44) for the letter fluency task. These findings are consistent with previous research comparing these two types of tasks (Paulesu et al., 1997). However, previous research (Paulesu et al., 1997) has also reported activation in the left retrosplenial region for the semantic fluency task, and this was not identified in the current study. Because participants not demonstrating activation were excluded from this analysis, these results need to be interpreted with caution, and only serve in helping to identify weaknesses with the protocols sensitivity.

One of the main differences between the verbal fluency tasks used in the original SVHM battery and those used by Paulesu et al. is the type of control condition used. Paulesu et al. used a resting state, whereas the control condition in the original SVHM verbal fluency fMRI tasks had the participant view Japanese Kanji characters. The Kanji characters were expected to serve as an appropriate control condition, unless the participant understood the Kanji characters, as this would introduce language processing

during this part of the task. The use of an active control condition, as used in the SVHM tasks, rather than a resting state, has been recommended (Bavelier et al., 1997; Binder et al., 1996; Carpentier et al., 2001), as it ensures some experimental control over mental activities during the control period of the task. In contrast, with a resting-state type control period, an unknown variety of mental activities occur when "resting". Also, control tasks, if similar to the experimental task, can allow subtraction of cognitive processes not of interest (e.g., visual processing) (e.g., Bavelier et al., 1997).

Picture Naming Task

From the first hypothesis, it was expected that the picture-naming task would consistently show significant activation in the frontal and temporal lobes. In its present format, the picture-naming task did not consistently activate frontal or temporal language areas, as activation in the frontal and temporal lobe was only found in 36.8% of cases. From the fourth hypothesis, it was expected that the picture-naming task would consistently show significant activation in the anterior temporal lobe. Anterior temporal pole activation was only produced in 15.8% of cases.

Although the picture-naming task did not exhibit consistent significant activation, when activation was observed, more significant activation was produced bilaterally in the temporal lobes (26.3%) than in the frontal lobes (10.5%). The bilateral temporal activation from the task is consistent with other picture naming tasks (Benson et al., 1999; Deblaere et al., 2002). Some of this activation was in the medial temporal (fusiform and parahippocampal gyri), which is also consistent with previous research (Benson et al., 1999; Deblaere et al., 2002; Spitzer et al., 1995). The bilateral activation

has also been observed by others, and it has been proposed that it could be due to the involvement of bilateral memory-encoding processes (Deblaere et al., 2002). The lack of any significant activation for the average group results (even when excluding participants demonstrating no activations), together with the limited number of participants who individually showed activation, give further support to the finding that the picture-naming task, when used in the original SVHM language battery with the old MRI scanner, does not consistently identify language areas in the frontal and temporal lobes.

Sentence Completion Task

Compared to the other three original SVHM language tasks, the sentence completion task demonstrated the most consistent significant activation, with 95% of healthy controls demonstrating significant activation. From the first and third hypotheses, it was expected that the sentence completion task would consistently show significant activation in the frontal and temporal lobes, particularly in the anterior temporal lobe. Temporal or frontal lobe activation was observed in 90% of cases, indicating consistent involvement of these areas in the task. Temporal lobe activations were the most consistent, with 75.0% of the participants exhibiting activation in this area. In most cases activity was located in the left hemisphere, near Wernicke's area. Anterior temporal lobe activation was not as consistent as expected, with only 21.1% participants exhibiting any activation in the area. Frontal activation was demonstrated in 57.9% of cases and there was also some involvement of precentral gyrus, parietal lobe, occipital lobe, and thalamus. The averaged group results did not demonstrate any significant areas of activation. The activity identified in individual controls and patients, particularly in the

temporal and frontal lobes near Broca's and Wernicke's areas, is consistent with previous research using fMRI semantic decision tasks (Binder et al., 1997; Deblaere et al., 2002; Sabsevitz et al., 2003) and reading tasks (Bavelier et al., 1997; Deblaere et al., 2002).

Overlapping Activations

One of the suggested benefits of using a battery of tasks is that the overlapping of results of the different language tests allows for more confident identification of critical language sites (Deblaere et al., 2002). From the results it was noted that 45.0% of participants in the control group showed overlapping areas of activation. Overlapping activation was seen in the left frontal lobe (mainly from both the verbal fluency tasks), bilaterally in the temporal lobes, in Wernicke's area, and in the thalamus.

It is likely that the activation in the thalamus was language related. The role of the thalamus with language function has been suggested by errors from patients with thalamic aphasia (Cappa & Vignolo, 1979; Crosson, 1994). Crosson (1994; 1999) suggested that the role of the thalamus, under guidance from the frontal cortex, is in the selective engagement of cortical mechanisms necessary to perform language tasks. In other words, specific thalamic structures are part of an attentional system that is involved in lexical retrieval. For example, using fMRI Crossen (1994) found that when neurologically normal participants generated words using a semantically based cue (category) as apposed to generating nonsense syllable generation, three left hemisphere structures were consistently activated; the pre- SMA, the dorsolateral caudate nucleus, and the ventral anterior thalamus.

Utility of Original SVHM Language Battery in Identifying Language Areas with Epilepsy Patients

Results for the patients in group A with the four original language tasks were similar to those in the control group. Specifically, the sentence completion task demonstrated consistent significant activation (90.9%) and the letter fluency, category fluency, and picture-naming tasks did not, with activation produced in 20 to 30% of cases for these tasks. There was only one patient (patient A4) who did not exhibit any activation with the sentence completion task. This patient also failed to show activation on any of the other three tasks, making him the only patient to not produce any significant activation from the battery of language tasks. There was no obvious reason (e.g., not engaging with the task, falling asleep, high levels of motion, etc.) to why the patient did not show any activation from any of the language tasks.

The most anterior temporal lobe activation was observed with the sentence completion task (36.3%). Language activations were observed near lesion sites in some patients (e.g., A1, A2, A8, & A10). On the original battery of language tasks, eight patients had language in the left hemisphere, one had language in the right (A2), one had possible bilateral language activation (A11), and results were inconclusive for the patient with no activation (A4).

Significant results for the patients in group B with the four original language tasks were more consistent than for the control group and patients in group A. Specifically, all of the patients showed significant language activation for all tasks attempted. The most anterior temporal lobe activation was observed with the picture naming (66.7%) and sentence completion tasks (66.7%). Frontal and temporal language sites (particularly

Broca's and Wernicke's area) were identifiable in all cases using the language battery and useful language activations were observed near lesion sites in some patients.

Summary and Interpretation

In summary, support for the first hypothesis that the original language tasks would consistently result in activations in the frontal and temporal lobes, was only found for the sentence completion task for both healthy controls and patients in group A. In contrast, patients in group B showed more consistent activation on all four of the language tasks.

The most parsimonious reason for the difference in activations between the two patient groups who underwent the original language battery involves a change in the quality of the fMRI data acquisition. The data for group B was obtained on a newer fMRI machine, which allowed for a larger area of the brain to be scanned with 25 slices. In comparison, data from group A and the control group was obtained on the older MRI scanner, which scanned a smaller area with only 10 slices. One of the problems to occur from epilepsy studies conducted using 1.5 Tesla clinical MRI scanners is that some of the brain regions of the most interest in epilepsy patients, such as the inferior frontal lobes and medial temporal lobes are subject to geometric distortions and signal loss during fMRI acquisition (Jezzard & Clare, 1999). This can result in reduced sensitivity and anatomical uncertainties when interpreting images. It is likely that this occurred in the current study with the 10-slice fMRI data obtained on the older MRI scanner. It has been suggested that the use of thin slice acquisitions may ameliorate these problems and improve fMRI quality (Powell & Duncan, 2005), thus providing a plausible explanation

for the increased frequency of activations seen with the newer MRI scanner. However, this explanation could not be confirmed, as there was no data from healthy controls with the original language tasks on the newer MRI scanner with which to compare.

Other possible reasons for the inconsistent activation with the verbal fluency and picture naming tasks for the control group and patients in group A could be due to the construction of the protocols, method of data analysis or differences between patients. However, problems with protocol construction are not likely, because very similar verbal fluency tasks protocols have repeatedly been shown to consistently show activation by other researchers. Although the tasks did not showing consistent activation, activation was in the areas expected. Additionally, all four tasks produced consistent and expected activation when fMRI data was acquired on the new MRI scanner with a larger number or slices. Another possible weakness with the task construction was with the use of Kanji characters in the control condition, however, Kanji characters were used in the control condition in all four tasks including the sentence completion task, which showed consistent significant activation, and the other tasks, while not showing consistent activation, showed activation in the expected regions. Also, all four tasks produced consistent and expected activation when fMRI data was acquired on the new MRI scanner with a larger number or slices.

It does not appear that there were any problems with the use of FSL to analyse the fMRI data because significant consistent activation was observed for one of the four tasks, and the results from the other tasks were in keeping with previous research. Also, FSL analysis on all four tasks showed activation when fMRI data was acquired on the new MRI scanner with a larger number or slices.

Differences between the letter and category fluency tasks could not be determined due to the lack of consistent significant activation for the tasks. While the verbal fluency tasks did not show consistent activation, particularly in the temporal lobe for the category fluency task, there was a trend for both tasks to lead to lateralised activation in the left frontal lobes, as expected.

The sentence completion task and the picture-naming task were expected to show consistent activation in the anterior temporal lobe. Compared to the verbal fluency tasks, the picture naming and sentence completion tasks tended to provide more activation in the temporal lobes, and near the anterior temporal lobe, than the frontal cortex. However, neither task showed high levels of consistent activation in the anterior temporal lobe for the control group and patients in group A (between 14.8% - 36.3% for both tasks). In contrast, patients in group B did show higher levels of consistent activation in the anterior temporal lobe for the picture naming and sentence completion tasks (66.7% for both tasks). Again, possibly due to the fMRI imaging occurring on a newer scanner with improved imaging acquisition parameters.

Overall, when the tasks are used together, language sites in the anterior temporal lobe were identified in 40.0% of the healthy controls, 50.0% of patients with epilepsy in group A, and 83.3% of patients in group B, sometimes confirmed from multiple tasks. While the entire language system for each participant and patient in group A was not consistently identified, some of the language network was found in the majority of cases. It therefore appears that in its current format, as used with the older MRI scanner, the battery is useful in some cases. However, there were cases where no information about language function was obtained at all, even with the epilepsy patients in group A. While

the battery is useful and worth conducting on epilepsy patients presurgically, there is marked room for improvement. Such improvements were observed when the tasks were used on patients on a newer MRI scanner and where fMRI scans covered a larger area and included more slices. For these patients in group B, the identification of the language system, particularly classic language areas, such a Broca's and Wernicke's area, were identifiable and confirmable from activations from multiple tasks in all cases.

CHAPTER THREE – TESTING OF TWO NEW FMRI LANGUAGE TASKS

Introduction

This chapter investigates the utility of a reading task and a new semantic decision task in detecting frontal and temporal language areas, particularly in the anterior temporal pole. Following on from the first part of the study, where the utility of the current SVHM language battery was evaluated, the second part of the study was intended to improve upon the SVHM battery of fMRI language tasks by developing, piloting, and testing two new language tasks; a new semantic decision-making task and a reading task. The tasks were administered to healthy controls and patients with epilepsy on the new MRI scanner at SVHM.

New Language Paradigms

New Reading Task

Bavelier and colleagues (1997) used a 4.0 Tesla MRI scanner to evaluate a block design reading task that consisted of sentence reading and viewing consonant strings. The advantage of such a task is with its use of relatively natural stimuli. When designing task paradigms for use with epilepsy patients, it is important to use tasks that patients are able to perform (Powell & Duncan, 2005). Sentence reading has been acknowledged to invoke many of the different aspects of language processing (orthography, phonology, syntax, semantics, and verbal short-term memory) as well as basic visual recognition routines (Bavelier et al., 1997). In contrast, the presentation of consonant strings is believed to activate basic visual recognition routines similar to those triggered during the recognition of visual shapes. Bavelier et al. suggest that by comparing sentence reading with

consonant string reading, brain activation due to language processing can be observed, as orthographic coding, short term memory processes, and visual recognition routines of visual shapes can be removed. (Bavelier et al., 1997). From their study, the individual results indicated focal and variable activation across participants. While activations were distributed throughout the left hemisphere of the brain, they were not restricted to the classical language areas (i.e., Wernicke's area, Broca's area, and the angular gyral region). The other areas activated included the left prefrontal cortex (including the dorsolateral prefrontal cortex), the left anterior temporal lobe, and the inferior portion of the precentral sulcus (an area near to, but separate from Broca's area). While participants were required to read silently, the activation in the precentral sulcus may correspond to the motor planning of articulation movements. In Wernicke's area, the most robust activation came in the superior temporal sulcus, and more diffuse and variable activation near the supramarginal gyrus. Activation was also noted in the angular gyrus, in keeping with the area's role in written language comprehension, and in the anterior and middle portion of the superior temporal gyrus. While activation was more robust in the left hemisphere, activation was also observed in the middle of the right superior temporal gyrus.

The current study developed a reading task based upon the one described by Bavelier and colleagues (1997), to determine if the task can demonstrate similar areas of activation on a 1.5 tesla MRI scanner. It was expected that such a task would show consistent frontal and temporal activation, particularly in the anterior temporal pole (see Hypothesis 4, page 84). In addition, as it is a natural language-based task, it is expected that neurologically impaired patients should be able to perform it easily. Bavelier and

colleagues used the reading task with a population of healthy controls. The ability of this task to activate language regions in patients with epilepsy has not been reported elsewhere. Using such a reading task with epilepsy patients and on a less sensitive MRI machine (1.5 tesla) would be of clinical importance as it would identify if such a reading task could easily be performed by patients with epilepsy and would also show if consistent frontal and temporal lobe language areas, particularly in the anterior temporal lobe could be identified prior to surgery.

New Semantic Decision Task

A new semantic decision task, based upon the task employed by Deblaere (2002) was developed and evaluated. Deblaere (2002) used a semantic decision task that was shown to activate the anterior temporal lobe. Activation from this task in the anterior temporal lobe was reported from healthy participants. It was expected that consistent frontal and temporal activation, particularly in the anterior temporal pole, would be replicated in the current study, in both healthy participants and patients with epilepsy (see Hypotheses 4).

Hypothesis

(4) The reading and new semantic decision tasks were expected to show consistent significant activation in both the frontal and temporal lobes, including the anterior temporal lobe, in healthy controls and patients with epilepsy.

Method

Participants

A new data sample, consisting of healthy controls and patients with epilepsy, was obtained to investigate the utility of two new fMRI language tasks, a semantic decision task and a reading task. Informed consent was obtained for the new control (NC) group consisting of 11 healthy participants who were associates of the student researcher, and six additional epilepsy patients, over the age of 18 years, admitted to SVHM for presurgical evaluation. The NC group consisted of five males and six females with a mean age of 29.5 years (*SD* = 5.15 years; range 23 - 42 years). The new patient (NP) group consisted of two males and four females with a mean age of 37.67 years (*SD* = 10.31 years; range 26 – 55 years). In Table 8 the seizure type and pathology location for each patient in the NP group are provided along with histological and surgical outcome data, where available. Four patients had been diagnosed with left TLE, one with right TLE, and one with partial epilepsy of right occipital lobe origin. Previous research has demonstrated that small sample sizes (n = 5 - 10) are adequate for fMRI activation using tasks similar to those used in the current study, as described below (Tsukiura et al., 2002). The NC group was used to pilot and evaluate the efficacy of the new fMRI protocols prior to their use with epilepsy patients. One of the 11 new control participants was used for the initial piloting of the two new language tasks, and to aid in allowing for familiarisation of collecting fMRI data. From this pilot test it was noted that there were slight timing problems with the presentation of the stimuli and fMRI acquisition. As a result, the presentation software used to present the stimuli was changed for the 10 new

control participants (see materials section below for further details).

All participants were right-handed and screened to rule out a history of neurological or psychiatric disorders, head trauma, substance abuse, and other serious medical conditions. Participant handedness was determined by the Edinburgh inventory, a self-report questionnaire assessing handedness (Oldfield, 1971) (see Appendix A).

Materials

Functional MRI Image Acquisition

The new fMRI paradigms for both the patients and healthy participants were performed at SVHM, but on the new Magnetom Avanto 1.5 Tesla MRI scanner with EPI capabilities, mentioned in chapter two.

Table 8

Details of patients in group NP.

Patient	Seizure Type & Pathology Location	Overlapping Activation	Brief Histology	Outcomes
NP1	11-year history of left temporal lobe epilepsy	Overlapping activation anterior temporal lobes and left frontal lobe	A specimen of neocortex was judged by a pathologist to show no abnormalities, however, hippocampal sclerosis was confirmed with very severe loss of neurons (>80%) and glosis from a specimen of hippocampus.	Left temporal lobectomy experienced mild word retrieval difficulties involving semantic and phonemic paraphasias and word fluency difficulties, as acknowledged from family and friends. Patient unaware of errors.
NP2	20-year history of left TLE. MRI was normal but an EEG study indicated left temporal lobe complex partial seizures.	Overlapping activation in the left temporal lobe	N/A	Left temporal lobectomy
NP3	10-year history of left TLE. Hippocampal sclerosis in the left temporal lobe was suggested from MRI and PET studies.	No	N/A	Left temporal lobectomy
NP4	Complex partial epilepsy. A SPECT study demonstrated a left temporal ictal focus	No	N/A	N/A
NP5	Epilepsy of probable right frontotemporal origin. MRI identified focal signal abnormality involving the white matter core of the right superior temporal gyrus.	No	N/A	N/A
NP6	Longstanding history of refractory complex partial seizures. MRI showed an unusual lesion in the inferior right occipital lobe consistent with small vessel ischaemia. SPECT brain studies suggested this area as the ictal focus.	No	N/A	N/A

Note: N/A, not available.

Stimuli and Instructions for New fMRI Activation Tasks

The two new fMRI language tasks were presented in the same block design as the original tasks, with the target and control conditions being presented for 45 seconds each, alternated in presentation, and repeated three times. Each task was therefore presented for a total of 270 seconds. Verbal instructions for each task were explained to participants before the beginning of each task while they lay in the MRI scanner, followed by the visual presentation of the same instructions along with practice items. Visual stimuli were presented in the same manner as describe for the original fMRI tasks with the exception of the presentation software. As mentioned earlier, it was noted from the pilot control participant that the Microsoft PowerPoint (MicrosoftCorporation, 2000) presentation software was not accurate enough, as the speed of presentation varied on different computers and was not timed accurately with the acquisitions. The software used to replace Microsoft PowerPoint for fMRI stimulus presentation was the FMRIB Enhanced Stimulation Tool (FEST) (de Jong, 2000). A possible future benefit of the software is the ability to link the FEST program up directly with the MRI machine so that the scanner can pace the experiment, thus ensuring visual presentations are synchronised with acquisition scans, and it also allows for button presses to be recorded, thus allowing for the recording of participant responses and reaction times. These additional features were not utilised in the current experiment due to the prohibitive cost of a response button and the unavailability of hardware to link the laptop with the MRI console. The FEST software was only used to allow for accurate timing of the stimulus. The tasks are now described in the order in which they were presented to the participants.

Reading task. The covert reading task had two conditions: reading meaningful text

(sentences, the experimental condition) and reading nonsense text (consonant strings, the control condition). The participant was asked to covertly read short declarative English sentences that appeared one word at a time for 45 seconds. A total of eight sentences were presented in each block, and each sentence was between four and nine words long, with a mean length of 6.5 words. Each word was presented for 400 msec with the presentation of a blank screen for 200 msec before the next word in the sentence was presented. At the end of each sentence there was a one-second presentation of a blank screen before the first word of the next sentence was presented. The first letter of the first word in each sentence was capitalised and each sentence ended with a full stop.

The control task involved the presentation of consonant strings one at a time for 45 seconds. The timing of the presentation and the order and length of the consonant strings was identical to the words in the sentences in the previous sentence reading block. For example, for the first sentence "Emma eats carrots every morning", the corresponding strings of consonants in the following block was "Jkyr nbvf zxswdpf swdhj kphznsd." Capitalised consonants, full stops and one second breaks between consonant strings also appeared and corresponded with where they would have appeared in the sentences in the previous sentence-reading block. This task is based on reading tasks described by Bavelier et al. (1997) and Deblaere et al. (2002).

The instructions, presented on the display and explained to the patient before the task began were; "For the first part of this task you will read some sentences. Each sentence will be presented one word at a time. Please read each sentence carefully." Participants were then given an example of what to expect. The instructions for the control condition followed; "For the second part of the task you will look at some rows of

letters. These will also be presented one at a time. Please look at each row of letters carefully." Participants were then given an example of what to expect before the task began.

Alternative semantic decision task. This task was based on one described by Deblaere et al. (2002). Patients were presented with the word of an animal or insect and the letters "Y" and "N" appeared at the bottom left and right of the screen respectively. While the participant's hands were resting on their thighs they were asked to lift their left fingers if the animal was a mammal and lift their right fingers if it was not. This allowed for the recording of responses by the experimenter, who observed in the MRI scanner room. In the control condition, participants were presented with a string of nine vowels (e.g., eiaouoeoi) and the letters "Y" and "N". Again, participants were asked to lift their left fingers if the character "a" was in the string, or their right fingers if it was not. A total of 15 animal names or strings of vowels were presented in each block for three seconds each. Eight of the words were mammals and eight of the strings of vowels contained the letter "a". The order in which the 15 words or strings of vowels were presented were randomised. No animal word or vowel string was repeated within or between blocks.

The instructions, presented on the display and explained to the patient before the task began, were: "You will see the name of an animal. You will need to decide if the animal is a MAMMAL or NOT. If it IS a mammal move your LEFT fingers. If it is NOT a mammal move you RIGHT fingers." Participants were then given two examples to practice. The instructions for the control condition followed; "You will see a row of vowels like this 'ieoiaooeei'. You will need to decide if the letter "a" is shown. If there is an "a" move your LEFT fingers. If there is NOT an "a" move your RIGHT fingers."

Participants were given two examples to practice for this control condition. (See Appendix C for further protocol details.)

Data Processing Software

As with the study reported in chapter two, FSL was used to analyse the fMRI data from the new tasks.

Procedures

Ethics approval for the study was obtained from the Victoria University and SVHM Human Research Ethics Committees (see Appendix D). All participants gave informed consent for their participation (see Appendix E & F for participant information and consent forms). All of the participants were given the standard Medical Imaging MRI information sheet (see Appendix G) and were interviewed by the MRI unit staff. As before, reasons for control participant exclusion from the study included implanted pacemaker or metal filings, left-handedness, history of neurological or psychiatric disorders, head trauma, substance abuse, and other serious medical conditions.

All participants initially underwent an anatomical T1 MRI volume of the head, followed by the fMRI language tasks. The test operator entered the MRI chamber at the beginning of each task to verbally explain the next test and present the instructions visually along with practice and example stimuli. All participants lay in the supine position with their head held in place with foam to prevent movement. A vitamin E tablet was taped to the right of each participant's head so that left-right orientation of the scans was not confused during data analysis.

Data Acquisitions for the Two New Language Tasks

Initially, five temporal lobe scout acquisitions were obtained. For anatomical reference, a high-resolution 3D T1-weighted image of the entire brain was obtained. The imaging parameters were TR = 2,130 ms, TE = 2.93 ms, flip angle of 15°, voxel size = .9375 mm^2 x 1 mm, pixel matrix = 256 x 256, and 256 interleaved slices per volume. Another partial head T1 anatomical volume image consisting of 25 slices was also obtained (TR = 579 ms, TE = 12 ms, flip angle = 70°, voxel size = .859375 mm^2 x 3 mm, slice spacing = 3.75mm, pixel matrix = 192 x 256). This scan covered the same areas of the brain as the fMRI scans would, particularly temporal and frontal lobe areas, and was used for the referencing of the fMRI data. For functional imaging a gradient-echo, T2-weighted echoplanar sequence was used. The images were obtained while patients and normal participants performed the language tasks. For each of the language tasks, 90 volumes were collected, one every three seconds (TR = 3000) and each volume consisted of 25 slices (TE = 51, flip angle = 90°, voxel size = 1.71875 mm^2 x 3 mm, slice spacing = 3.75 mm, pixel matrix = 640 x 640). The time required to completed both the language tasks and obtain the MRI scans took up to 30 minutes.

Preparation and Analysis of New Data

As with the original MRI data described in chapter two, the new data was acquired in the DICOM format and was converted to the Analyze format with the MRIcro software package (Rorden, 2005) so it could be analysed with FSL. Before conversion to the Analyze format, the scans of the data were organised into the following

computer files; scouts for localisation of the temporal lobe (one file), the anatomical T1 MRI head volume (one file) (t1_mpr_ss_tra_1mm), the T1 fMRI ROI set based on the template (one file) (t1_se_tra_25_slice). There were also files for each of the two new tasks; scouts for the fMRI (one file), the fMRI data for the task (90 files, one for each volume) (ep2d-Pace_language_1(2), motion corrected fMRI data (90 files), the intermediate t-maps (60 files), EvaSeries-tTest (one file), and Mean_&_t-maps (one file). These were all 3D image files consisting of 2D slices stacked together. As in chapter two, the ninety 3D fMRI image files for each task were converted into the 4D (3D + time) format so that they could be analysed with FSL. The 25 slice T1 ROI structural images for use in registration were brain-extracted using the BET software before being used in analysis.

Prior to the analysis of the new tasks, the same model (e.g., 45 sec on and off cycle) and pre-statistical processing that was applied to the data, with the addition of slice-timing correction using Fourier-space time-series phase shifting. As each slice of a volume is acquired at slightly different times, slice-timing correction adjusts the data so that it appears that all voxels in a volume were acquired at the same time (Smith, 2004). In addition, the functional images were first registered to the high-resolution structural T1-weighted EPI volume after non-brain structures had been removed (7 DOF and normal search). The high-resolution structural T1-weighted EPI volume was then subsequently registered to the MNI template (12 DOF and normal search), using FLIRT. The DOFs and searches were chosen based on visual inspection of the results using different parameters.

Higher-level statistics were carried out using mixed effects higher-level modeling

and implemented in FLAME. The individual data sets were registered into standard space using FLIRT as described in chapter two. Second-level mixed effects were then carried out using the first-level statistic maps to identify the group average activation for each task. The resulting statistic maps were thresholded using clusters formed by $Z > 2.3$ and then tested with $p < 0.05$. Group averaging of activations was not undertaken with the patient data, given the heterogeneous nature of the sample (i.e., differing types of epilepsy and pathology sites) and because the aim of the study was to investigate on a case by case basis.

Results

Results for Healthy Controls with New Language Tasks

All of the new control participants (n = 11) reported being right handed. This was confirmed by the Edinburgh inventory (Oldfield, 1971), where the mean laterality quotient was 91.1 (SD = 10.5; range 80 - 100). Laterality quotients range from 100 (right handed) to –100 (left handed).

Reading Task Results

The averaged group results of the 11 controls on the reading paradigm showed bilateral language activation in temporal lobe (BA 21, 38) and activation near Wernicke's area (left BA 22) (see Figure 5and Table 9).

Table 9

Reading task results for all control participants.

Localisation	Cluster Size	Z	x	y	z
L STG BA21/38	637	4.16	60	-10	-4
L MTG BA22	452	4.03	66	-46	2
R STG BA21	188	3.64	-52	-6	-12

Note. Local maxima in MNI coordinates. Only the local maxima with highest Z score in each cluster are provided in the table. Cluster size is in voxels. When the cluster encompasses more than one anatomical location, the localization given corresponds to the local maxima with the highest Z score. L, left; R, right; MTG, middle temporal gyrus; STG, superior temporal gyrus.

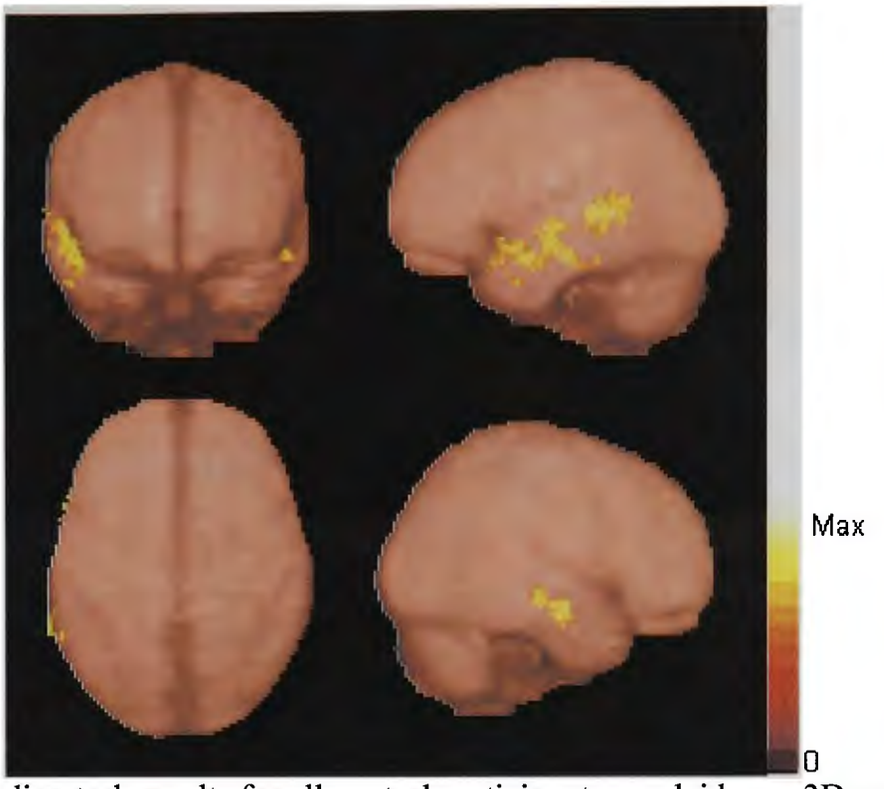


Figure 5. Reading task results for all control participants overlaid on a 3D anatomical image. (Darker colours correspond to lower Z scores).

As seen in Table 10, all 11 of the control participants displayed significant activation as a result of the task (100.0%). Temporal lobe activation was seen in 10 participants (90.0%), predominantly near Wernicke's area (BA 22). This activation was either only in the left hemisphere or bilateral, and extended to the anterior pole in most cases (72.7%). There was also evidence of frontal lobe activation in six participants (54.4%); left in five, and right in one. Other areas of activation were around the central sulcus, left parietal lobe, and cingulate gyrus (see Tables 51 – 61 & Figures 51 – 61 in Appendix J for further details).

Table 10

Areas activated by the reading and semantic decision tasks in 11 controls.

	Frequency	1	2	3	4	5	6	7	8	9	10	11
Reading Task												
Any Activation	100.0% (n=11)											
FL / TL Activation	100.0%											
FL	54.5%			L	L			L	L	R	L	
Middle/Posterior TL	90.9%	L	B	B	B	L	L	B	B	L	L	
Anterior TL	72.7%	L	B	B	B			B	L	B	B	
Other	90.9%		L	B	B	R	R	B	B	B	B	L
Semantic Decision Task												
Any Activation	90.9% (n=11)											
FL / TL Activation	90.9%											
FL	90.9%	B		B	B		B	L	B	L	L	B
Middle/Posterior TL	63.6%	B		L	B	R	L		L			B
Anterior TL	18.2%				B			B				
Other	90.9%	B		B	B	L	B	L	B	B	B	B

Note. L, left; R, right; B, bilateral; FL, frontal lobe; TL, temporal lobe.

Semantic Decision Task Results

The mean accuracy for deciding whether an animal was a mammal or not from the semantic decision task was 97% for 10 of the 11 participants (*SD* = 2.56%; range 94.44 - 100%). The mean for only 10 of the 11 participants is given, because one of the participants (New Control 2 (NC2)) incorrectly made decisions about whether the letter 'a' was present in names of animals, instead of deciding whether the animal was a mammal or not. Data from this participant was excluded from the group analysis. Group results for the 10 participants showed language activation in the left and right frontal gyrus (BA 46, 47), the left and right cingulate gyrus (BA 32), and the left inferior temporal gyrus (BA 20) (see Figure 6, and Table 11).

Table 11

Semantic decision task results for all normal participants (excluding NC2).

Localisation	Cluster Size	Z	x	y	z
L IFG BA46	2452	4.26	54	30	10
R MFG BA46	459	4.11	-46	34	14
R IFG BA47	390	3.78	-30	34	-12
L/R CingG BA32	196	4.26	4	22	36
L ITG BA20	174	3.53	34	-8	-40

Note. Local maxima in MNI coordinates. Only the local maxima with highest Z score in each cluster are provided in the table. Cluster size is in voxels. When the cluster encompasses more than one anatomical location, the localization given corresponds to the local maxima with the highest Z score. L, left; R, right; MFG, middle frontal gyrus; IFG, inferior frontal gyrus; CingG, cingulate gyrus; ITG, inferior temporal gyrus.

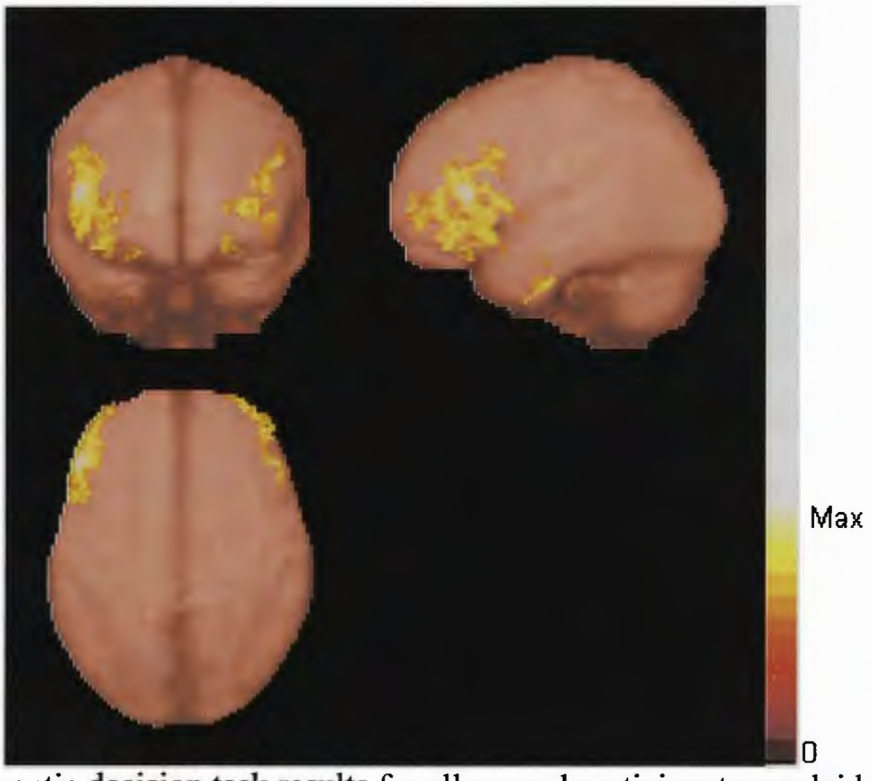


Figure 6. Semantic decision task results for all normal participants overlaid on a 3D anatomical image. (Darker colours correspond to lower Z scores).

With the individual results, 10 of the 11 control participants displayed significant activation as a result of the task (90.0%). The only participant not to show any activation was participant NC2, who performed the experimental condition similarly to the control

condition of the task. As seen in Table 10, individual results were similar to the group results. Eight participants (72.7%) displayed activation in the temporal lobe, often this activation was in the inferior temporal lobe (near BA 20; five cases). Bilateral anterior temporal lobe activation was only seen in 2 cases (18.2%). Frontal lobe activation was seen in 10 participants, near Broca's area (90.9%). In most cases this activation was in the left hemisphere or bilateral. Other areas of activation were around the central sulcus, parietal lobe, and cingulate gyrus (See Tables 51 – 61 & Figures 51 – 61 in Appendix J for further details.)

Overlapping Activation Areas between Tasks

For the group results, neither of the new tasks exhibited much overlap in the language areas they activated, except for the left inferior temporal gyrus. Of the individual participants, seven showed overlapping activation from the two tasks. Overlapping activation was shown in the left posterior temporal lobe (Wernicke's area), the left inferior/anterior temporal lobe, and the left frontal lobe.

Results for Patients with Epilepsy on New Language Tasks

Table 12 shows that for the six patients who undertook the new reading task, all but one (83.3%) displayed significant activation as a result of the task. Five of the six patients (83.3%) who did the animal semantic decision task, also displayed significant activation as a result of the task. Areas of activation for both tasks, specifically in the frontal and temporal lobe, including the anterior temporal lobe, were consistent to those

identified from the NC group. (See Figures 62 – 67 & Tables 62 – 67 in Appendix K for further details.)

Table 12

Areas activated by the reading and semantic decision tasks in 6 patients.

	Frequency	1	2	3	4	5	6
Reading Task							
Any Activation	83.3% (n=6)						
FL / TL Activation	83.3%						
FL	83.3%	B	B		L	B	B
Middle/Posterior TL	83.3%	L	L		L	B	B
Anterior TL	66.6%	L	L			B	B
Other	83.3%	L	B		B	B	B
Semantic Decision Task							
Any Activation	83.3% (n=6)						
FL / TL Activation	83.3%						
FL	83.3%	B	B	L	L	B	
Middle/Posterior TL	33.3%	B	L				
Anterior TL	50.0%	B	B		R		
Other	66.6%	B	B		R	L	

Note. L, left; R, right; B, bilateral; FL, frontal lobe; TL, temporal lobe.

The mean accuracy for deciding whether an animal was a mammal or not from the semantic decision task was 87.8% for five of the six patients (*SD* = 9.13%; range 76.67 - 97.78%). The mean accuracy for deciding whether the letter "a" was present within a string of vowels was 98.2% for the same five patients (*SD* = 1.69%; range 96.67 - 100%). The mean for only five of the six patients is given, as it was difficult to confidently determine the accuracy of a patient's (NP5) responses. This was due to the patient omitting multiple responses, and switching response patterns during testing

(initially lifting the left fingers as a yes response but later changing to the right fingers for a yes response).

The results for each individual patient on the reading and semantic decision task are presented in Table 12 in an attempt to identify how well they identify language areas in the frontal and temporal lobe, in individual cases, specifically in anterior temporal pole. From Table 8 it can been seen that there was little overlapping activation for patients (33.3%) with the reading and semantic decision tasks. As this information was provided for the language battery in chapter two it is provided for consistency, but has limited applicability.

Discussion

Utility of the New Reading and Semantic Decision Tasks in Identifying Language Areas

Reading Task

As expected from the fourth hypothesis, the new reading task consistently showed significant activation in the frontal and temporal lobes, including the anterior temporal lobe, for both healthy controls and patients. From the averaged group results for the healthy controls, bilateral activation was noted in the temporal lobes, predominantly on the left. Activation on the left extended from Wernicke's area to the anterior of the temporal lobe. Individually, significant temporal and frontal lobe activation was consistently seen in 100.0% of participants and anterior temporal lobe activation was observed in 72.7%. The current study also investigated the utility of the reading task in identifying language areas with a heterogeneous sample of epilepsy patients. Anterior temporal lobe activation for patients (66.6%) from the reading task was comparable to healthy participants.

Temporal lobe activation was seen more often than frontal lobe activation with controls (90.9% versus 54.5%, respectively). Results were not strongly lateralising, as much of the activation was bilateral, however, the new reading task was successful in localising temporal language sites. Other specific areas of activation included Wernicke's area, central sulcus, left parietal lobe, and cingulate gyrus. The consistent activation in the temporal and frontal lobes near Broca's and Wernicke's areas, and in the anterior temporal lobe, is consistent with previous research using reading tasks (Bavelier et al., 1997; Brockway, 2000; Deblaere et al., 2002; Gaillard et al., 2002; Gao et al., 2001;

Thickbroom et al., 2003).

Similar to Bavelier et al.'s (1997) findings, activation was more robust in the left hemisphere, compared to observed activation in the middle of the right temporal gyrus. Also, the individual results for participants indicated focal and variable activation across participants, and were not restricted to the classical language areas (i.e., Wernicke's area and Broca's area). While Bavelier et al. (1997) had healthy participants perform their reading task on a 4.0 tesla MRI scanner, the current study found similar results using a 1.5 tesla MRI scanner, suggesting this task can be used with a 1.5 tesla MRI scanner to localise language activity in healthy participants.

New Semantic Decision Task

From the fourth hypothesis, it was expected that the new semantic decision task would consistently show significant activation in the frontal and temporal lobes, particularly in the anterior temporal lobe. While consistent activation was found in the frontal (90.9% of NC group and 83.3% of NP group) and temporal lobes (72.7% of NC group and 83.3% of NP group), anterior temporal lobe activation from the semantic decision task was more common in patients than healthy participants (50.0% & 18.2%, respectively). Unfortunately, due to the low number of participants a χ^2 statistical test could not be conducted to confirm if this difference was significant (Pallant, 2001). While small sample sizes (n = 5-10) are adequate for comparing averaged group fMRI results between tasks (Tsukiura et al., 2002), when comparing the instance of areas of activation on an individual basis between tasks small sample sizes are inadequate.

The averaged group results for the healthy controls who were able to successfully

engage in the task demonstrated significant bilateral activation in the inferior frontal lobe (BA 46, 47) predominantly in the left; bilateral cingulate gyrus activation (BA 32), and left inferior temporal gyrus activity (BA 20). As with the averaged group results, all participants showed consistent significant frontal and temporal activation. Other areas of activation included the central sulcus, parietal lobe, and cingulate gyrus.

The consistent activity in the frontal and temporal lobe language areas from the semantic decision task are in keeping with other semantic decision tasks (Deblaere et al., 2002; Sabsevitz et al., 2003). As with Deblaere et al.'s (2002) semantic decision task, on which the current semantic decision task was based, averaged group results for the healthy controls produced activation in the prefrontal region (BA 8, 45 and 47), the anterior cingulate, and the middle and inferior temporal gyrus (BA 20 and 21).

One of the difficulties noted with the new semantic decision task was that some participants and patients were not able to follow the instructions for the task. The difficulty appeared to be with the participant changing mental set (i.e., performing a task one way and then performing it another). While a clear explanation of the task and some examples were provided to participant before scanning, more extensive training on the task by practicing the task, before it is conducted in the MRI scanner (but with different stimuli and questions) would help ensure the participant's comprehension. Such piloting of the task with participants would also identify those who have difficulty with changing mental set and who would be unable to perform the task properly.

Summary and Interpretation

In summary, the second study provided support for the fourth hypothesis, that the

reading and semantic decision tasks would consistently identify activations in the frontal and temporal lobe. The same finding was found for both healthy control participants and patients with epilepsy. There are a few reasons why the reading task is preferable over the semantic decision task. Firstly, support for the utility of the reading and semantic decision tasks in identifying anterior temporal lobe activity was strongest for the reading task. Secondly, there was a trend for the reading task to identify more areas of temporal lobe activation and for the semantic decision task to identify more areas of frontal lobe activation. Thirdly, the reading task was reported to be an easier task by some of the healthy control participants and patients and some of the participants did not perform the task correctly leading to invalid data. While providing more explanation and training on the task may make it easier to perform, it would also increase the time required to administer the task. Alternatively, reading tasks do not require extensive explanation and training because reading is a natural language-based activity.

CHAPTER FOUR – DISCUSSION

Findings of the Study Explained

Brain surgery on patients who suffer from intractable epilepsy can lead to impairments in language functioning, particularly when the surgery occurs near language regions. In the past, the IAP has been used to classify language lateralisation. FMRI has been introduced as an alternative to replace the IAP, particularly as fMRI is non-invasive and can provide information on language localisation. The locations of brain regions important for language function need to be identified in individual patients preoperatively, to help surgeons when making decisions about the suitability of surgery and how to best perform the surgery to minimise any possible postoperative language problems. While it is important to identify frontal lobe language areas when frontal lobe surgery is performed, the current research has focused more on identifying language function in the temporal lobe, specifically the anterior temporal lobe, an area resected in an ATL procedure.

This study investigated the utility of fMRI measures of language function in two phases. Firstly, the fMRI data from the original SVHM fMRI battery was analysed in controls and epilepsy presurgical patients. The second part of the study developed, piloted, and tested two new language tasks, a new semantic decision-making task and a reading task in order to improve upon the fMRI language battery's ability to detect anterior temporal pole activation.

Activation from Original Language Battery

When used with the older MRI scanner, the verbal fluency and picture-naming tasks in the original language battery did not show the expected consistent activation in the frontal and temporal lobes. However, the sentence completion task did consistently activate the frontal and temporal lobes, with some activation in the anterior temporal lobe, for both healthy participants and patients with epilepsy on the older MRI scanner. These findings indicate that the sentence completion task was the most reliable for significant activation when using the older MRI scanner. While the verbal fluency tasks did not show consistent activation for healthy controls and patients in group A, there was a trend for them to result in lateralised activation in the left frontal lobe, consistent with previous research (Deblaere et al., 2002; Herholz et al., 1996; Hertz-Pannier et al., 1997; Lehericy et al., 2000; Spreer et al., 2001; van der Kallen et al., 1998; Yetkin et al., 1998). Compared to the verbal fluency tasks, the picture naming and sentence completion tasks tended to provide more activation in the temporal lobes than in the frontal lobe for both controls and epilepsy patients.

Differences in activations between the verbal fluency tasks were investigated to confirm if additional useful information could be obtained by administering both tasks, or whether a second task was redundant. For controls and patients, both tasks provided consistent activation in the frontal lobes. Based on previous research the category fluency task was expected to activate more temporal lobe areas than the letter fluency task, (Paulesu et al., 1997; Rende et al., 2002). Results from control participants and patients on the older MRI magnet did not support a difference in areas of activation between the two tasks. However, while the numbers were low, patients in group B showed a tendency

for a higher frequency for temporal lobe activation with the category fluency task (100.0%) than for the letter fluency task (66.7%). These results provide little clarification on the differences in activation between the category and letter fluency tasks due to the lack of significant activation for healthy control participants on the older MRI magnet (see below for discussion), the low number of patients, and differences between patient and control groups (e.g., type of MRI magnet used and type of epilepsy). Also, differences in how easy or difficult participants found the tasks were not controlled. For example, a recent study reported that fMRI language maps of epilepsy patients on a semantic decision task differed depending on their performance levels (Weber, Wellmer, Schur et al., 2006) (see section below on behavioural responses for further discussion).

Even though no language activation, and hence no information about language lateralisation and localisation was obtained in some individuals, the original language battery used with the older MRI scanner provided useful information for other individuals. If there was a need to use an older MRI imager to identify language areas, it appears that the sentence completion task should be administered, as it provided the most consistent activation, together with one of the verbal fluency tasks. The picture-naming task did not consistently provide any useful information on language function in the temporal lobe and could be excluded when used on the older MRI imager.

It may be possible to identify more areas of activation by lowering the threshold for accepted activations (level of significance), however, doing so would also increase the chance of a Type II error. With individual patients, changing the threshold for significant activation could show useful activations, however, care should be taken with result interpretation, as decreasing thresholds increased signal detection and deceases signal to

noise ratios.

Comparison of Old and New MRI Scanners

When fMRI data from the original battery of tasks was acquired from patients with epilepsy (group B) on a newer MRI scanner, where a larger number of slice acquisitions were obtained covering a larger area of the cortex, more consistent significant activation, specifically in the anterior temporal lobe, was observed. The most parsimonious reason for this was thought to be due to the use of the newer MRI imager and with the acquisition of more slices. However, this explanation could not be confirmed, as there was no data from healthy controls with the original language tasks on the newer MRI scanner.

Additional support comes from the high frequencies of frontal and temporal lobe activation for both controls and patients with the new semantic decision-making task, based on a task used by Deblaere (2002), and the reading task, based on a task used by Bavelier et al. (1997) (between 83.3% to 100.0% for both tasks). In particular, the high frequencies of activation for the new control participants (group NC) on the newer MRI scanner support the possibility that the low frequencies of activations with the original control participants and patients (groups C & A) were due to factors related to the older MRI imager rather than differences between control and patient groups. However, this could not be confirmed, as none of the healthy controls in group NC (or patients in group NP) underwent the original language tasks on the newer MRI scanner.

Anterior Temporal Lobe Activation

From the third and fourth hypotheses, it was expected that the picture naming and sentence completion tasks from the original language battery, and the new reading and new semantic decision tasks, would show consistent activation in the anterior temporal lobe. The tasks to produce the highest levels of anterior temporal lobe activation were the new reading task for patients and controls (66.6% & 72.7%, respectively), the new semantic decision task with patients (50.0%), and the picture naming and sentence completion tasks when used with group B (66.7%). It was expected that naming and reading tasks would provide important clinical data in identifying language regions in the anterior temporal lobe, as these are skills that are at most risk from ATL surgery (Devinsky et al., 1993; Schwartz et al., 1998). It is possible that the sentence-reading component of the sentence completion task was a factors contributing to the consistent anterior temporal lobe activation, rather than the task incorporating a semantic decision aspect. This would support Bavelier and colleagues (1997) suggestion that the anterior portion mediates the syntactic analysis of sentence-type material (i.e., where there are conceptual relationships between the words presented). The decision-making component of the sentence completion task and the semantic decision task could require greater cognitive demand than reading, hence the higher frontal lobe activation. However, this cannot be determined from the current study and could be an area of further investigation. Anterior medial temporal lobe (fusiform and parahippocampal gyri) activation from the picture-naming task, possibly due to the involvement of bilateral memory-encoding processes (Deblaere et al., 2002), appears to be different from the anterior temporal activity found with the reading and semantic decision tasks. This supports the inclusion

of the naming task in a modified fMRI language battery.

The new semantic decision task only showed similar levels of anterior temporal lobe activation to the new reading task when used with patients. Due to the low number of patients it is difficult to conclude whether this difference between control and patients is significant. Another possible explanation for the higher frequency of anterior temporal lobe activation in patients with the new semantic decision task could be due to the group having an early onset of seizures. Research has shown that patients with early onset of seizures show greater anterior temporal pole language activation (Devinsky et al., 1993).

Methodological Considerations

One obvious limitation of this study includes not having a healthy control group undertake the original language tasks on the new MRI scanner. This would have allowed for a comparison of activations from patients and controls for these tasks and on the new MRI scanner, as was done with the older MRI scanner. Such a comparison would aid in determining if differences in activation between patient groups A and B were due to the MRI scanner and acquisition parameters. In the same vein, having the new participants in the second study undertake the original language tasks would have allowed for a more direct comparison between the new language tasks and original language tasks. This was not done because of time constraints. The addition of the original battery would have increased testing time by 20 to 30 minutes per person, which is of concern in patients with epilepsy, but also because of funding issues for the MRI scanner and MRI technician time.

The sample size for the patients in the second study was smaller than the 20

patients, initially planned for, due to a decrease in frequency of patients presenting for ATL. As a result, the patient sample was also more heterogeneous than the pure TLE group planned for, thus making it difficult to generalise the results to mesial temporal TLE patients, as initially planned.

There are also a number of general limitations with interpreting fMRI activations from a task. Firstly, within the language system there are regions that are essential, and non-essential (Bookheimer et al., 1997). The fMRI technique can only give information about the involvement of a structure in language processing. It cannot give information about whether it is essential to the language task. While fMRI techniques provide important information for presurgical assessment of language function, fMRI carries the risk of misinterpretation, as it is a correlative technique. That is, activation does not necessarily imply that the activated piece of tissue is necessary for the task. It is conceivable that an area may be activated without direct involvement in the task, particularly if thresholds are set too low. Although this potential to misinterpret fMRI activations precludes replacement of electrical stimulation mapping with fMRI, fMRI could be used to speed up intracranial mapping procedures and to guide the extent of the craniotomy (Powell & Duncan, 2005).

Secondly, statistically thresholding fMRI data in an attempt to dissociate true activation from spurious activations (to minimise type I errors) only reduces the errors, it cannot completely avoid them (Kloppel & Buchnel, 2005). Using fMRI for presurgical planning poses a different problem, namely that of sensitivity, minimising the Type II error rate (false negative results). This is difficult because when a very low threshold is used in fMRI analyses, most of the brain is activated leading to Type 1 errors (false

positive results). With the analysis of the data from the original language battery, the threshold may have been set too high, as there were multiple cases where there was no significant activation. In contrast, when the original language task and the new semantic decision and reading tasks were used on the new MRI scanner, activation was noted in nearly every case with the same thresholds as for the old scanner. However, activation was more widespread.

It has been suggested that a set threshold for a whole population may not be the best method, as the BOLD signal differs significantly between individuals (Kloppel & Buchnel, 2005). Because the priority with individual patients is to identify all brain regions that are involved in a task, less stringent statistical thresholds may be required, and indeed the thresholds used may need to vary on an individual basis (Powell & Duncan, 2005).

Thirdly, it does not necessarily follow that all areas involved in a task will be activated by a particular fMRI paradigm (Powell & Duncan, 2005). While the use of multiple tasks in a battery format can help to reduce this problem, by allowing greater opportunity to observed language activation on a variety of tasks, it does not eliminate it.

Fourthly, while the validity of fMRI in identifying cognitive and behavioural function in healthy individuals is considered to be well established, its validity with a clinical population has been questioned (Brown, 2007). It is possible that medications or diseases common with a clinical population could impact upon the vascular dynamics mediating neural activity and the BOLD response. This could complicate interpretation.

Reliability of fMRI

In the current study, attempts were made to generate group averaged statistical maps for the tasks in the original language battery and for the two new tasks with the healthy control participants. The purpose of this was to allow for the comparison of results with other studies that used similar tasks and averaged group results. Interpretations from grouped averaged statistical maps are limited when the group is heterogeneous, as was the case with all the patient groups in the current study. A difficulty in the interpretation of average statistical maps also arises because of the error introduced when different shaped brains are warped into a standard sized space (see Method section in Chapter 2 for further discussion on registration difficulties and interpretation). While it is plausible that meaningful information can be obtained by averaging group data from healthy control participants, averaging group data from patients with epilepsy (particularly in this study) who vary in areas of pathology, and type of epilepsy, would have limited generalisability. Additionally, group averaged statistical maps for tasks provide little information about the stability of fMRI measures for individual patients (Brown, 2007).

Directions for Future Research

Assessing Postoperative Symptoms

Although the current study was not able to follow up on patients post surgically, medical records were reviewed for post operative outcomes. Details of some postoperative language changes were reported for some patients, but for others, there

were no details in medical records at the time of the study. No data was available for most of the patients in groups B and NP because surgery had not yet occurred or was not going to occur. In the majority of cases, the outcome data was based on assessments by speech pathologists or anecdotal evidence from the patient and their family. The lack and variety of outcome data, particularly for patients in group A, highlight the need for a standard protocol for reviewing postoperative symptoms. A preoperative and postoperative neuropsychology assessment, which included language assessment, would be a suitable method and is indeed part of the standard protocol for patients undergoing standard ATL's for mesial TLE at SVHM. It would have been interesting to compare the language results from patients with the outcome from surgery. Unfortunately, patients referred for fMRI assessment in this study did not usually get neuropsychology assessments because they were generally fast-tracked for surgery because of their pathology. Postoperative neuropsychology results for the patients who were assessed were not available at the time of the study.

Influence of Pathology on Atypical Language Representation

The results from the current study were from patients who differed in their pathology. There were patients with left mesial TLE, left and right lateral TLE, and focal epilepsy arising from the left frontal, left parietal and right occipital lobes. Also, as previously mentioned, patients did not represent typical epilepsy surgery candidates because they were generally fast-tracked due to their pathology. It should be noted that the diverse pathology makes it difficult to generalise group findings to regular surgerical candidates with medial TLE syndrome, especially since the lesions were not due to a

single type of pathology and the time of acquisition was not controlled. Due to time constraints with recruitment, all potential candidates for epilepsy surgery at SVH were included in the study and as a result pathology was not controlled. A patient sample more representative of regular surgery candidates would further support the wider applicability of the studies findings.

In addition, it is important to note the possible confounding influence the diverse pathology would have had on group results. The location of lesions and the onset of epilepsy are important factors in atypical language lateralisation and localisation. For example, it has been shown that early damage to the left hemisphere can result in atypical (i.e., bilateral or right lateralised representation of language (Rasmussen & Milner, 1997; Staudt et al., 2002). Using a fMRI reading comprehension task and neuropsychology testing, Berl and colleagues (2005) found that patients with complex partial seizures with a left hemisphere focus had more atypical language than those with a right hemisphere focus and normals (21% versus 0% and 3%, respectively). In addition, atypical language representation was also associated with early seizure onset or a history of risk factors for left hemisphere brain injury before the age of six years.

The temporal lobe in general has been suggested to be the critical structure for language lateralisation (Janszky, Jokeit, & Heinemann, 2003; Liegeois et al., 2004). However, more recent research suggests that lesions in the left hippocampus are particularly relevant and predictive of atypical language dominance, rather than lesions near classic language areas or even in the temporal lobe in general (Weber, Wellmer, Reuber et al., 2006). For adults whose epilepsy was present during language acquisition, Weber and colleagues (2006) found that hippocampal sclerosis was associated with an

increase in the displacement of both frontal and temporal aspects of cortical language representations to the right hemisphere. This displacement was not seen with patients who had lesions in the frontal lobes or lateral areas of the temporal lobes. It has been suggested that higher epileptic activity with medial temporal lobe epilepsy compared to other focal lesions (Hamer, Najm, Mohamed, & Wyllie, 1999; Pfander et al., 2002; Stuve, Dodrill, Holmes, & Miller, 2001) may lead to stronger involvement of the otherwise non-dominant hemisphere in language functions (Regard, Cook, Wieser, & Landis, 1994; Weber, Wellmer, Reuber et al., 2006). An alternative explanation is that the hippocampus is important for the acquisition of language (Knecht, 2004), and that damage to the left hippocampus may lead to the right hippocampus playing a more prominent role prior to or during language acquisition.

A higher incidence of atypical language representation for patients with hippocampal sclerosis compared to those with lesions elsewhere was seen with the patients in group A. Specifically, the patients with left hippocampal sclerosis exhibited right or bilateral language lateralization whereas those with frontal or lateral temporal lobe lesions did not. However, such a clear finding was not evident with patients in groups B and NP, where bilateral activation was seen in most cases, not just those with left hippocampus sclerosis. Results from this study were most useful on an individual basis rather than as a group, given the diversity in pathology within patient groups.

Standardisation of fMRI Procedures

From the collection of fMRI data to its analysis there are a large number of steps and decisions that need to be made. For many of these decisions there is no considerable

agreement on how to make them. Some of these decisions include how to correct for movement, whether to blur images to smooth spatial noise, how to warp brains of different sizes and shapes into a common atlas space, and how to identify regions of interest (Brown, 2007). These decisions are often made in relation to the tradition of a laboratory in which the researcher works (Brown, 2007).

Variability in fMRI results can arise from the differences in magnet strength, differences in the sampling of image information, or even manufacturer of the magnet (Zou et al., 2005). Brown (2007) suggests that while it is important to establish the reliability of a task used in an fMRI battery, it is also important to reestablish the task's reliability again when significant changes have been made in the core image-acquisition protocol or to image-analysis. As observed in the current study, there was some evidence that tasks performed on different MRI imagers produced differences in how consistently they showed activation. This highlights the need for the reliability of activation from fMRI tasks to be established on a task-by-task basis.

Behavioural Responses

Without behavioural responses from patients during the fMRI tasks, the cognitive state of the patient remains unknown. Recording responses can act as a way of determining how challenging the participant found the task. The importance of this was seen with responses obtained from the new semantic decision task. This information enabled the identification of participants who did not perform the task as required, thereby helping to accurately interpret the activation results. From the current study, responses to task stimuli involved the participant making hand movements. Having

participants move can introduce and encourage motion artifact, and also requires an observer to record responses, thus introducing possible error. While the best solution would be the use of a magnet safe response button(s) connected to the MRI scanner, this was found to be prohibitively costly in the current study. Alternatively, the testing of a participant's engagement with a task could include asking questions about the task material after the task. For example, with the reading task, participants could be asked questions to test their recognition memory of the presented sentences to confirm they were paying attention to the task. It has also been suggested that the task include certain oddball targets to test the vigilance of the participant (Kloppel & Buchnel, 2005). As noted earlier, task training prior to fMRI scanning can help familarise the participant with an unfamiliar tasks (e.g., the new semantic decision task), ensuring the appropriate participant engagement and the obtaining of useful data.

Individuals differ considerably in their language ability and this in turn affects the magnitude of the blood flow response during tasks (Bookheimer et al., 1997). Therefore, differences in language ability may provide a possible explanation for why some participants demonstrated strong language activation and others did not. Other reasons could include how cognitively challenging, engaging, or repetitive the participants find the tasks. There appears to be problems with tasks that are too cognitively challenging, and those that are not challenging or engaging enough. A PET study first demonstrated that the harder a participant worked, the greater the blood flow changes (Fox & Raichle, 1984). Cognitively challenging tasks have been found to show greater changes in blood flow that simple tasks (Bookheimer, Zeffiro, Blaxton, Gaillard, & Theodore, 1995). However, when tasks are too difficult to perform, fMRI results are meaningless

(Bookheimer, 2007). For example, it has been shown that patients who find a task too difficult show activation in sensory input regions, but fail to show activation in higher processing areas (Stern et al., 2000). In contrast, with highly practiced tasks, there are reports of a large reduction in activity in primary language areas with different cortical regions being activated (Bookheimer, 2007). It may therefore be worthwhile to incorporate the ability to vary tasks in how challenging they are, and the patient can therefore be given a version of the task that would be the most appropriate and elicit the best activations.

New Approaches to Language Localisation

A new approach that can be used with fMRI in surgical planning to help identify important tracts connecting critical language areas is diffusion tensor imaging tractography. It is a relatively new approach and is a recently added feature to FSL (Behrens et al., 2003).

Another new approach is Functional Near-Infrared Spectroscopy (fNIRS), a non-invasive optical neuroimaging technique that utilises near infrared wavelengths of light, which is absorbed by haemoglobin, but passes through the scalp, skull, meninges and neural tissue (Voelbel & Wylie, 2007). Light not absorbed by haemoglobin is collected by a detector, which is placed near the source on the scalp, enabling the detection of changes in blood flow and oxyhaemoglobin and deoxyhaemoglobin concentrations (Villringer & Chance, 1997). While FNIRS is still in the validation stage of development it could become a widely used clinical tool in the language assessment in the future (Voelbel & Wylie, 2007). FNIRS has been suggested as a potential superior alternative to

fMRI in detecting the changes in haemoglobin concentration due to its higher temporal resolution (Strangman, Culver, Thompson, & Boas, 2002). Additional benefits of fNIRS over fMRI include its relatively low cost. It is also relatively insensitivity to minor head movements, allowing for vocalisations in paradigms. Patients are not restricted to lying down, they can be sitting, and hand and arm movements are not restricted, thus allowing for bedside functional neuroimaging. Also, patients with metallic material in their bodies are not excluded, as they would be with fMRI, because fNIRS does not use magnetic fields. Lastly, statistical methods developed for fMRI analysis can be used because fNIRS data can be converted into an image format utilised by fMRI software (Voelbel & Wylie, 2007).

Conclusions

A number of conclusions can be made from the results of the current study. Firstly, only the sentence completion task can be recommended for use with the older MRI scanner. Secondly, not only can differences in task construction effect how consistently activation is demonstrated, but also how fMRI images are acquired. It appeared that the 25 slice fMRI acquisitions obtained on the newer MRI scanner provided more consistent activation than the 10-slice fMRI acquisitions obtained on the older scanner. All four original language tasks appeared to show more consistent significant language activation when acquired on the newer MRI scanner with thinner slices. However, this was only based on comparisons between patients completing the original language battery and healthy controls and patients completing the new language tasks. Thirdly, from the information obtained from the current study, the proposed fMRI

battery to identifying language regions in the anterior temporal lobe would consist of the new reading task, the sentence completion task, the picture-naming task, and the category fluency task as they were the best in identifying anterior temporal pole activation. Other tasks were omitted as they may have added little additional information or were found to be too difficult to perform for some participants. In relation to the two new tasks, given that some of the control participants and patients were unable to perform the semantic decision task properly and that it mainly identifies similar frontal activation to the verbal fluency tasks, its value in a language battery is limited. The new reading and sentence completion tasks appear comparable in their ability to identify anterior temporal lobe language activity.

In summary, fMRI is a noninvasive and widely available neuroimaging tool that allows for the identification of language areas of the cortex in patients with epilepsy. Despite there being some limitations, research has shown that preoperative fMRI information does change surgical decision-making and techniques. Van Westen, Skagerberg, Olsrud, Fransson, & Larsson, (2005) found that although fMRI activation for language was less reliable than for sensory and motor function (75 - 95% as opposed to 90 - 95%), surgical decision, surgical approach, and the amount of tumor removed in the majority of cases was significantly altered by the fMRI activation information. By using task paradigms that localise the specific language skills most at risk following temporal and frontal lobe resections, it is possible to map relevant language functions in the epilepsy surgery population. This information thereby allows for better assessment of the risks posed by surgery.

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APPENDIX A: Edinburgh Inventory

Handedness Questionnaire

Instructions

Please indicate your preferences in the use of hands in the following activities.
If you are really indifferent, select "**Either**".
Where the preference is so strong that your would never try to use the other hand select "**No**".

When:	Which hand do you prefer?	Do you ever use the other hand?
Writing:	L | R | either	Yes | No
Drawing:	L | R | either	Yes | No
Throwing:	L | R | either	Yes | No
Using Scissors:	L | R | either	Yes | No
Using a Toothbrush:	L | R | either	Yes | No
Using a Knife (without fork):	L | R | either	Yes | No
Using a Spoon:	L | R | either	Yes | No
Using a Broom (upper hand):	L | R | either	Yes | No
Striking a Match:	L | R | either	Yes | No
Opening a Box (lid):	L | R | either	Yes | No

Thank you for your responses

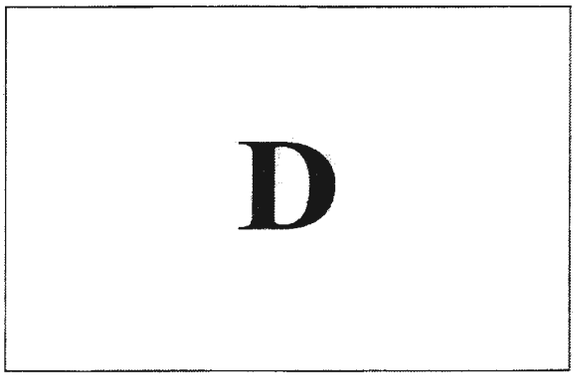
Updated: Feb 27, 2004

Task 1

WORD GENERATION

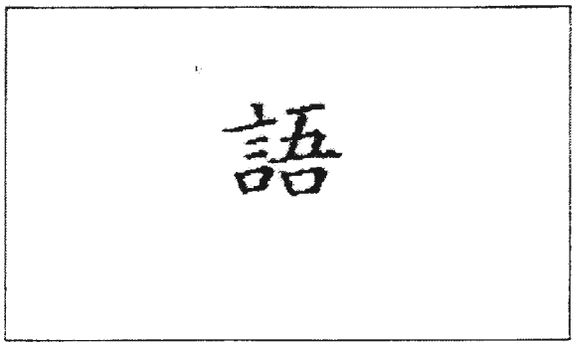
When a **letter** is displayed, think of words beginning with that letter.
When the **Japanese characters** are displayed, look at them and concentrate on breathing evenly.

Instruction screen



A sample word generation ('ON') screen.
Think of as many words beginning with "D" as you can. (e.g. Dog, Dad, Daisy, Doll, . . .) .

Each letter will be displayed for 45 seconds.



A sample 'OFF' screen.
Just look through the Japanese characters and concentrate on breathing evenly.

Each set will be displayed for 3 seconds.

Task 2

Generating words from a specified Group or Category

When a **category** is displayed, think of as many examples as you can.

When the **Japanese characters** are displayed, look at them, and concentrate on breathing evenly.

Instruction screen

Groceries

A sample category ('ON') screen.
Think of as many words in the group as you can. (e.g Butter, bread, sugar, foil, soap . . .).
Each group will be displayed for 45 seconds.

語母半左火聞

A sample 'OFF' screen.
Just look through the Japanese characters and concentrate on breathing evenly.
Each set will be displayed for 3 seconds.

Task 3

OBJECTS

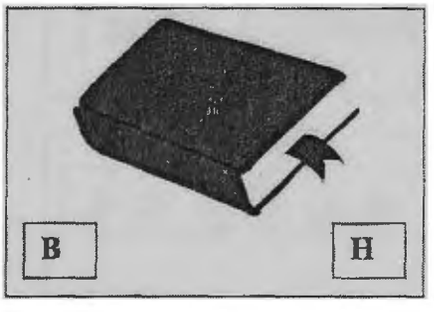
Press the **LEFT** button if the object displayed starts with the **LEFT** letter.
Press the **RIGHT** button if the object starts with the **RIGHT** letter.

JAPANESE SYMBOLS

One symbol from each group is repeated at the bottom of the screen. Press the button which corresponds to this symbol.

(Press any button if you can't decide!)

Instruction screen

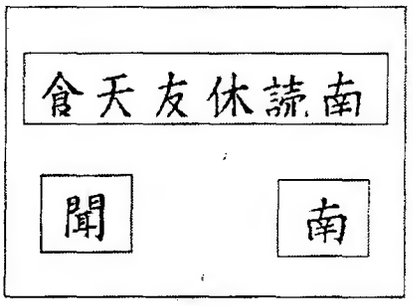


A sample 'object' screen.

Each object will be displayed for 3 seconds.

In this case, press the LEFT button as the object (a Book) begins with "B", the letter on the LEFT of the screen.

Do not worry if you can't decide, or you press the wrong button. The pictures will only be displayed



A sample 'OFF' screen

Each screen will be displayed for 3 seconds.

In this case, press the RIGHT button as the Japanese character from the top row is on the bottom right of the screen.

Do not worry if you can't decide, or you press the wrong button. The pictures will only be displayed

Task 4

Sentence Completion

When a sentence is displayed, choose the word that goes in the space, and press the corresponding button.

When you see Japanese characters, choose the bottom character which is also in the displayed group, and press the corresponding button.

Press any button if you can't decide.

Instruction screen

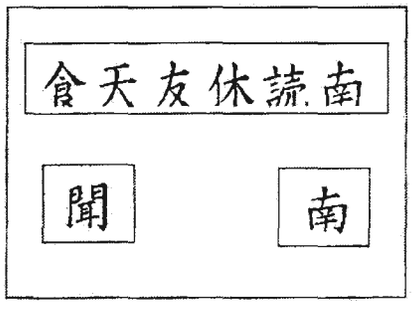
He slept in ..... noon.

until | **from**

A sample sentence completion screen.

Each sentence to be completed will be displayed for 3 seconds.
In this case, press the LEFT button as the word "until" best completes the sentence.

Do not worry if you can't decide, or you press the wrong button.



A sample 'OFF' screen

Each screen will be displayed for 3 seconds.

In this case, press the RIGHT button as the Japanese character from the top row is on the bottom right of the screen.

Do not worry if you can't decide, or you press the wrong button.

APPENDIX C: New fMRI Language Protocols

Reading Task

	No. words	No. seconds
Emma eats carrots every morning.	5	3.8
Behind the big red barn is a magnificent pond.	9	6.2
This car can only fit five people.	7	5
The sheriff was happy to give the reward.	8	5.6
The first thing when introduced is to bow.	8	5.6
We were wrong about the weather.	6	4.4
I do not understand your concern.	6	4.4
Sarah knew who the old gentleman was	7	5
The assistant weighed the bag of bananas	7	5
Jkyrs nbvf zxswdpf swdhj kphznsd.	5	3.8
Dwjpkv sfr hfw ykl pksww yj s lpstyrwhjy knlj.	9	6.2
Hjyg jdf yph njkg hdw trps ycfghd.	7	5
Whj lkphgqs vhf sdjjk tr dfvk lpt gpfbvx.	8	5.6
Qdw gtrps xcfghj qwhj lkphgqsdcf vf hb dsj.	8	5.6
Nt dfvk dqlyt tpfbvx fhgb kjnvfdg.	6	4.4
P jg sfv lkjklgfvbh pqtl jghfjyt.	6	4.4
Dkghs nvgb xyh hwf qpl kjghybhsd fpl.	7	5
Hih kflfhygtf pdphyhlkd ghf wdf pt sdjdjpw.	7	5
The sum of three and five equals eight.	8	5.6
All Martians like pepperoni on their pizza.	7	5
He stepped quickly across the room.	6	4.4
Powdered sugar from the donuts was on his chin.	9	6.2
I wish we could go.	5	3.8
There was no doubt about the matter.	7	5
To keep a secret was beyond Mary's ability.	8	5.6
It startled everyone in the room.	6	4.4
She just had puppies four weeks ago.	7	5

Hjs yhs kj wfthg qwk jhbnv sdcvbh kjtsx.	8	5.6
Lhg Ksdtyhnd hgfd wdrfgthbn jn jklp hjktt.	7	5
Sd dfgthhh kjzxnmb gfbnps hrv gnjj.	6	4.4
Kjmnscvv djfgh nbxd hdn ljnhr tfg qw swd sfgv.	9	6.2
P yjnh kj dswcv nb.	5	3.8
Pklhg yjn mj sgfbh jhgnd qwb jkhhty.	7	5
Yj hjyy g dfrgh ght gnhjkn Kjhg'd vfbghn.	8	5.6
Rf dfghgfthb gbgthyjkm mj hjk ljjs.	6	4.4
Khg jhyt dfr gthhjkp kjhg sdfvg dcf.	7	5

I need two more dollars from him.	7	5
The librarian promptly led them to the book.	8	5.6
The car arrived in town with an unusual passenger.	9	6.2
That afternoon the card game started early.	7	5
Patrick never did his homework.	5	3.8
The clock had just struck nine.	6	4.4
A strange green mist emanated from the craft.	8	5.6
It was a portrait of her mother.	7	5
They all sat around the table.	6	4.4

P hggf hyj jksw fghhwsd hnmv nmz.	7	5
Jkj kjldscvbn jkpthgtrfw hgs yjln mj sgh jhnd.	8	5.6
Lwb jkh Yjjkplb hy gght dfgh ht gnhjknk jhgkljbgf.	9	6.2
Yghn sdftghyn dfg yjkm mkkj hjkhtrw ljjsk.	7	5
Khgyhjn jhytn dfr gth kjhgjkhy.	5	3.8
Hvg dcfl hyh gght dfgh htnj.	6	4.4
D jhgkljf hghn sdft dfgkljpph yjkm mkj hjkht.	8	5.6
Kj hjn n dfrjkytr gt kjj vgklvz.	7	5
Ykfl mkj hjk hjgfxzc hjn nghjk.	6	4.4

New Semantic Decision Task (Animals)

leopard	oeiuoeuuu	cheetah	oaiuuieei	camel	ueoeeioiu
rooster	euuiaeiuo	lizard	uoeeeuoie	pelican	eauiieuee
bear	oouiooiui	rabbit	ooauouiee	goat	oeuauuuii
cat	oeioeoio	giraffe	oeouuauui	puma	iiooeeuae
ladybird	ieoiaooee	ant	aeiiueeuo	tiger	oiiuueooi
parrot	auuuoiuei	zebra	oiouoieeu	crocodile	ieioiioou
dolphin	oueeaeoio	fish	eeeeoeoie	goanna	iauoiuiee
pig	oeuoiuooi	butterfly	iiuieeoui	starfish	euaeuoioi
antelope	eoioooeeu	chicken	ueaooeiou	shark	ueeueeuai
budgie	iooiaeoue	fly	uoooeioio	gorilla	iiiiiuoio
jelly fish	ooeiaeuee	seal	euiueieoi	rhinoceros	iiouuoieo
koala	ouiieaooi	cow	ueueioioo	peacock	iioioaeio
seahorse	ioieoooue	deer	uieaeueee	possum	uoieuueui
walrus	ooueuoiie	ostrich	ieiioieua	penguin	uioiuauui
snake	iueeieuae	elephant	iaoeeooeu	kangaroo	oieiuoieo

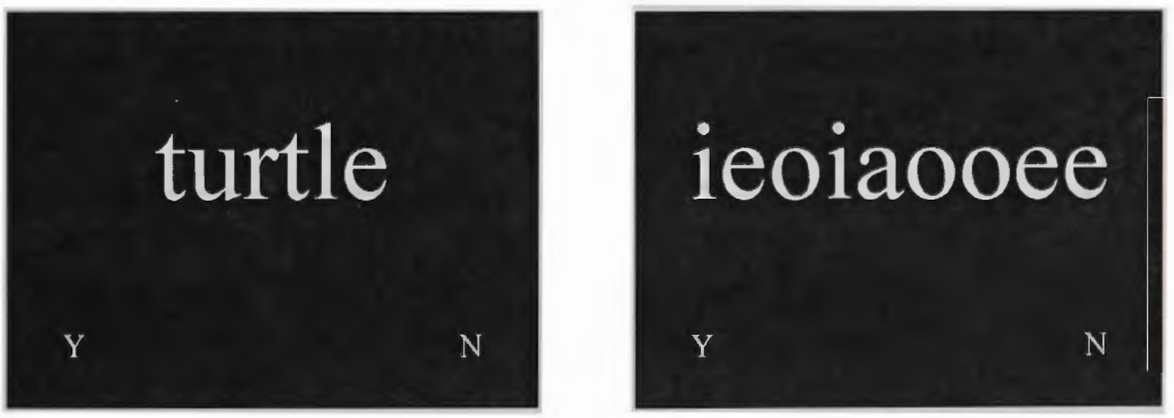


Figure 7. Examples of the screens presented for the animal semantic decision task.

APPENDIX D: Victoria Univeristy and SVHM Human Research Ethics Committees

ST VINCENT HEALTH

Research and Grants Unit
Ph: (03) 9288 3930 Fax: (03) 9288 3205

Thursday, 15 September 2005

Ms F Bardenhagen
Clinical Neurosciences
SVH

Dear Ms Bardenhagen

Protocol No: HREC-A 009/05

'Review of fMRI language mapping in patients with temporal lobe epilepsy.'

Ms F Bardenhagen Prof M Cook A/Prof S Bowden Mr M Murphy
Dr K Morris Dr N Trost Mr M Nairn

The Human Research Ethics Committee-A (HREC-A) has granted final approval to the following amendment:

Updated PICFs (both Clinical Participants and non-Clinical Participants) with changes resulting from the Victoria University Ethics Committee review. (Also applies to #010/05)

This approval will be noted by the full Human Research Ethics Committee - A at its next meeting on Wednesday 12 October 2005.

There will be no further correspondence regarding this amendment unless a member of the HREC-A raises a concern at that meeting.

The conditions of approval of this amendment are the same as those governing approval of the original protocol.

Please ensure that you use the Participant Information and Consent Forms emailed to you from Louise Berns on the morning of 14 September 2005.

Yours sincerely

Jill Hambling

Secretary, Human Research Ethics Committee-A

Research and Grants Unit
Ph: (03) 9288 3930 Fax: (03) 9288 3205

Monday, 28 August 2006

Dr F Bardenhagen
Clinical Neurosciences
SVH

PO Box 2900
Fitzroy Victoria 3065 Australia
Telephone 03 9288 2211
www.svhm.org.au

Dear Dr Bardenhagen

Protocol No: HREC-A 009/05

'Review of fMRI language mapping in patients with temporal lobe epilepsy.'

The Human Research Ethics Committee-A (HREC-A) has granted final approval to the following amendment:

> Protocol Amendment due to a 75% lower than expected number of TLE patients scheduled for surgery. Proposal to also utilise epilepsy patients with lesions in other areas. Revised Module One and PICF (Clinical Participants) version 6 dated 3 August 2006. (Also to HREC-A 010/06).

This approval will be noted by the full Human Research Ethics Committee - A at its next meeting on Wednesday 13 September 2006.

There will be no further correspondence regarding this amendment unless a member of the HREC-A raises a concern at that meeting.

The conditions of approval of this amendment are the same as those governing approval of the original protocol.

Yours sincerely

Jill Hambling

Secretary, Human Research Ethics Committee-A

St Vincent's

Continuing the Mission of the Sisters of Charity

Human Research Ethics Committee

MEMORANDUM

TO: Dr Fiona Bardenhagen, *Matthew Nairn
Principal Investigators
Psychology

FROM: A/P Ross Williams
Chair, University Human Research Ethics Committee

DATE: 30 July 2005

SUBJECT: **Approval of application involving human subjects**

Dear Fiona,

Thank you for your submission detailing amendments to the research protocol for the project titled, ***Review of fMRI mapping in Patients with Temporal Lobe Epilepsy*** (HRETH.026/05).

The proposed amendments have been accepted by the Human Research Ethics Committee and approval for application HRETH.026/05 has been granted from 30/07/05 to 01/12/06.

Please note that, the Human Research Ethics Committee must be informed of the following: any changes to the approved research protocol, project timelines, any serious or unexpected adverse effects on participants, and unforeseen events that may effect continued ethical acceptability of the project. In these unlikely events, researchers must immediately cease all data collection until the Committee has approved the changes.

If you have any queries, please do not hesitate to contact me on 9919 4590.

The Committee wishes you all the best for the conduct of the project.

A/P Ross Williams
Chair, University Human Research Ethics Committee

APPENDIX E: Participant Information and Consent Form (Non-Clinical)

ST. VINCENT'S HEALTH

PARTICIPANT INFORMATION AND CONSENT FORM

NON-CLINICAL PARTICIPANTS

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.

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 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 it is important for us to identify the areas of the brain that are involved in language in healthy volunteers, so that we can compare these areas with those involved in the language function of patients with epilepsy. Your participation 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.

3. 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 and through psychological testing that will be conducted at St. Vincent's Hospital. The psychological testing will take approximately 1 hour, 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.

4. Possible Benefits

You will not personally benefit from participating in this study. 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.

5. 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 is a possibility that the MRI scan may reveal an abnormality in your brain that you would otherwise not know about. If this occurs, you will be informed after the scan has been reviewed by a radiologist, and you will be offered an appointment with Professor Cook, Head of Neurology at St. Vincent's Hospital to discuss the results further.

There may be additional unforeseen or unknown risks.

6. Alternatives to Participation

You may decide that you do not wish to participate in this project.

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 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 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 - NON 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- NON-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 F: Participant Information and Consent Form (Clinical)

ST. VINCENT'S HEALTH

PARTICIPANT INFORMATION AND CONSENT FORM

CLINICAL PARTICIPANTS

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.

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 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.

3. 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.

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.

5. 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.

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.

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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.

15. 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 G: Medical Imaging MRI Information Sheet

Reviewed 11/1/06
Approved Dr Peter Smith

Transport Details:
Wheelchair
Bed
Oxygen
Suction

MEDICAL IMAGING DEPARTMENT
MRI SAFETY QUESTIONNAIRE

PLEASE COMPLETE THE FOLLOWING QUESTIONNAIRE AS ACCURATELY AS POSSIBLE: THIS FORM MUST BE FILLED OUT AND FAXED TO MRI ON 3089.INPATIENTS WILL NOT BE SENT FOR UNTIL THE MRI SAFETY QUESTIONNAIRE IS RECEIVED AND REVIEWED BY THE MRI STAFF.

PART A
Do you have any of the following?

LIVER DISEASE	YES / NO	ANAEMIA	YES / NO
KIDNEY DISEASE	YES / NO	DIABETES	YES I NO
ALLERGIES	YES / NO	EPILEPSY	YES / NO
REMOVABLE DENTAL APPLIANCES	YES / NO	PATIENT'S WEIGHT:	

PART B
Please circle if you have any of the following:

CARDIAC PACEMAKER	NEUROSTIMULATOR
IMPLANTED CARDIAC DEFIBRILLATOR	PREVIOUS CARDIAC SURGERY
IMPLANTED DRUG INFUSION DEVICE	INNER EAR IMPLANT
PROSTHETIC CARDIAC VALVE	SHRAPNEL/BULLET
VASCULAR CLIPS	EMBOLIZATION COILS
PROSTHESIS – HIP/KNEE REPLACEMENT	INTRAVENTRICULAR SHUNT
IUD	RENAL SHUNT
TATTOOED EYELIDS	WIRE SUTURES
METAL IMPLANTS EG PINS/PLATES/SCREWS	BODY PIERCING JEWELLERY

PART C
Please circle correct option:
Have you ever had any operations/surgical procedures YES / NO

If YES what type:.....

.....

Have you ever been a welder/sheet metal worker or had an injury involving metal to your eye? YES / NO

Are you pregnant or suspect you may be pregnant or currently breast-feeding? YES / NO

Do you have a cardiac pacemaker? YES / NO

Do you have an implanted cardiac defibrillator? YES / NO

Do you have aneurysmal or vascular clips? YES / NO

Have you ever had brain, eye/ear or vascular surgery? YES / NO

Relevant previous radiological investigations:
Plain X-rays Ultrasound CT Scan MRI

It essential that you complete this form as accurately as you can. For further information contact MRI on 9288 3084.

Patient's Name (print):.....
Signature:..... Date .....

Please ensure that an RN or Doctor has signed this form prior to faxing to MRI.

Checked By (print) .....

Signature: .....Date:.....

APPENDIX H: Additional Tables and Figures for Original Healthy Controls

Table 13

Language task results for C1.

Localisation	Cluster Size	Z	x	y	z
Letter Fluency					
	Nil				
Category Fluency					
L MFG	164	5.73	38.3	16.9	24
Picture Naming					
	Nil				
Sentence Completion					
	Nil				

Note. Local maxima in MNI coordinates. Only the local maxima with highest Z score in each cluster are provided in the table. Cluster size is in voxels. When the cluster encompasses more than one anatomical location, the localization given corresponds to the local maxima with the highest Z score. L, left; MFG, middle frontal gyrus.

Category Fluency Task

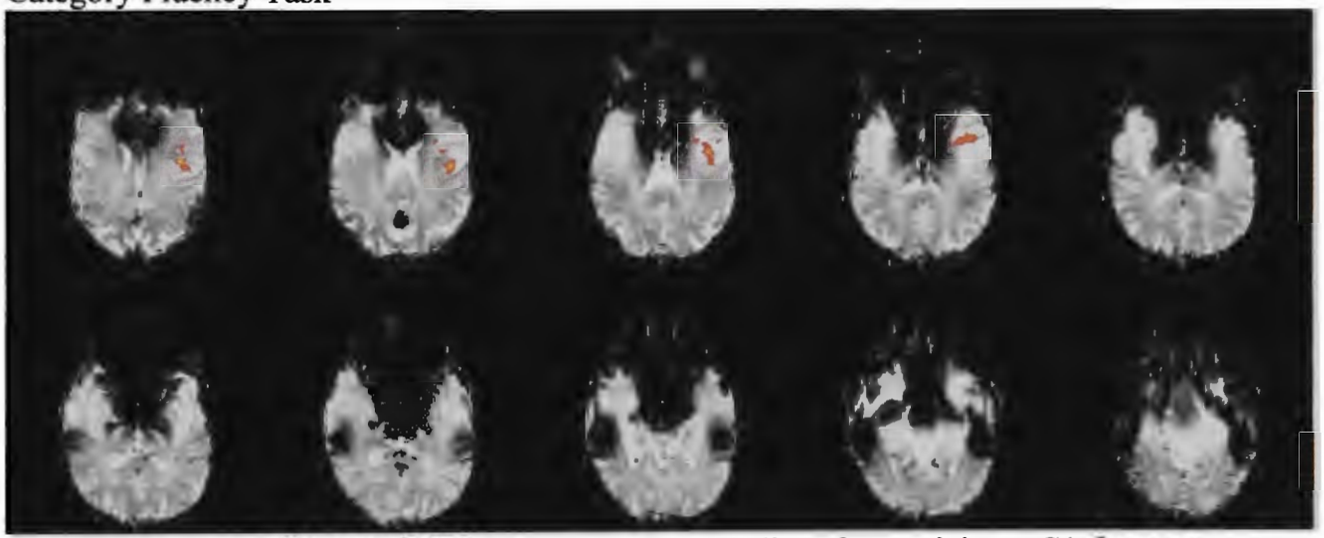


Figure 8. Category fluency fMRI activation on axial slices for participant C1. Images are shown in radiological convention: the left hemisphere is displayed on the right side of the image.

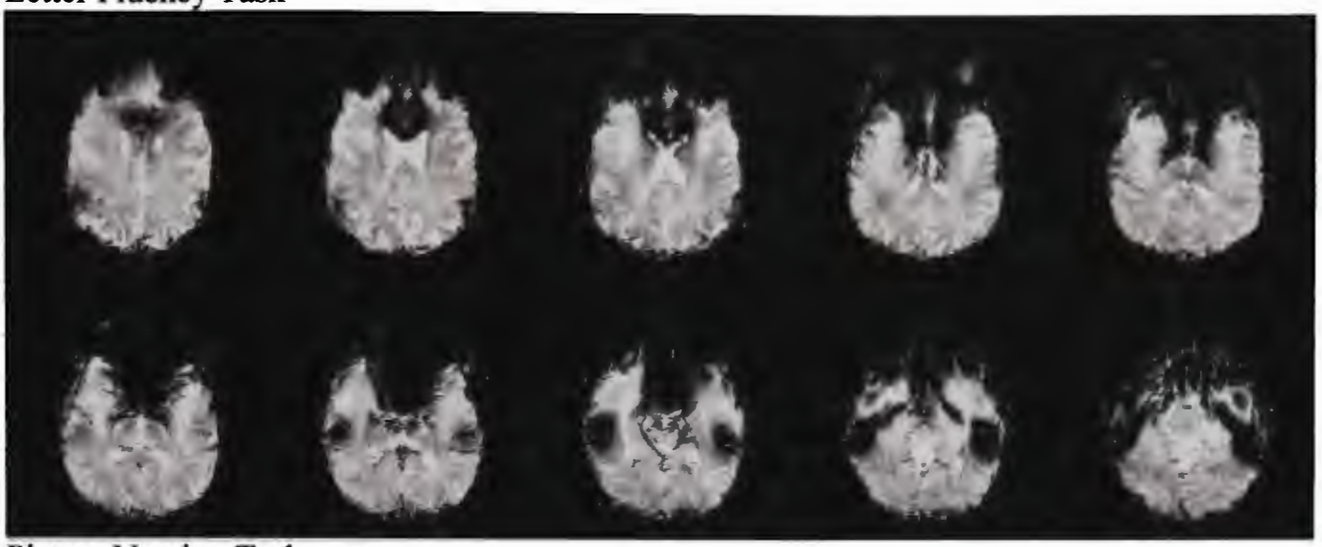
Table 14

Language task results for C2.

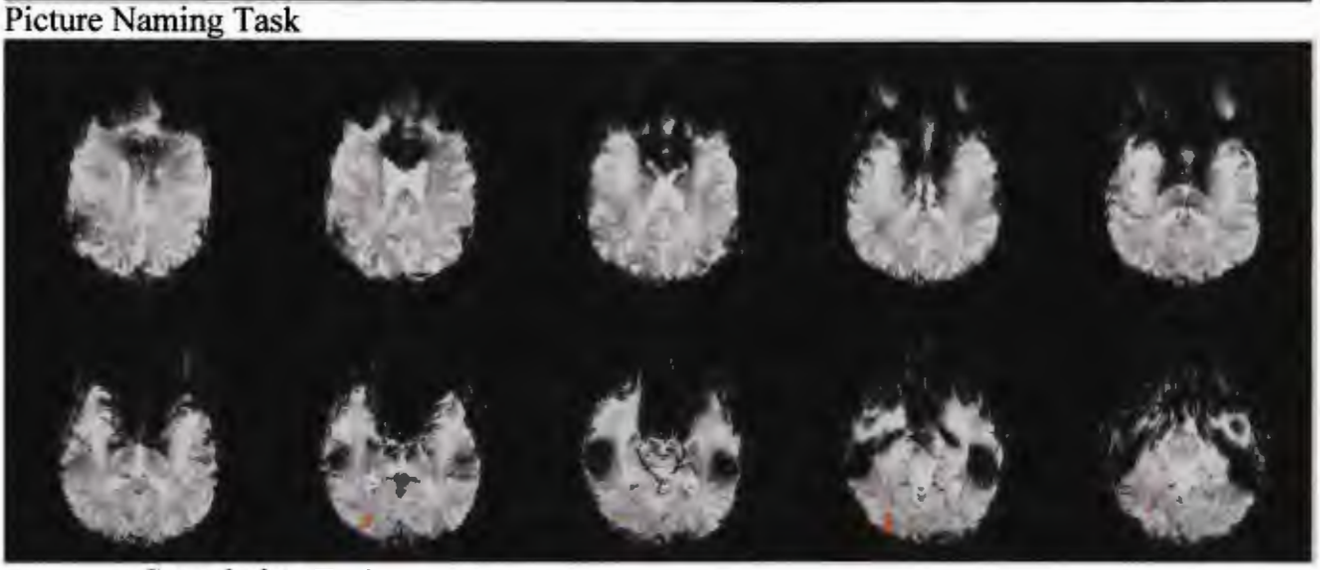
Localisation	Cluster Size	Z	x	y	z
Letter Fluency					
L IFG BA9	263	6.56	50.4	15.8	26
Category Fluency					
	Nil				
Picture Naming					
R SOG BA19	109	4.8	-35.5	-78.6	23.2
Sentence Completion					
L IFG BA47	386	6.56	27.5	27.9	-1.71
R FL	283	6.38	-16.5	32.2	2.51
L STG MA39	137	6.49	53.1	-57.1	12.5

Note. Local maxima in MNI coordinates. Only the local maxima with highest Z score in each cluster are provided in the table. Cluster size is in voxels. When the cluster encompasses more than one anatomical location, the localization given corresponds to the local maxima with the highest Z score. L, left; R, right, IFG; inferior frontal gyrus; SOG, superior occipital gyrus; FL, frontal lobe; STG, superior temporal gyrus.

Letter Fluency Task



Picture Naming Task



Sentence Completion Task

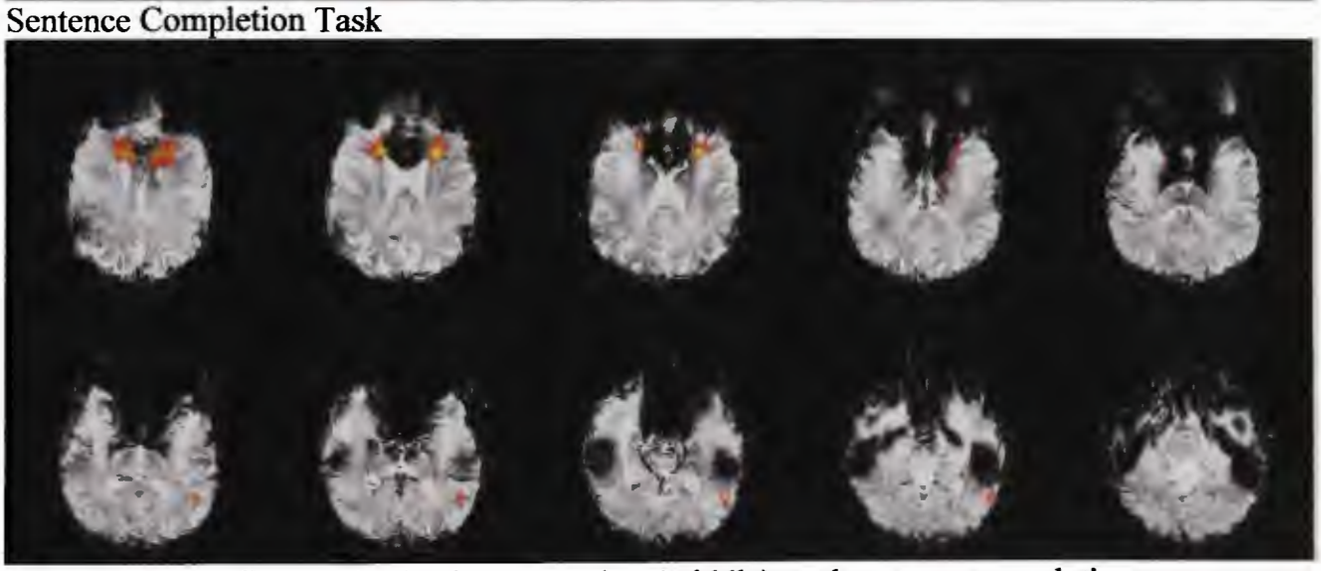


Figure 9. Letter fluency (top), picture naming (middle), and sentence completion (bottom) fMRI activation on axial slices for participant C2. Images are shown in radiological convention: the left hemisphere is displayed on the right side of the image.

Table 15

Language task results for C3

Localisation	Cluster Size	Z	x	y	z
Letter Fluency					
	Nil				
Category Fluency					
	Nil				
Picture Naming					
	Nil				
Sentence Completion					
L IFG BA47	185	6.82	41	26.3	-6.53
L Insula BA13	133	6.39	39.2	0.809	19.8

Note. Local maxima in MNI coordinates. Only the local maxima with highest Z score in each cluster are provided in the table. Cluster size is in voxels. When the cluster encompasses more than one anatomical location, the localization given corresponds to the local maxima with the highest Z score. L, left; MFG, middle frontal gyrus.

Sentence Completion Task

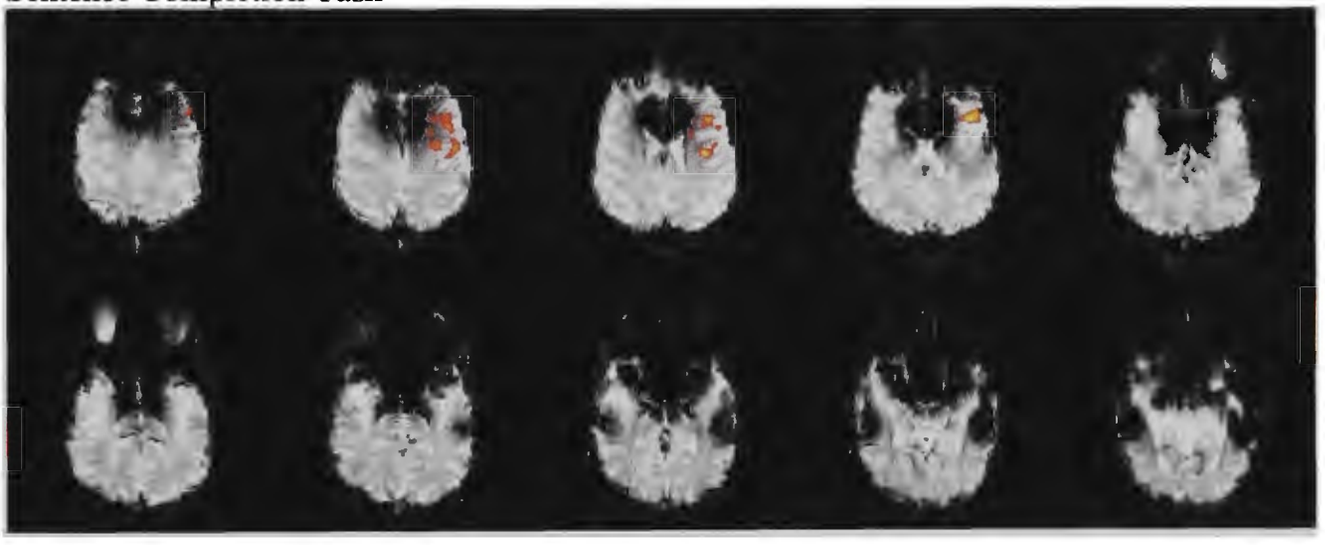


Figure 10. Sentence completion fMRI activation on axial slices for participant C3. Images are shown in radiological convention: the left hemisphere is displayed on the right side of the image.

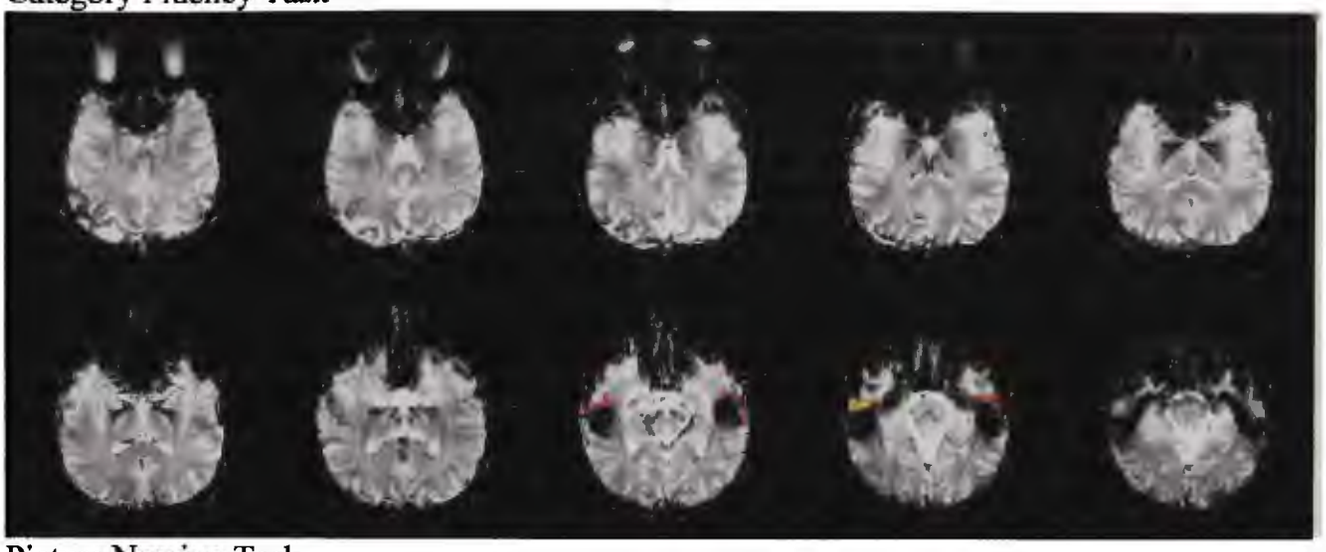
Table 16

Language task results for C4.

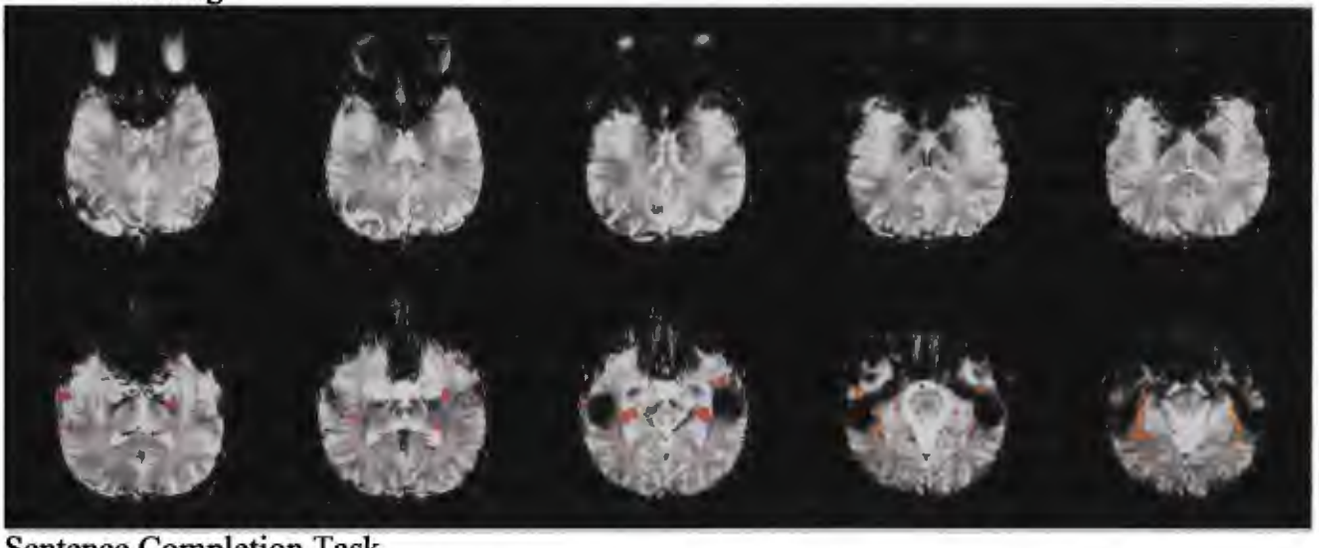
Localisation	Cluster Size	Z	x	y	z
Letter Fluency					
	Nil				
Category Fluency					
R Fusiform BA20	132	5.51	-57	-18.8	-27.6
L MTG BA21	102	4.23	68.2	-19.8	-15.7
Picture Naming					
R ParahipG BA19	217	5.79	-40.6	-41.7	-6.74
L Fusiform BA20	163	5.99	37.3	-36.3	-20.2
L ITG BA20	111	4.1	46.4	-13.4	-31.3
R Fusiform BA20	91	5.14	-57.8	-17.3	-29
Sentence Completion					
L STG BA42	94	5.5	58.1	-32.9	5.45

Note. Local maxima in MNI coordinates. Only the local maxima with highest Z score in each cluster are provided in the table. Cluster size is in voxels. When the cluster encompasses more than one anatomical location, the localization given corresponds to the local maxima with the highest Z score. L, left; R, right; MTG, middle temporal gyrus; ParahipG, parahippocampal gyrus; Fusiform, fusiform gyrus; ITG, inferior temporal gyrus; STG, superior temporal gyrus.

Category Fluency Task



Picture Naming Task



Sentence Completion Task

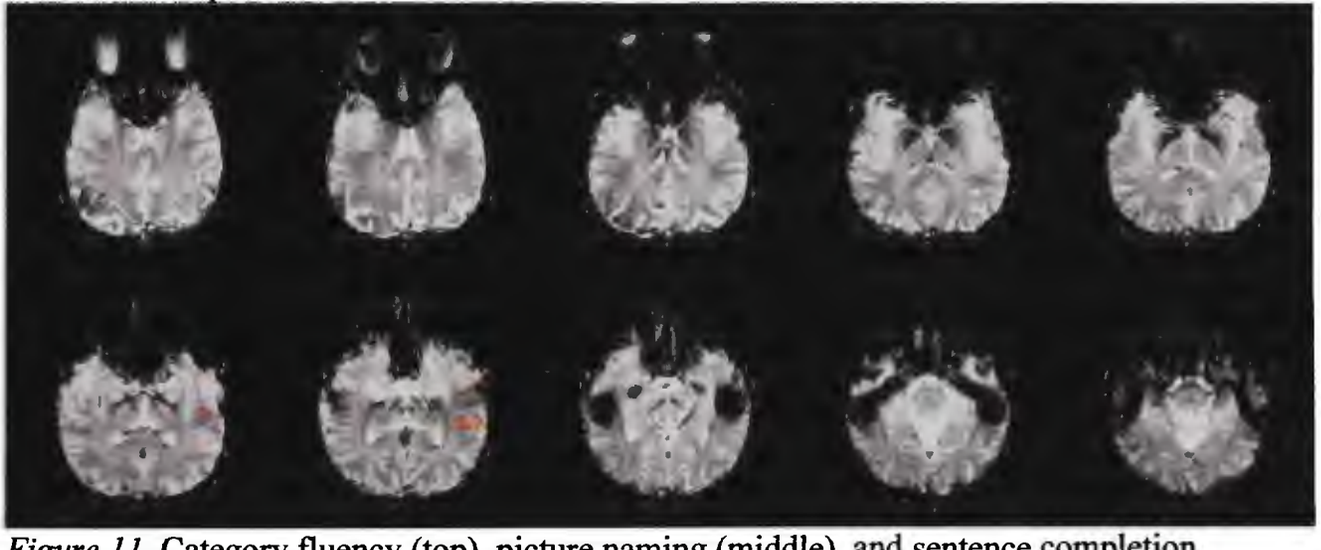


Figure 11. Category fluency (top), picture naming (middle), and sentence completion (bottom) fMRI activation on axial slices for participant C4. Images are shown in radiological convention: the left hemisphere is displayed on the right side of the image.

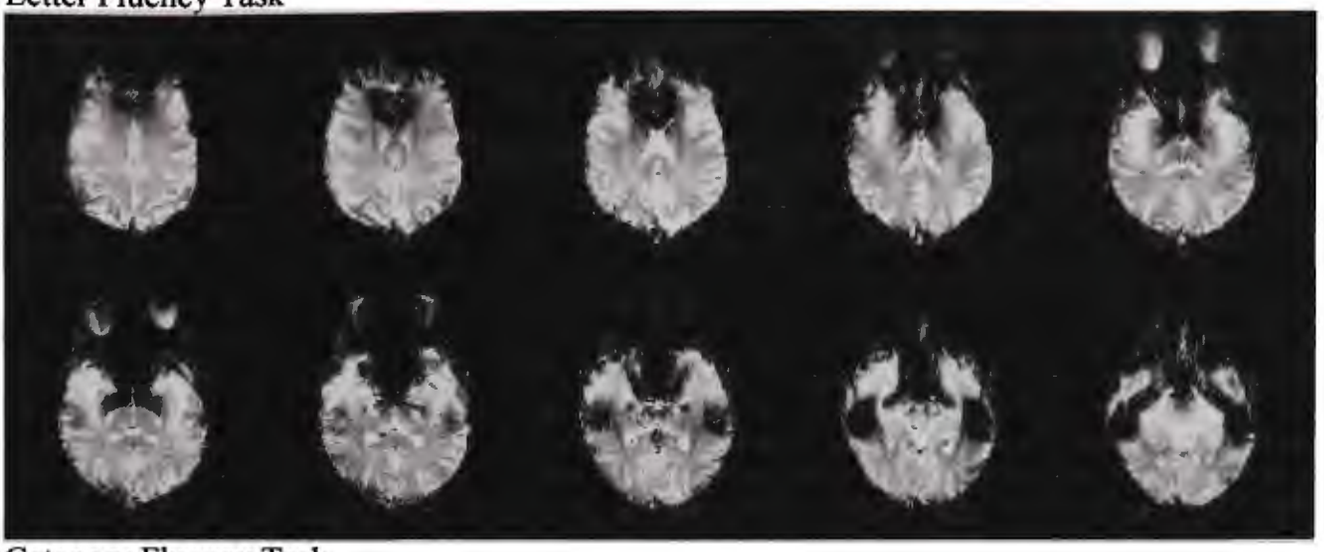
Table 17

Language task results for C5.

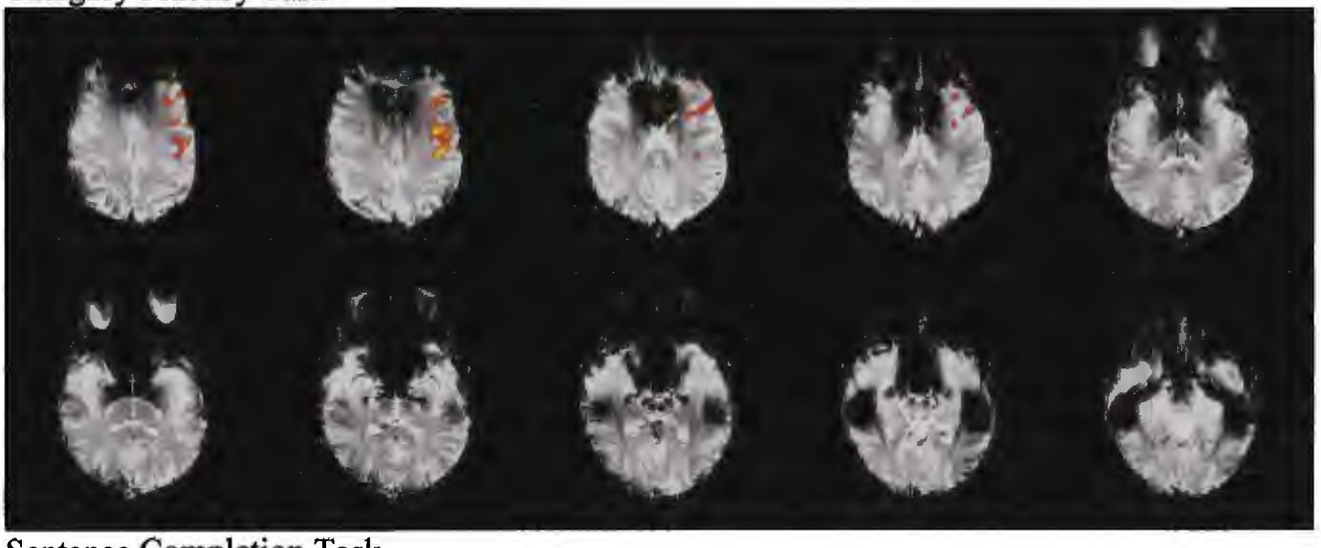
Localisation	Cluster Size	Z	x	y	z
Letter Fluency					
L MFG BA46	271	5.62	45.1	17.7	24
Category Fluency					
L IFG BA9	447	7.15	39.4	14.1	26.2
Picture Naming					
	Nil				
Sentence Completion					
L IFG BA44	127	7	53	4.73	13.6
L MTG BA21	119	6.66	60.8	-42.6	-2.98

Note. Local maxima in MNI coordinates. Only the local maxima with highest Z score in each cluster are provided in the table. Cluster size is in voxels. When the cluster encompasses more than one anatomical location, the localization given corresponds to the local maxima with the highest Z score. L, left; MFG, middle frontal gyrus; IFG, inferior frontal gyrus; MTG, middle temporal gyrus.

Letter Fluency Task



Category Fluency Task



Sentence Completion Task

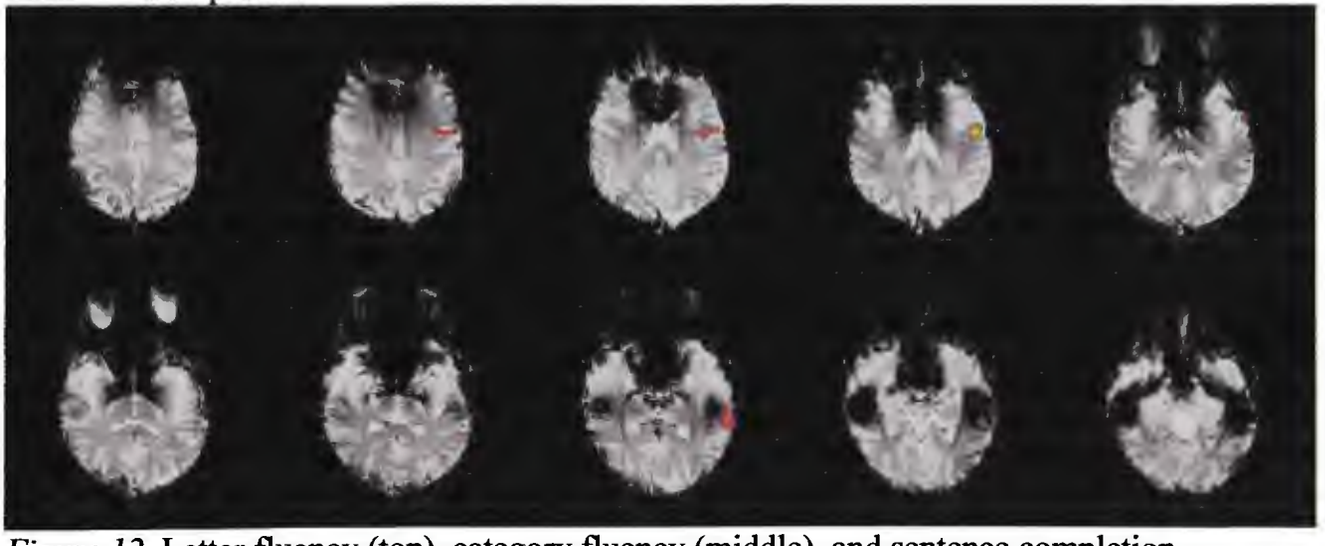


Figure 12. Letter fluency (top), category fluency (middle), and sentence completion (bottom) fMRI activation on axial slices for participant C5. Images are shown in radiological convention: the left hemisphere is displayed on the right side of the image.

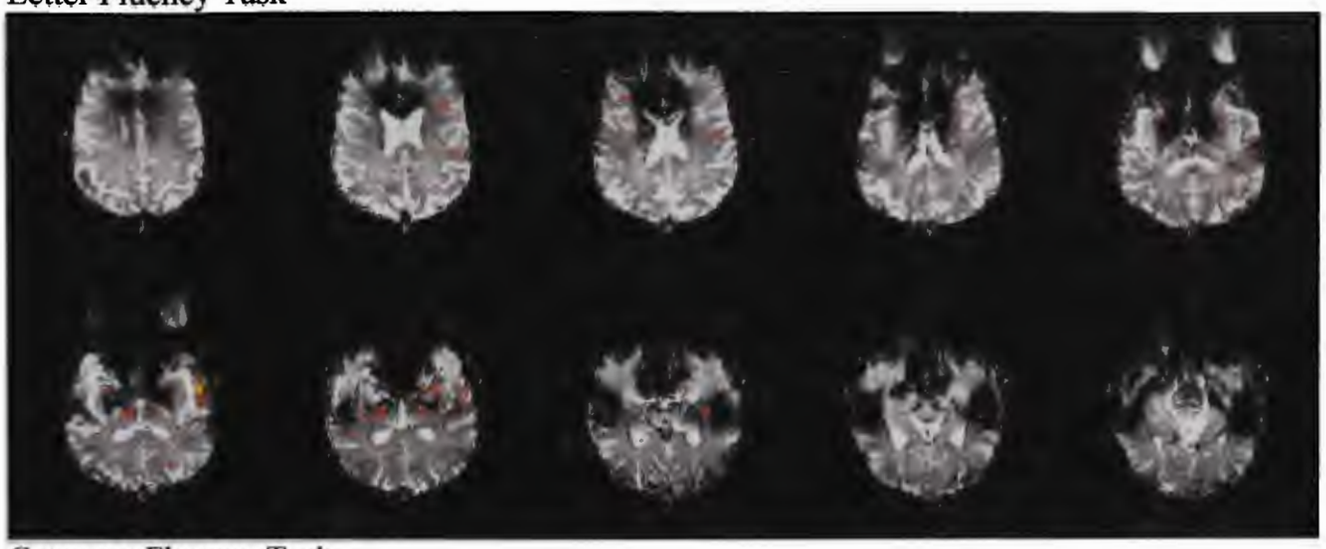
Table 18

Language task results for C6.

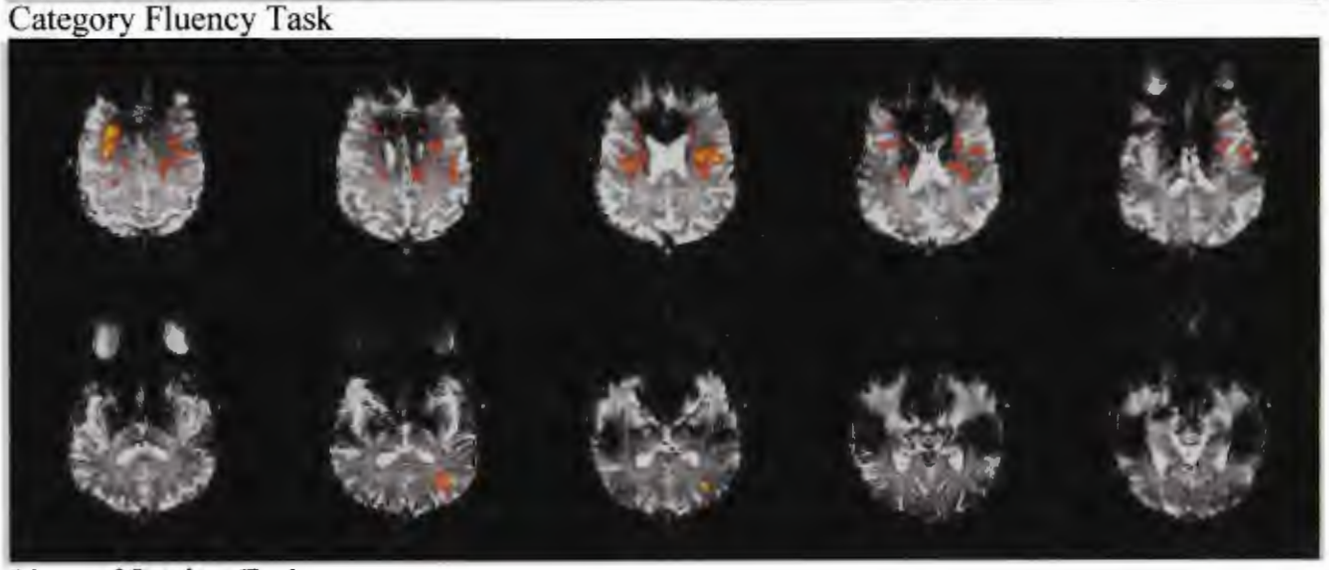
Localisation	Cluster Size	Z	x	y	z
Letter Fluency					
L STG BA22	3298	9.05	55.4	0.125	1.33
R Thalamus	1722	7.08	-7.38	-19.7	7.45
Category Fluency					
L PreCG BA4	637	5.96	46	-10.8	41.5
R MFG	513	6.43	-28.5	33.4	16.9
L MTG BA39	109	5.87	31.1	-69.6	23.5
Picture Naming					
L STG BA38	1908	6.08	45.9	19	-36.7
R STG BA38	376	5.61	-41.2	24.1	-39.2
L Fusiform BA19	213	4.85	51.8	-67.1	-23.9
L STG BA22	183	4.51	56.5	-42.9	9.86
L Precuneus BA7	183	6.25	10.7	-81.4	54.6
R SPL BA7	168	5.19	-13.1	-80.8	60.7
R Fusiform BA20	167	5.42	-41.7	-28.8	-24.8
R MTG BA19	89	4.23	-49.4	-82.5	6.56
Sentence Completion					
L MTG BA21	1660	8.32	41.6	1.37	-35.2
L IPL BA40	1288	8.86	46.4	-49.7	56.2
L PreCG BA6	347	7.2	39.8	-0.267	26
L MTG BA21	228	6.94	65.7	-60.4	3.94
R SPL BA7	197	7.32	-22.8	-67.1	60.3
R Fusiform BA37	193	6.46	-44.6	-41.5	-17.5
R MOG BA19	98	6.33	-50.3	-83.5	15.7

Note. Local maxima in MNI coordinates. Only the local maxima with highest Z score in each cluster are provided in the table. Cluster size is in voxels. When the cluster encompasses more than one anatomical location, the localization given corresponds to the local maxima with the highest Z score. L, left; R, right; STG, superior temporal gyrus; PreCG, precentral gyrus; MFG, middle frontal gyrus; MTG, middle temporal gyrus; Fusiform, fusiform gyrus; SPL, superior parietal lobule; IPL, inferior parietal lobule; MOG, middle occipital gyrus.

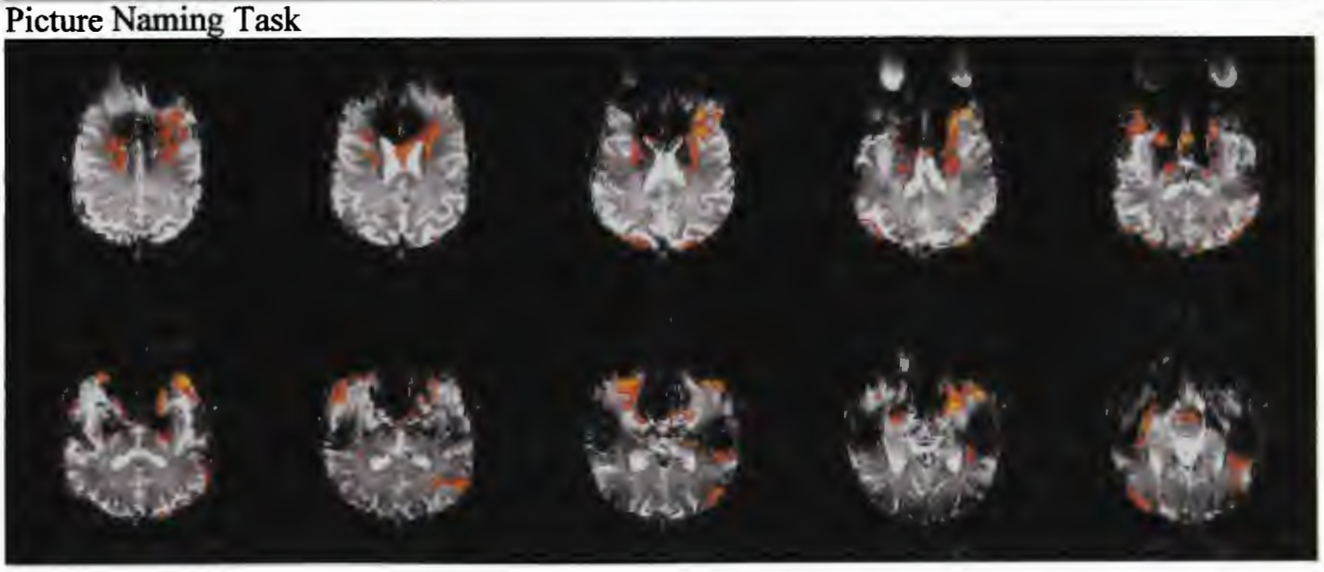
Letter Fluency Task



Category Fluency Task



Picture Naming Task



Sentence Completion Task

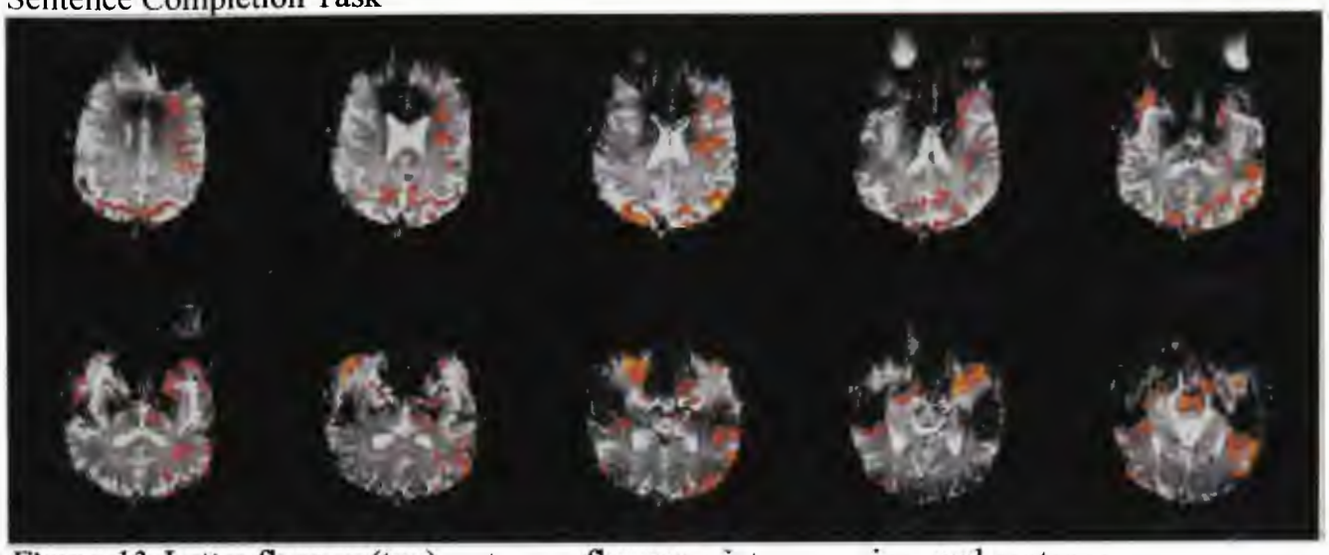


Figure 13. Letter fluency (top), category fluency, picture naming, and sentence completion (bottom) fMRI activation on axial slices for participant C6. Images are shown in radiological convention: the left hemisphere is displayed on the right side of the image.

Table 19

Language task results for C7.

Localisation	Cluster Size	Z	x	y	z
Letter Fluency					
	Nil				
Category Fluency					
	Nil				
Picture Naming					
	Nil				
Sentence Completion					
L STG BA22	146	8.78	49.3	-36.1	1.56

Note. Local maxima in MNI coordinates. Only the local maxima with highest Z score in each cluster are provided in the table. Cluster size is in voxels. When the cluster encompasses more than one anatomical location, the localization given corresponds to the local maxima with the highest Z score. L, left; STG, superior temporal gyrus.

Sentence Completion Task

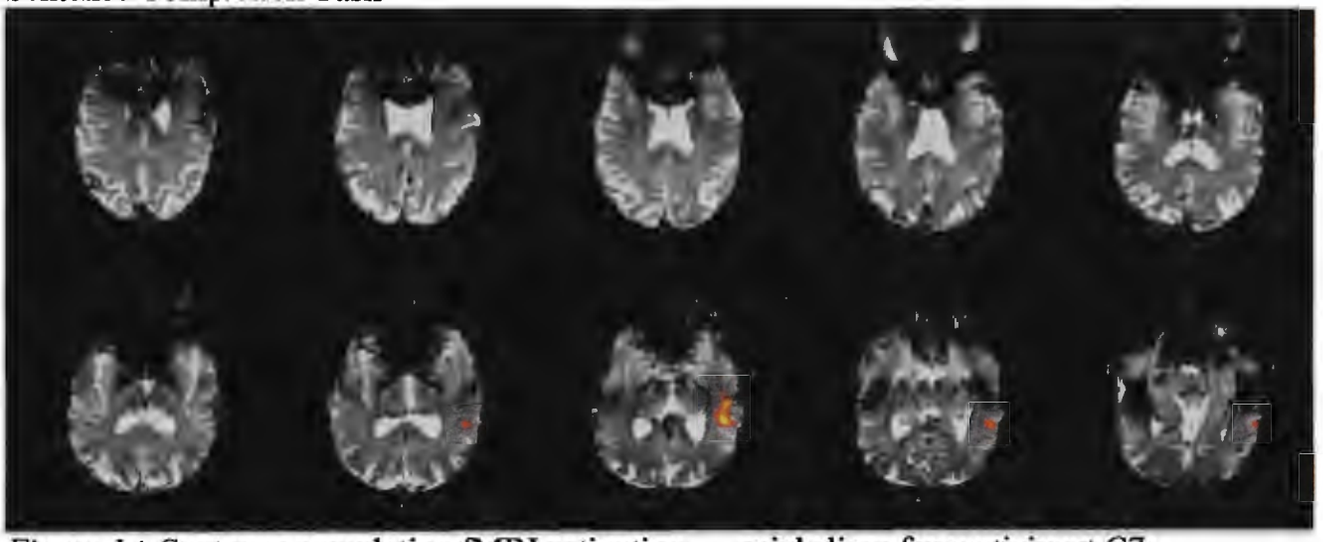


Figure 14. Sentence completion fMRI activation on axial slices for participant C7. Images are shown in radiological convention: the left hemisphere is displayed on the right side of the image.

Table 20

Language task results for C8.

Localisation	Cluster Size	Z	x	y	z
Letter Fluency					
	Nil				
Category Fluency					
	Nil				
Sentence Completion					
L IFG BA9	444	8.32	42.1	9.08	30.7
L STG BA22	174	8.83	62.4	-40.5	16.4
R Insula BA13	173	5.18	-31.4	16.2	15
R IFG BA13	139	7.43	26.3	-55.1	35.1
L STG BA38	102	4.88	53.5	5.68	-5.15

Note. Local maxima in MNI coordinates. Only the local maxima with highest Z score in each cluster are provided in the table. Cluster size is in voxels. When the cluster encompasses more than one anatomical location, the localization given corresponds to the local maxima with the highest Z score. L, left; R, right, IFG, inferior frontal gyrus; STG, superior temporal gyrus.

Sentence Completion Task

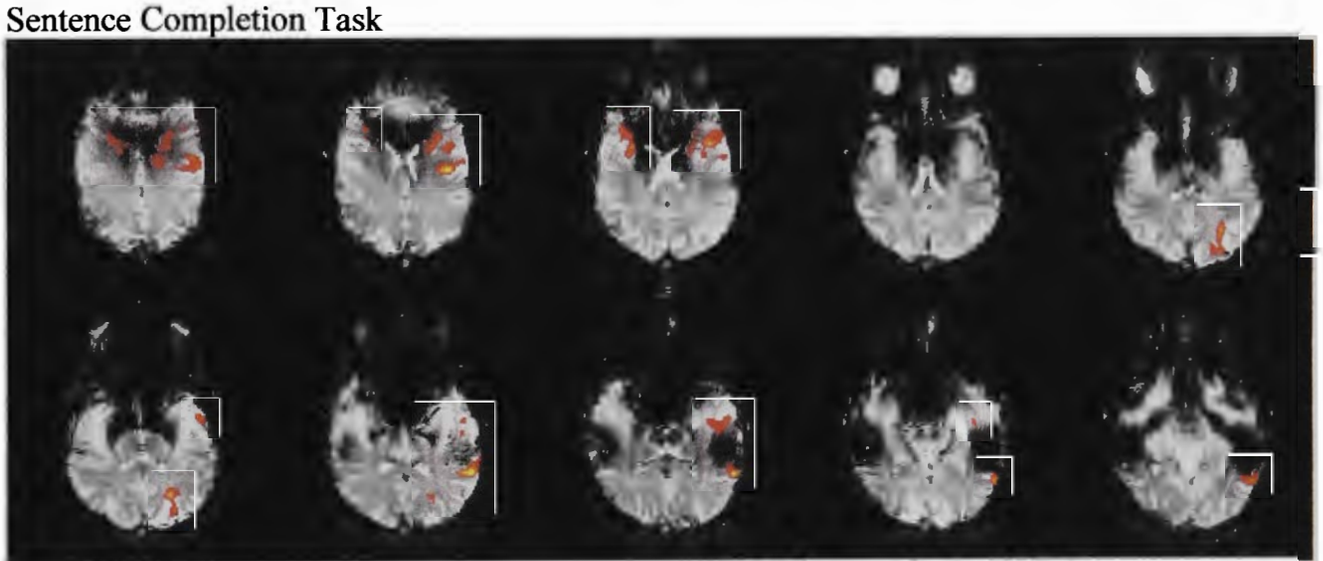


Figure 15. Sentence completion fMRI activation on axial slices for participant C8. Images are shown in radiological convention: the left hemisphere is displayed on the right side of the image.

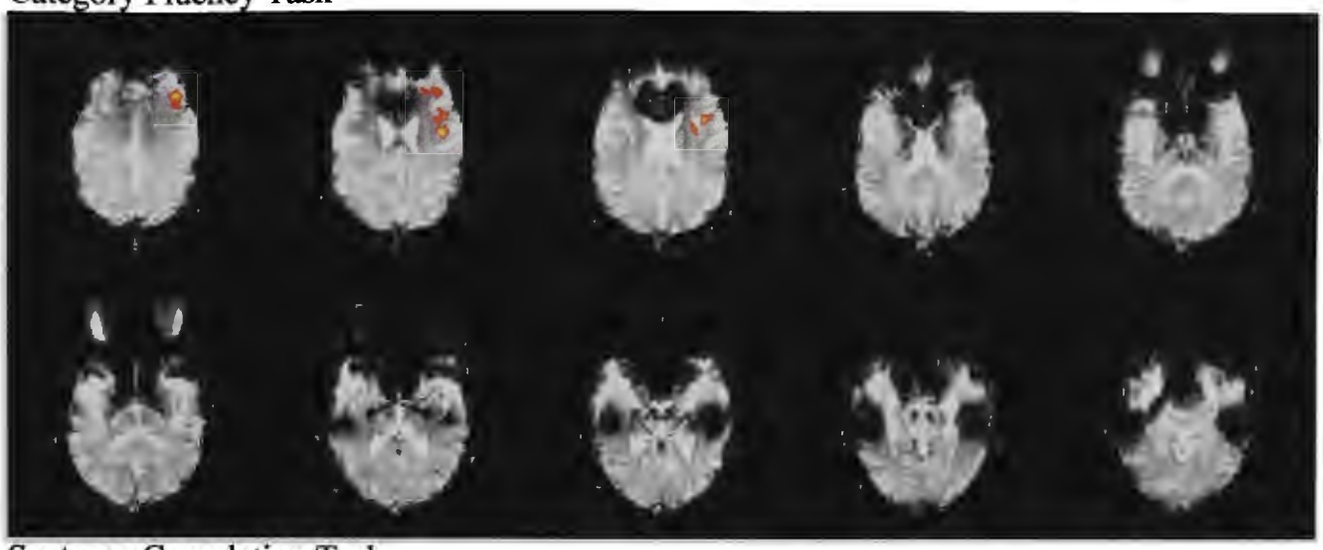
Table 21

Language task results for C9.

Localisation	Cluster Size	Z	x	y	z
Letter Fluency					
	Nil				
Category Fluency					
L IFG BA9	199	6.51	44.1	11.6	22.2
Picture Naming					
	Nil				
Sentence Completion					
L MTG BA37	172	7.37	61.5	-47.8	-10.8
L IFG BA45	121	6.48	52.3	24	9.22

Note. Local maxima in MNI coordinates. Only the local maxima with highest Z score in each cluster are provided in the table. Cluster size is in voxels. When the cluster encompasses more than one anatomical location, the localization given corresponds to the local maxima with the highest Z score. L, left; MTG, middle temporal gyrus; IFG, inferior frontal gyrus.

Category Fluency Task



Sentence Completion Task

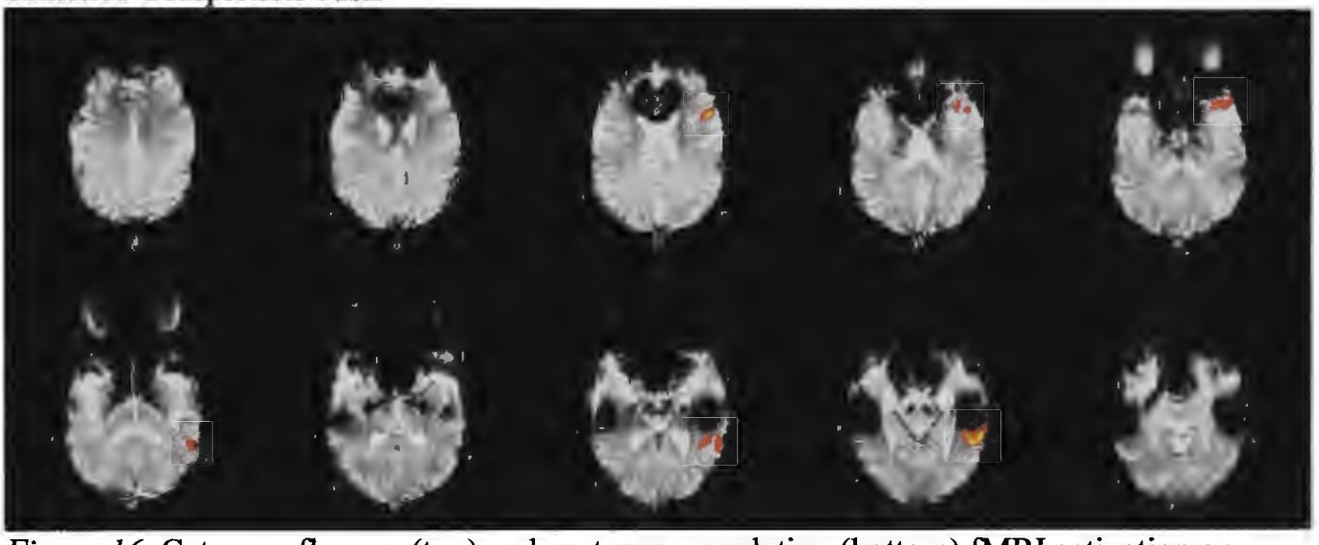


Figure 16. Category fluency (top) and sentence completion (bottom) fMRI activation on axial slices for participant C9. Images are shown in radiological convention: the left hemisphere is displayed on the right side of the image.

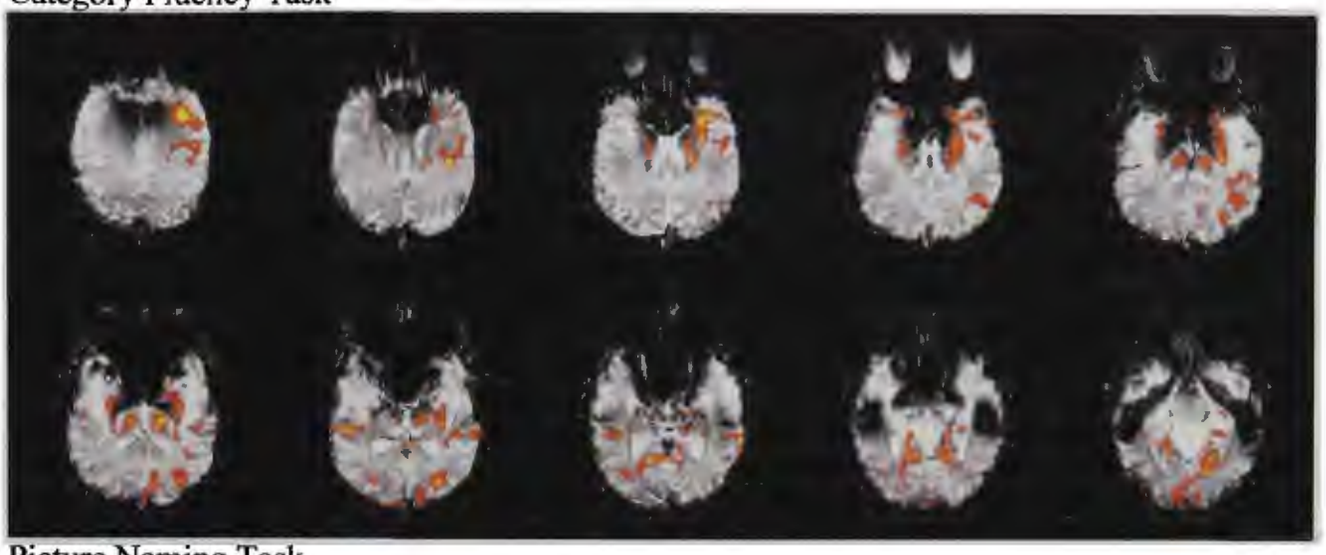
Table 22

Language task results for C10.

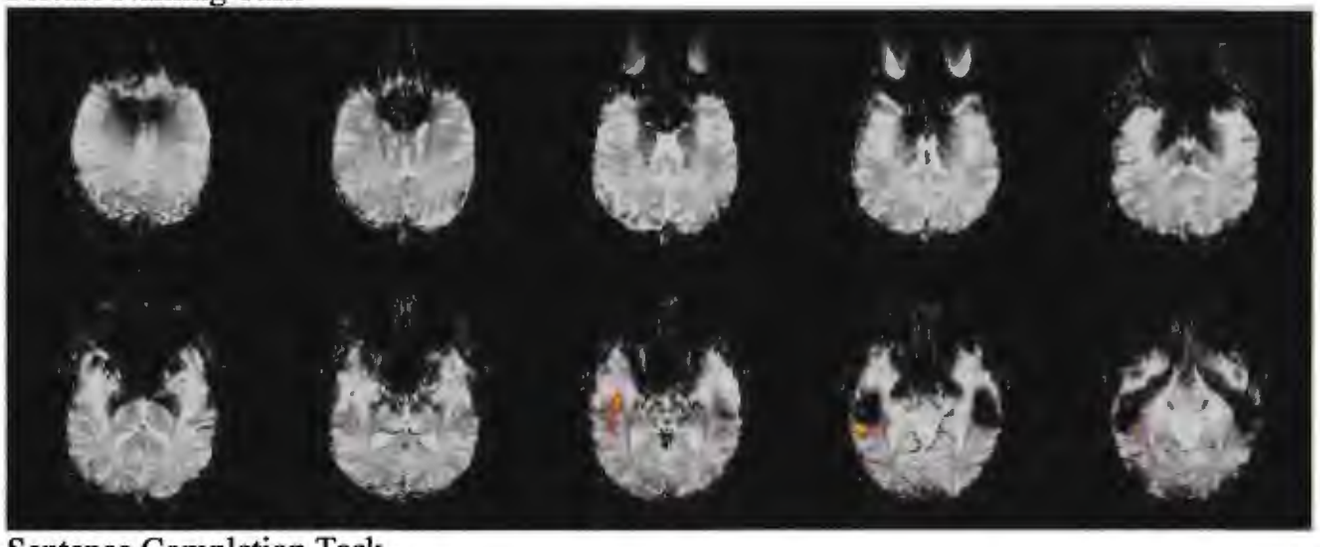
Localisation	Cluster Size	Z	x	y	z
Letter Fluency					
	Nil				
Category Fluency					
L MTG BA21	2789	6.6	69.6	-38.6	1.42
R IFG BA47	263	4.96	-30	27	-4.99
R STG BA41	119	6.02	-52.5	-30.7	7.76
R Thalamus	111	5.06	-10.9	-18.1	7.51
Picture Naming					
R MTG BA21	193	4.87	-59.3	-41.8	-3.32
Sentence Completion					
L MTG BA22	234	7.71	69.7	-38.9	1.57

Note. Local maxima in MNI coordinates. Only the local maxima with highest Z score in each cluster are provided in the table. Cluster size is in voxels. When the cluster encompasses more than one anatomical location, the localization given corresponds to the local maxima with the highest Z score. L, left; R, right; MTG, middle temporal gyrus; IFG, inferior frontal gyrus; STG, superior temporal gyrus.

Category Fluency Task



Picture Naming Task



Sentence Completion Task

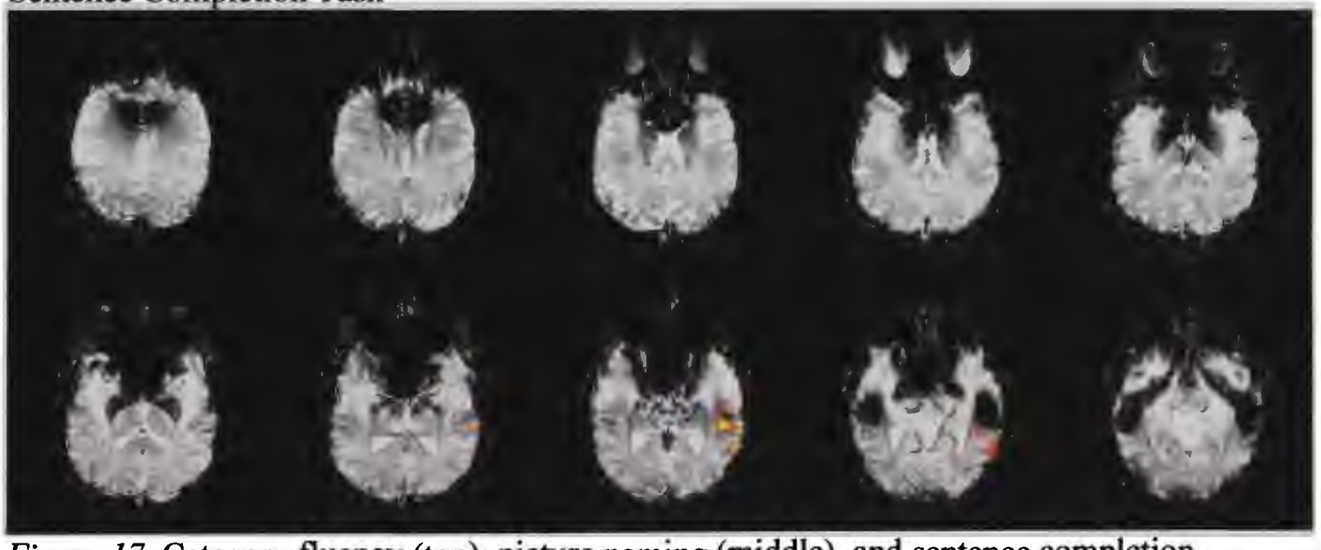


Figure 17. Category fluency (top), picture naming (middle), and sentence completion (bottom) fMRI activation on axial slices for participant C10. . Images are shown in radiological convention: the left hemisphere is displayed on the right side of the image.

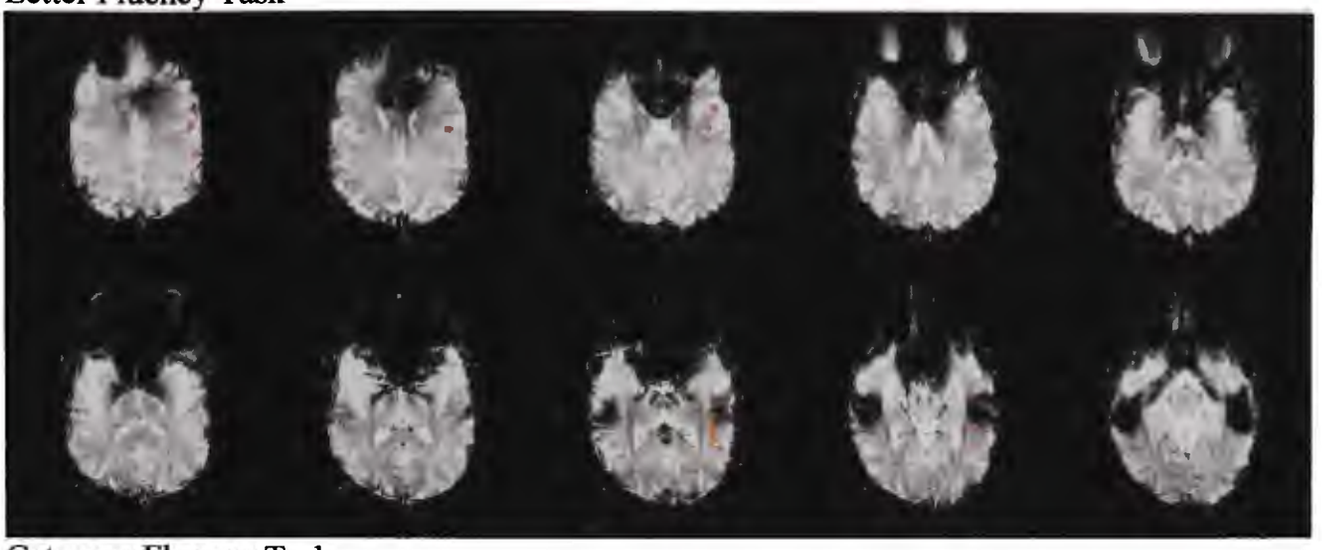
Table 23

Language task results for C11.

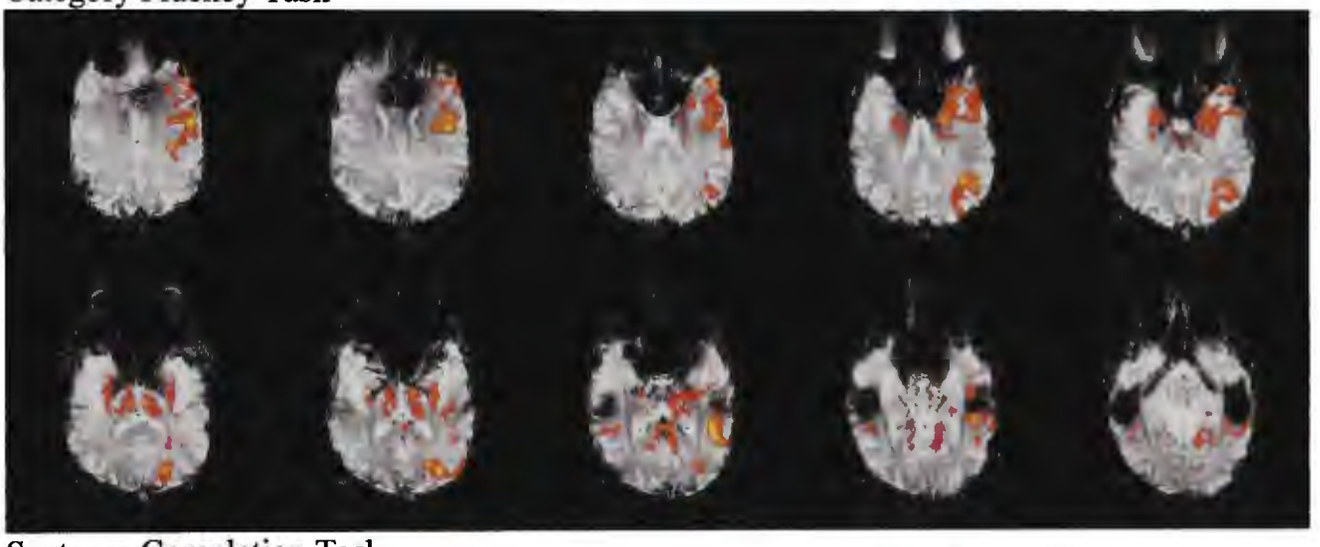
Localisation	Cluster Size	Z	x	y	z
Letter Fluency					
L IFG BA46	523	7.38	58.7	37.9	8.08
L Thalamus	292	4.66	7.91	-19.7	1.2
L STG BA13	203	8.15	45.6	-48.7	12.5
R Putamen	139	4.59	-20.3	9.93	16
L PreCG BA6	112	7.47	56.5	-7.51	46.9
L MTG BA39	106	5.35	29.1	-69	25.6
Category Fluency					
L STG BA41	2574	8.4	45.9	-43.8	9.24
L Precueus BA19	650	7.65	32.8	-71.8	36.2
R Thalamus	418	5.6	-7.46	-15.9	7.09
R MTG BA21	86	5.69	-49.5	-46	8.47
Picture Naming					
	Nil				
Sentence Completion					
L STG BA22	1053	10.8	53.2	-52.6	15.2
L IFG BA46	638	9.46	57.1	37.2	8.49
L Thalamus	187	4.65	17.9	-17.2	-0.233
L OL BA19	154	6.22	12.1	-99.9	28.1
R STG BA22	135	5.28	-55.3	-43.4	6.62

Note. Local maxima in MNI coordinates. Only the local maxima with highest Z score in each cluster are provided in the table. Cluster size is in voxels. When the cluster encompasses more than one anatomical location, the localization given corresponds to the local maxima with the highest Z score. L, left; R, right; MTG, middle temporal gyrus; IFG, inferior frontal gyrus; STG, superior temporal gyrus; PreCG, precentral gyrus; OL, occipital lobe.

Letter Fluency Task



Category Fluency Task



Sentence Completion Task

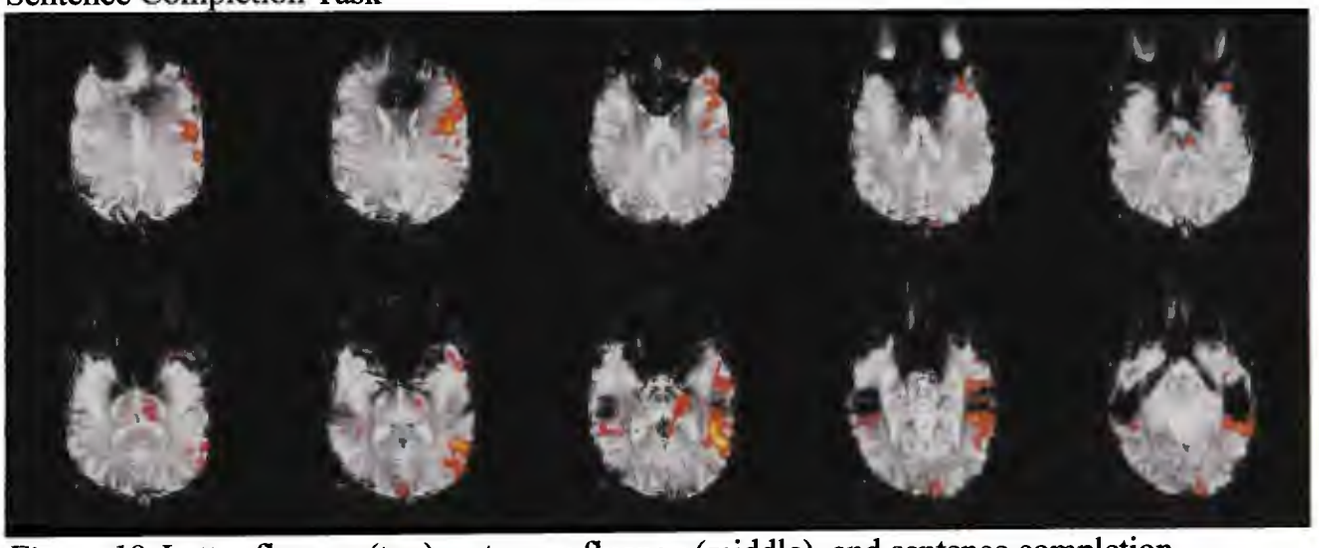


Figure 18. Letter fluency (top), category fluency (middle), and sentence completion (bottom) fMRI activation on axial slices for participant C11. Images are shown in radiological convention: the left hemisphere is displayed on the right side of the image.

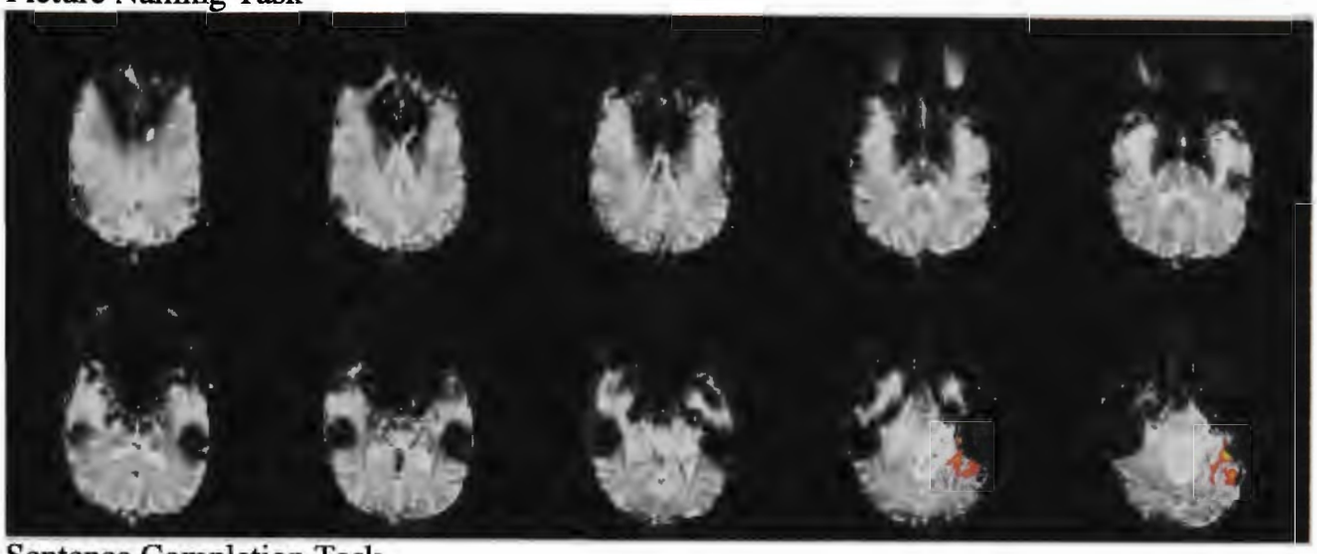
Table 24

Language task results for C12.

Localisation	Cluster Size	Z	x	y	z
Letter Fluency					
	Nil				
Category Fluency					
	Nil				
Picture Naming					
L Fusiform BA37	249	5.98	43.9	-51.8	-27.3
Sentence Completion					
L OL BA31	90	5.35	21.1	-71.5	22.7

Note. Local maxima in MNI coordinates. Only the local maxima with highest Z score in each cluster are provided in the table. Cluster size is in voxels. When the cluster encompasses more than one anatomical location, the localization given corresponds to the local maxima with the highest Z score. L, left; Fusiform, fusiform gyrus; OL, occipital lobe.

Picture Naming Task



Sentence Completion Task

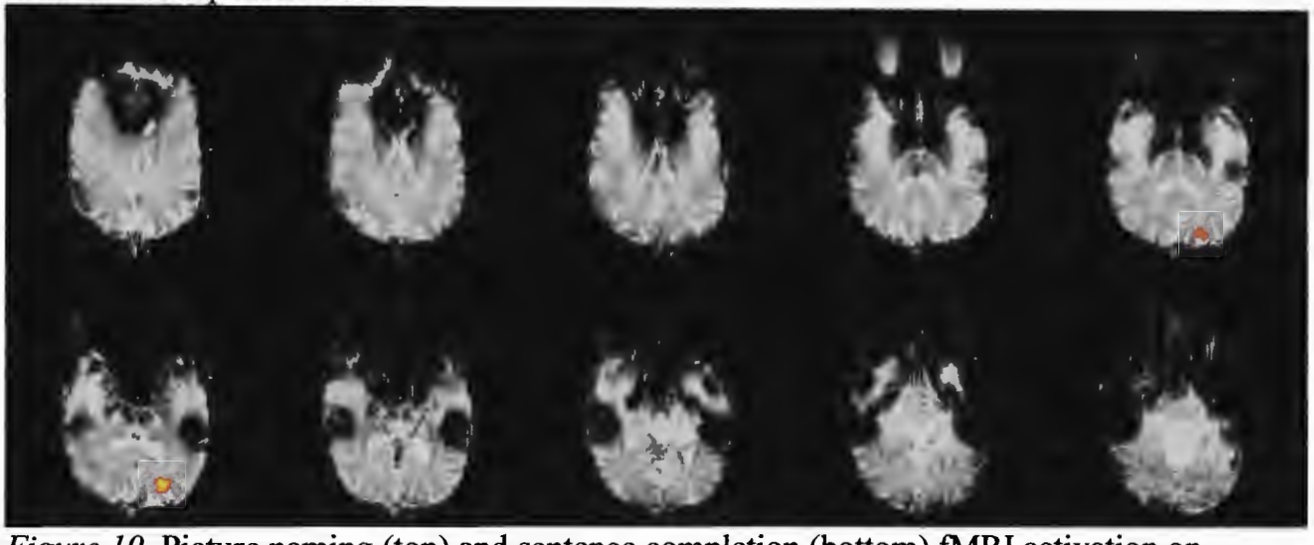


Figure 19. Picture naming (top) and sentence completion (bottom) fMRI activation on axial slices for participant C12. Images are shown in radiological convention: the left hemisphere is displayed on the right side of the image.

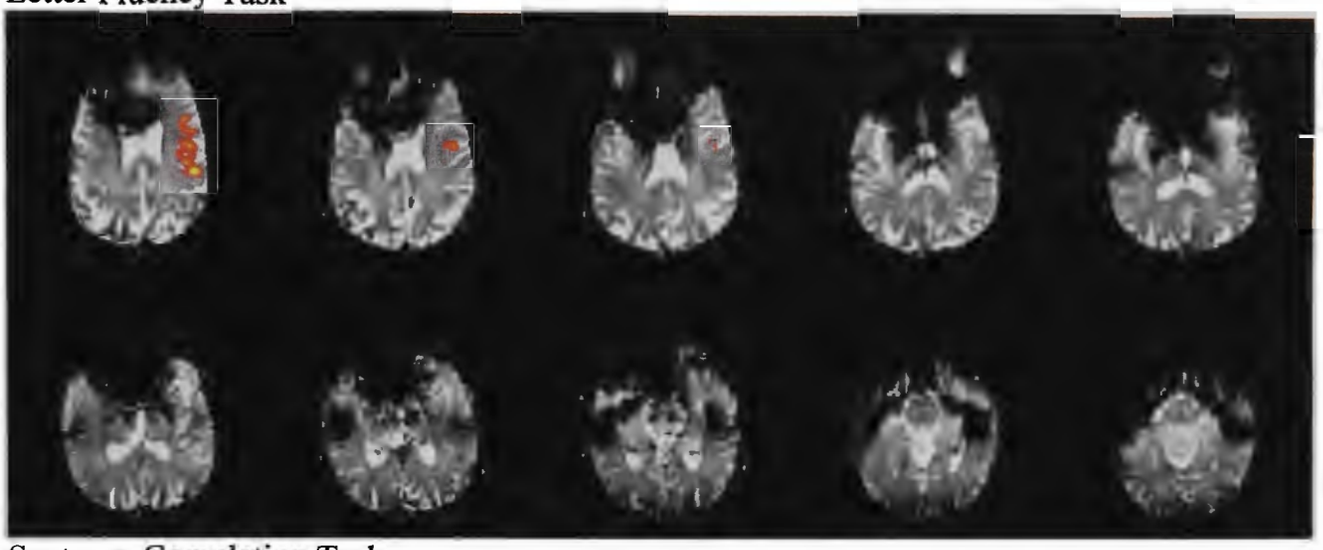
Table 25

Language task results for C13.

Localisation	Cluster Size	Z	x	y	z
Letter Fluency					
L MFG BA6	268	8.15	46.6	0.362	43.8
Category Fluency					
	Nil				
Picture Naming					
	Nil				
Sentence Completion					
L STG BA22	157	6.31	58.8	-53.7	4.9

Note. Local maxima in MNI coordinates. Only the local maxima with highest Z score in each cluster are provided in the table. Cluster size is in voxels. When the cluster encompasses more than one anatomical location, the localization given corresponds to the local maxima with the highest Z score. L, left; MFG, middle frontal gyrus; STG, superior temporal gyrus

Letter Fluency Task



Sentence Completion Task

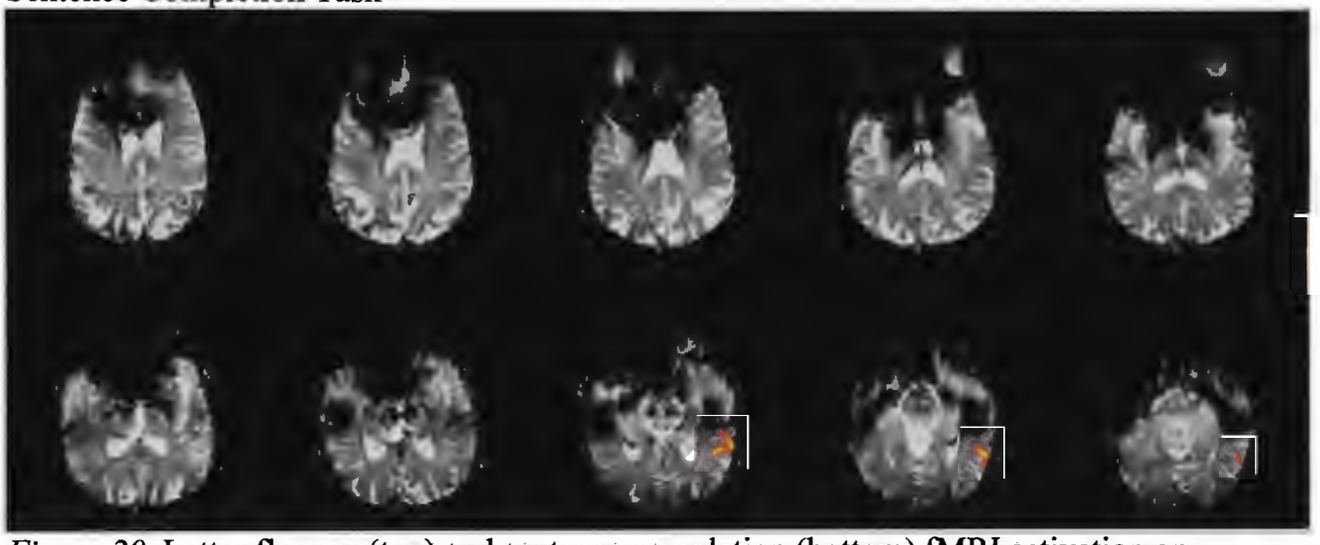


Figure 20. Letter fluency (top) and sentence completion (bottom) fMRI activation on axial slices for participant C13. Images are shown in radiological convention: the left hemisphere is displayed on the right side of the image.

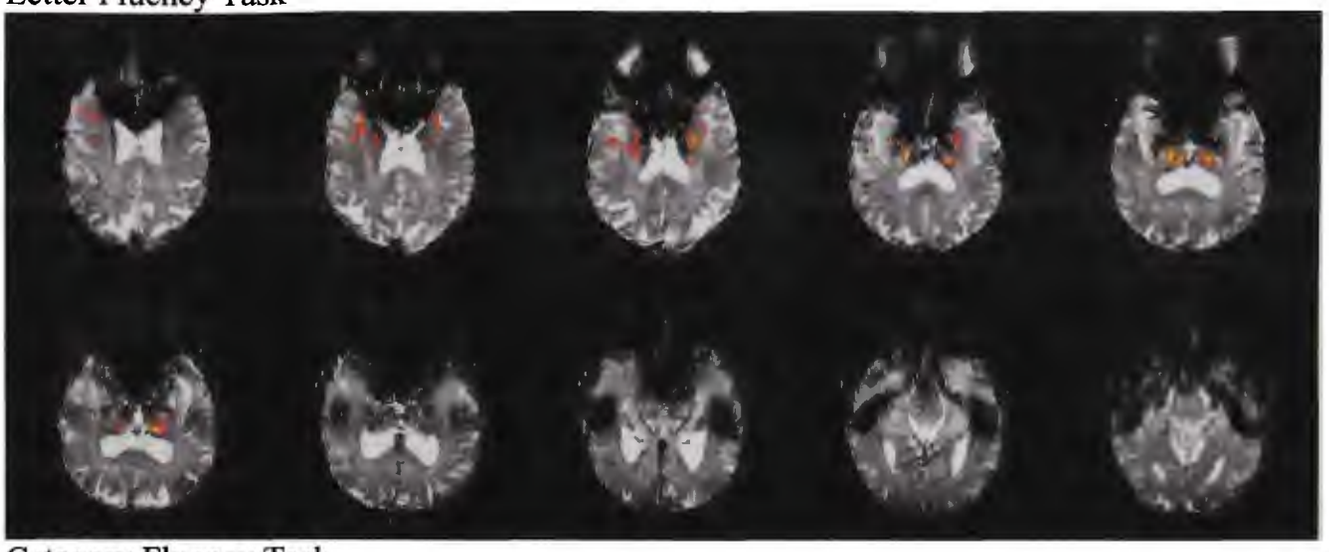
Table 26

Language task results for C14.

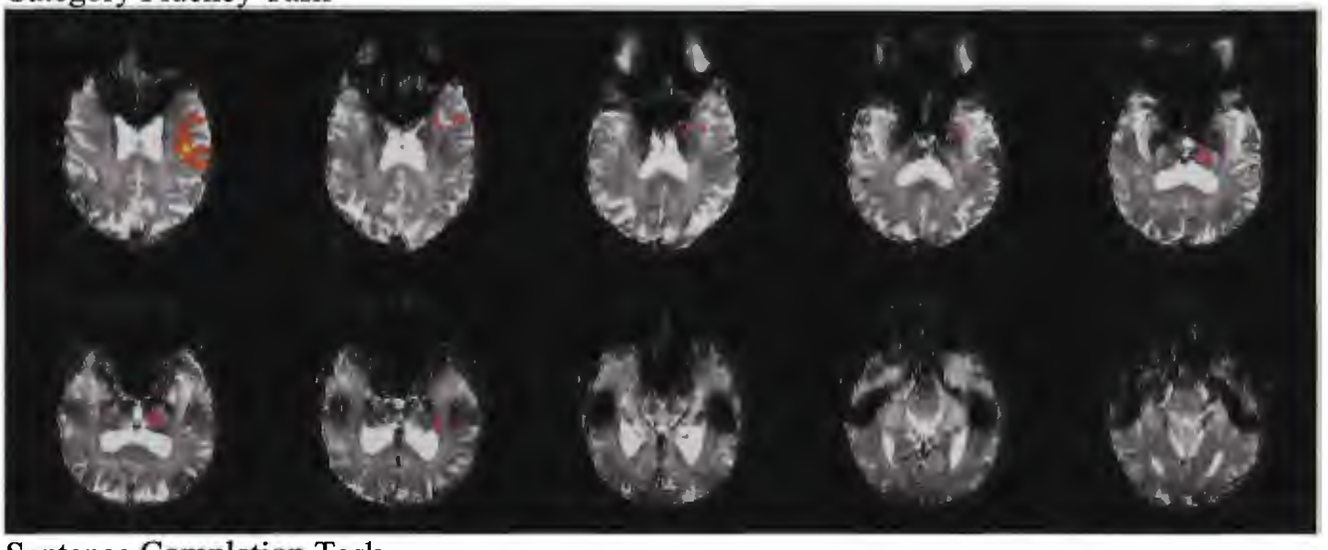
Localisation	Cluster Size	Z	x	y	z
Letter Fluency					
R Thalamus	384	6.46	-8.11	-16.8	8.17
L Thalamus	343	5.96	17.7	-16.1	9.23
Category Fluency					
L IFG BA9	329	8.46	42.9	4.8	33.2
L Thalamus	125	5.79	15.9	-16	9.07
Picture Naming					
	Nil				
Sentence Completion					
L MTG BA21	282	7.35	62.4	-48.1	5.15

Note. Local maxima in MNI coordinates. Only the local maxima with highest Z score in each cluster are provided in the table. Cluster size is in voxels. When the cluster encompasses more than one anatomical location, the localization given corresponds to the local maxima with the highest Z score. L, left; R, right; MTG, middle temporal gyrus; IFG, inferior frontal gyrus.

Letter Fluency Task



Category Fluency Task



Sentence Completion Task

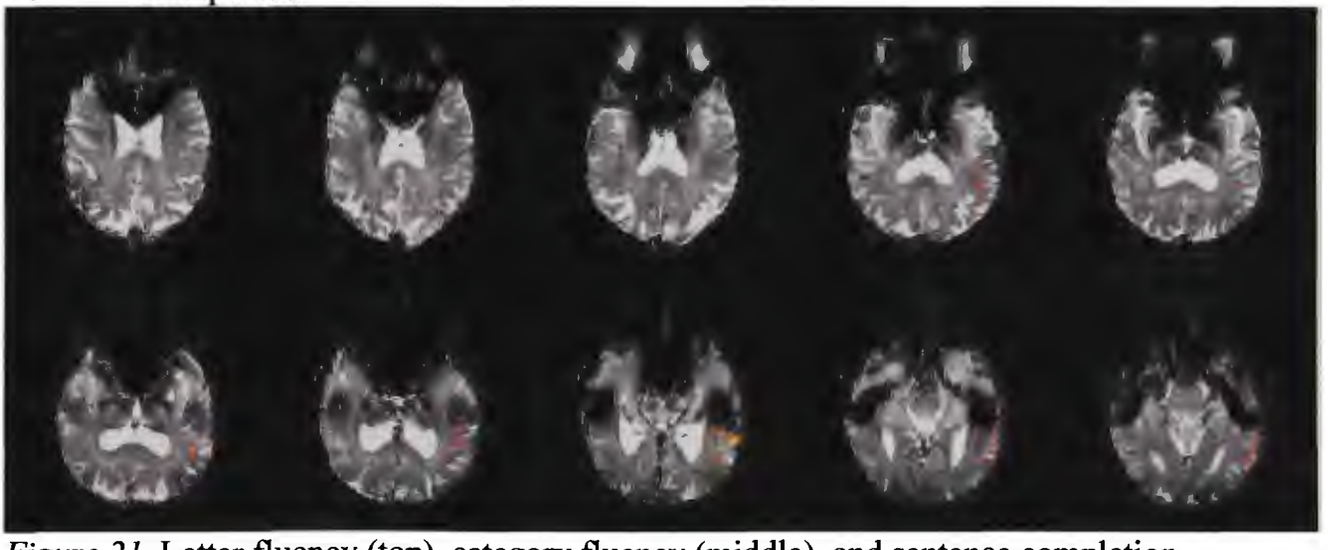


Figure 21. Letter fluency (top), category fluency (middle), and sentence completion (bottom) fMRI activation on axial slices for participant C14. Images are shown in radiological convention: the left hemisphere is displayed on the right side of the image.

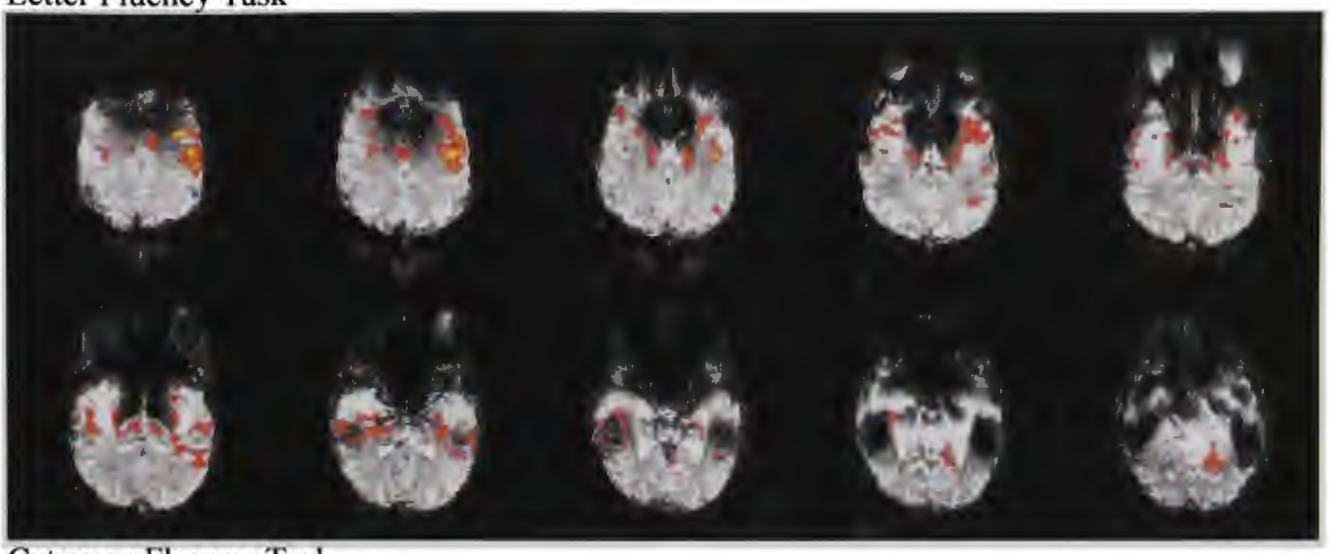
Table 27

Language task results for C15.

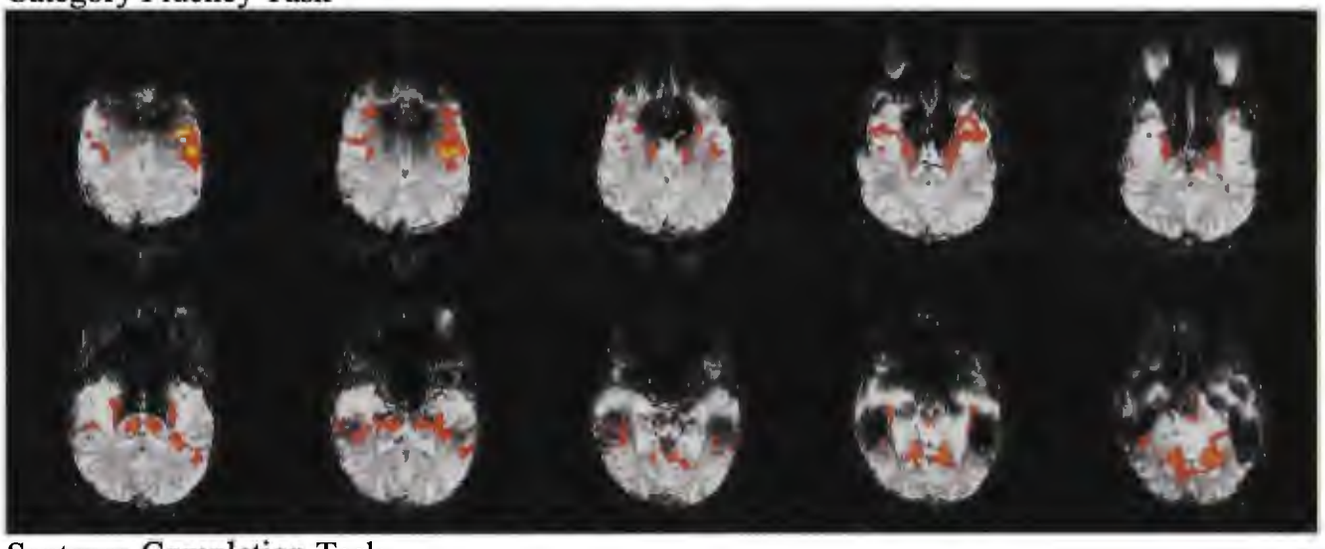
Localisation	Cluster Size	Z	x	y	z
Letter Fluency					
L MFG BA9	1357	7.85	35.3	25.8	30
L CingG BA32	1039	5.5	13.1	27.5	28.8
L ParahipGBA30	124	3.72	17.6	-50.6	0.559
Category Fluency					
L MFG BA9	2570	7.45	35.4	25.5	30.1
R STG BA41	289	4.73	-44.8	-30.2	6.72
Picture Naming					
	Nil				
Sentence Completion					
L PreCG BA6	1554	7.49	52.8	-3.62	47.4
R Putamen	1169	6.39	-24.4	10.7	1.31
L Precuneus	761	6.85	15.9	-64	45.6
R STG BA41	314	5.14	-43	-38.8	2.54

Note. Local maxima in MNI coordinates. Only the local maxima with highest Z score in each cluster are provided in the table. Cluster size is in voxels. When the cluster encompasses more than one anatomical location, the localization given corresponds to the local maxima with the highest Z score. L, left; R, right; MTG, middle temporal gyrus; IFG, inferior frontal gyrus.

Letter Fluency Task



Category Fluency Task



Sentence Completion Task

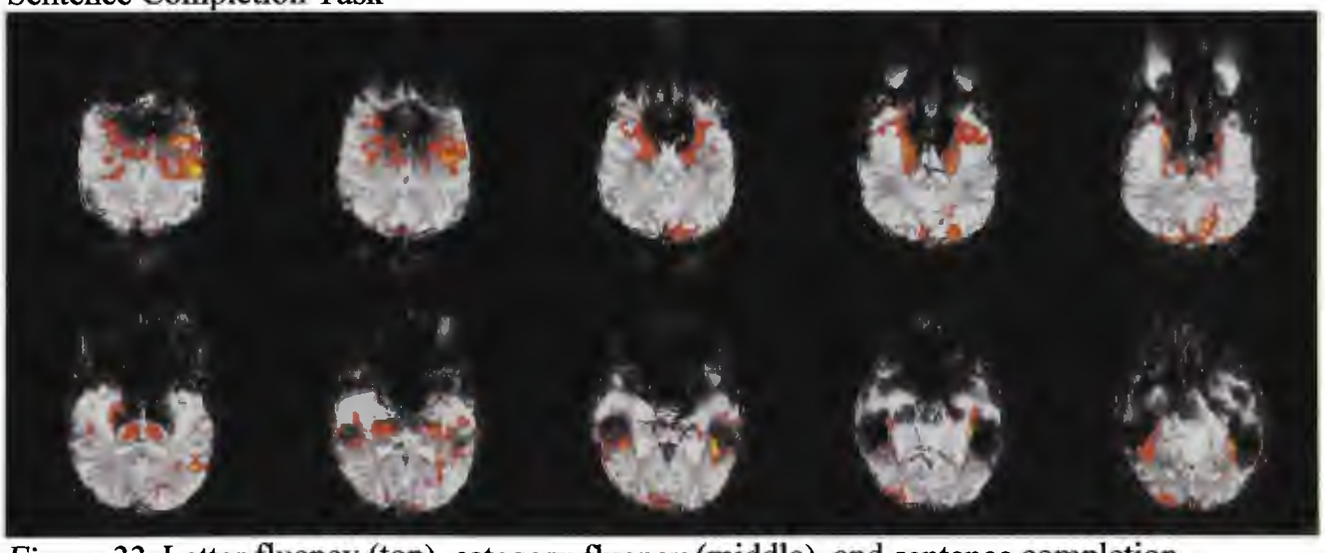


Figure 22. Letter fluency (top), category fluency (middle), and sentence completion (bottom) fMRI activation on axial slices for participant C15. Images are shown in radiological convention: the left hemisphere is displayed on the right side of the image.

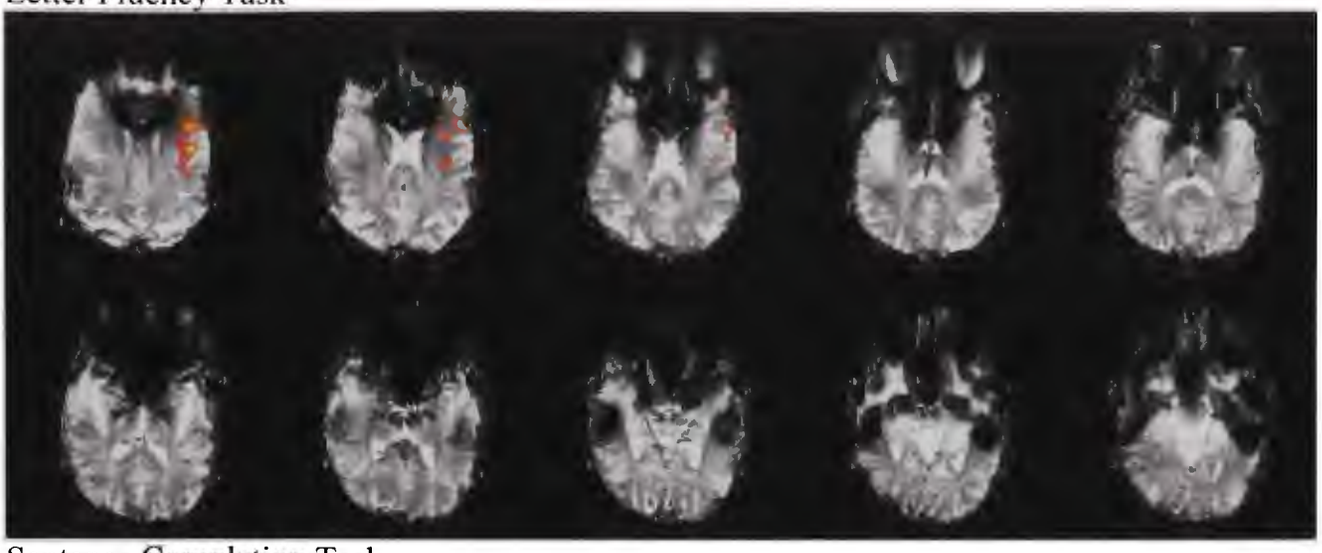
Table 28

Language task results for C16.

Localisation	Cluster Size	Z	x	y	z
Letter Fluency					
L MFG BA46	362	7.88	46.5	17.8	28.3
Category Fluency					
	Nil				
Picture Naming	Nil				
Sentence Completion	473	9.34	53.9	-53.7	1.36
L MTG BA37	251	8.74	37.5	7.47	34.2
L PreCG BA9					

Note. Local maxima in MNI coordinates. Only the local maxima with highest Z score in each cluster are provided in the table. Cluster size is in voxels. When the cluster encompasses more than one anatomical location, the localization given corresponds to the local maxima with the highest Z score. L, left; MTG, middle temporal gyrus; MFG, middle frontal gyrus; PreCG, precentral gyrus.

Letter Fluency Task



Sentence Completion Task

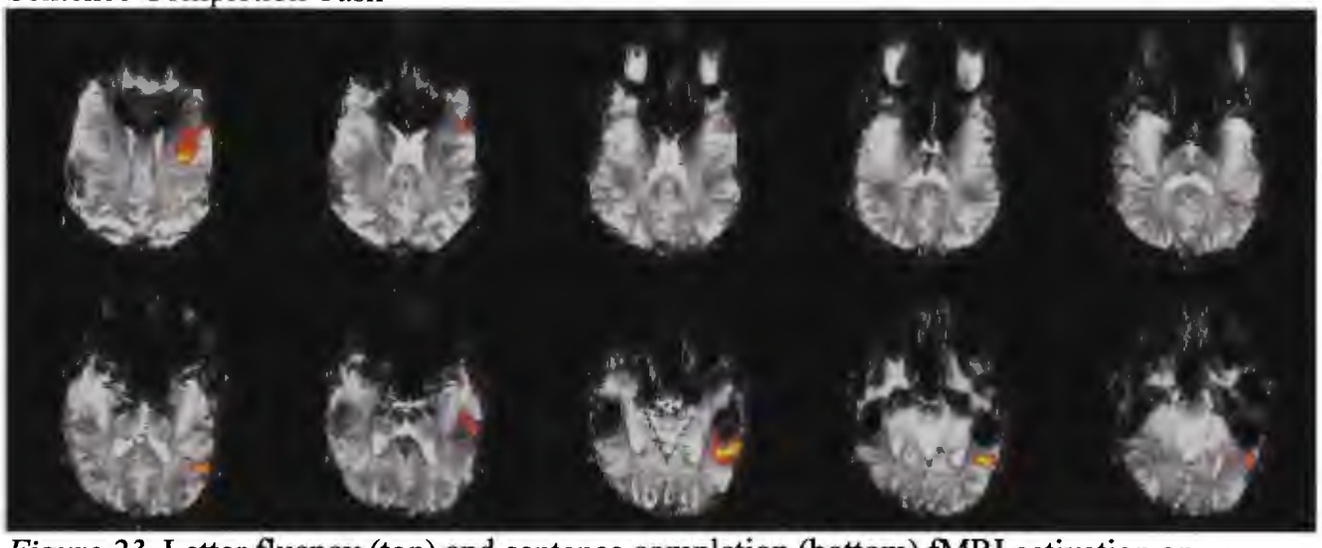


Figure 23. Letter fluency (top) and sentence completion (bottom) fMRI activation on axial slices for participant C16. Images are shown in radiological convention: the left hemisphere is displayed on the right side of the image.

Table 29

Language task results for C17.

Localisation	Cluster Size	Z	x	y	z
Category Fluency					
	Nil				
Picture Naming					
	Nil				
Sentence Completion					
L MTG	123	8.27	46.7	-44.7	-3.54

Note. Local maxima in MNI coordinates. Only the local maxima with highest Z score in each cluster are provided in the table. Cluster size is in voxels. When the cluster encompasses more than one anatomical location, the localization given corresponds to the local maxima with the highest Z score. L, left; MTG, middle temporal gyrus.

Sentence Completion Task

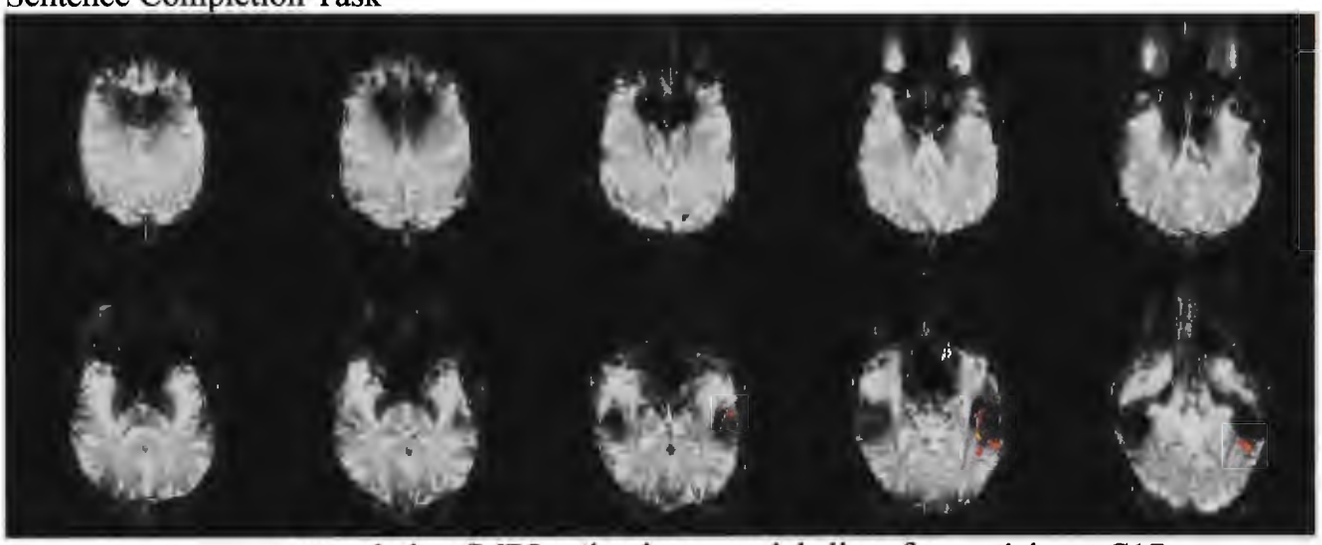


Figure 24. Sentence completion fMRI activation on axial slices for participant C17. Images are shown in radiological convention: the left hemisphere is displayed on the right side of the image.

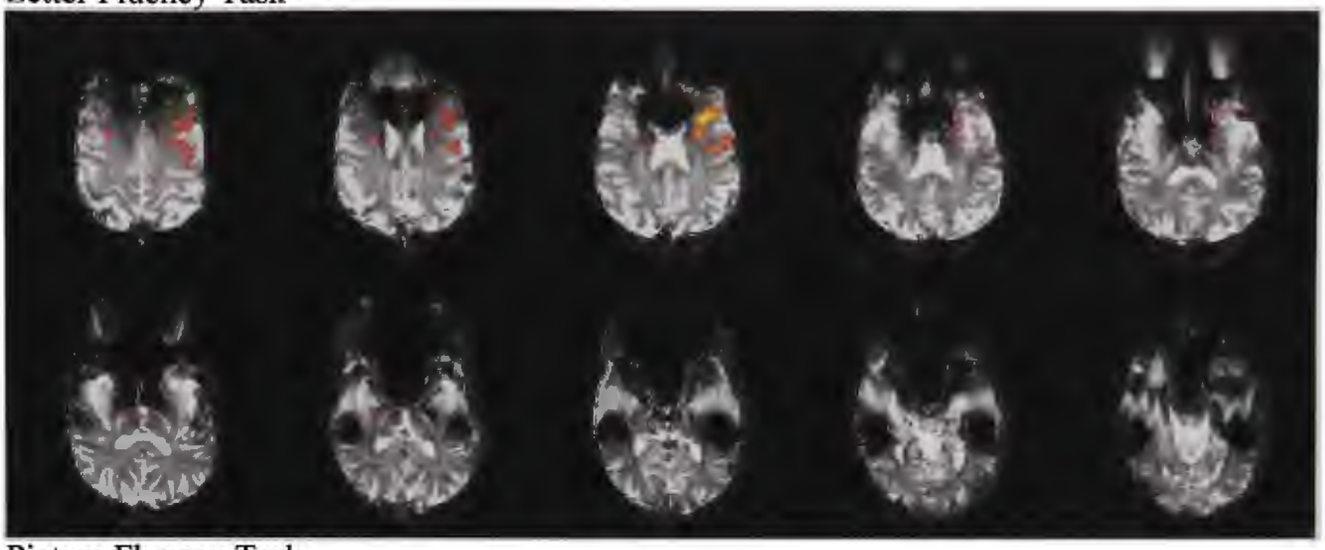
Table 30

Language task results for C18.

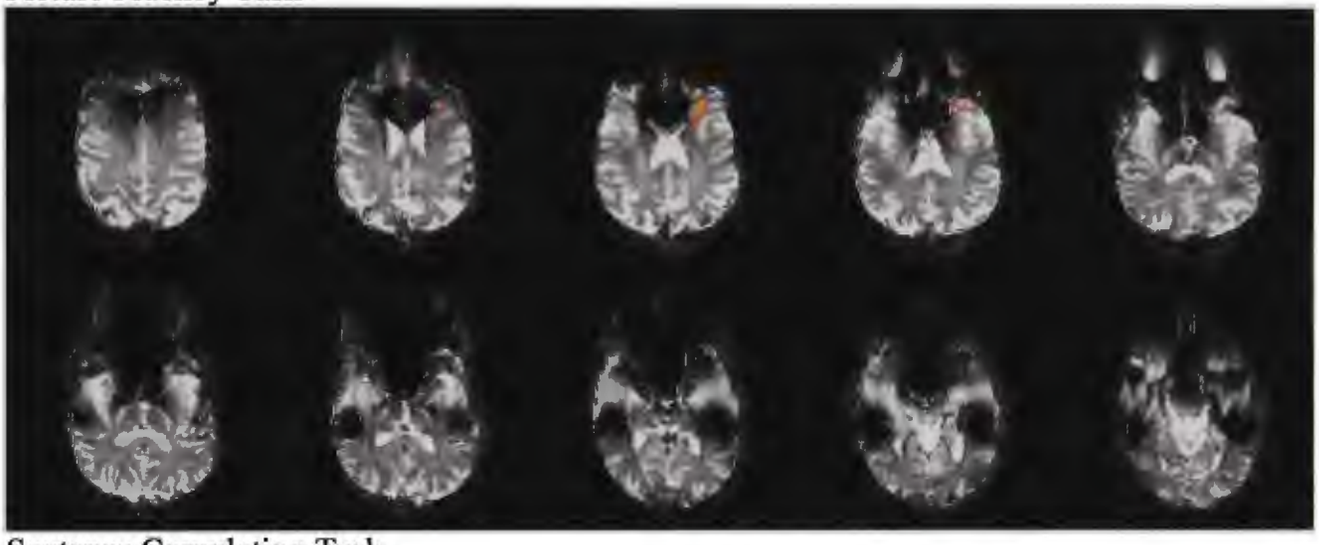
Localisation	Cluster Size	Z	x	y	z
Letter Fluency					
L IFG BA45	600	7.26	36	30.1	8.9
R Insula BA13	135	4.81	-28.4	9.98	25.6
Category Fluency					
	Nil				
Picture Naming					
L MFG BA10	183	5.09	30.1	43.3	9.58
Sentence Completion					
L IFG BA46	117	7.48	39.6	33.3	7.3

Note. Local maxima in MNI coordinates. Only the local maxima with highest Z score in each cluster are provided in the table. Cluster size is in voxels. When the cluster encompasses more than one anatomical location, the localization given corresponds to the local maxima with the highest Z score. L, left; MFG, middle frontal gyrus; IFG, inferior frontal gyrus.

Letter Fluency Task



Picture Fluency Task



Sentence Completion Task

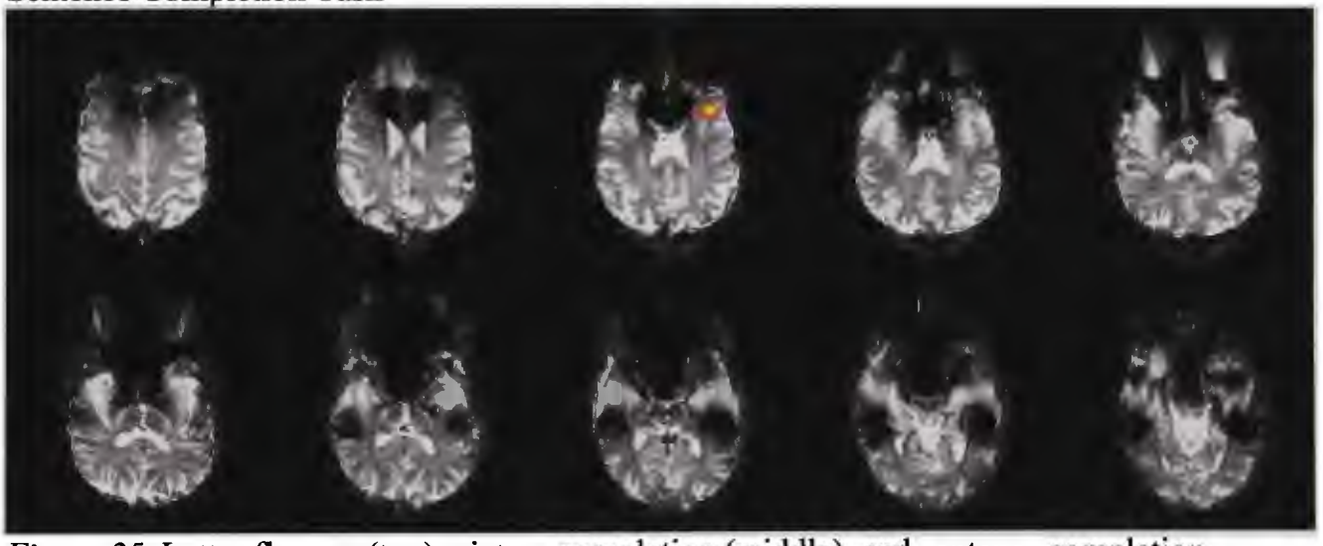


Figure 25. Letter fluency (top), picture completion (middle), and sentence completion (bottom) fMRI activation on axial slices for participant C18. Images are shown in radiological convention: the left hemisphere is displayed on the right side of the image.

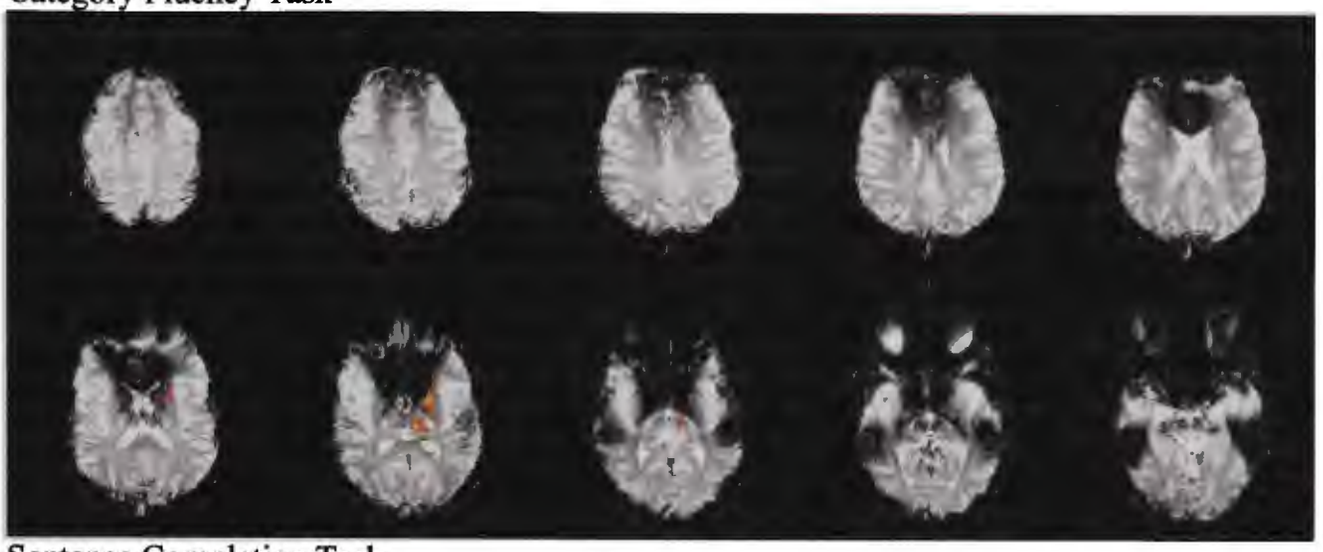
Table 31

Language task results for C19.

Localisation	Cluster Size	Z	x	y	z
Letter Fluency					
	Nil				
Category Fluency					
L LentiformN	163	5.28	20.5	-5.48	-9.94
Picture Naming					
	Nil				
Sentence Completion					
L STG BA22	349	9.38	59.1	4.35	1.92
L STG BA22	171	10.6	56	-49.7	7.12
L PreCG BA 6	152	7.49	47.4	-5.01	34.3

Note. Local maxima in MNI coordinates. Only the local maxima with highest Z score in each cluster are provided in the table. Cluster size is in voxels. When the cluster encompasses more than one anatomical location, the localization given corresponds to the local maxima with the highest Z score. L, left; MFG, middle frontal gyrus; IFG, inferior frontal gyrus.

Category Fluency Task



Sentence Completion Task

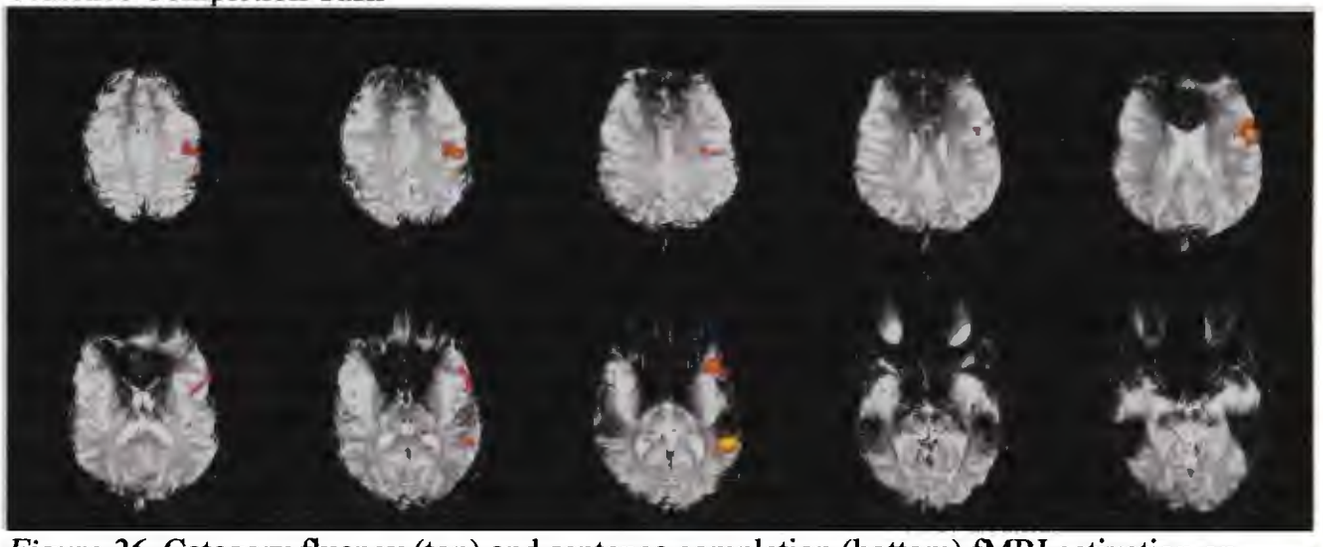


Figure 26. Category fluency (top) and sentence completion (bottom) fMRI activation on axial slices for participant C19. Images are shown in radiological convention: the left hemisphere is displayed on the right side of the image.

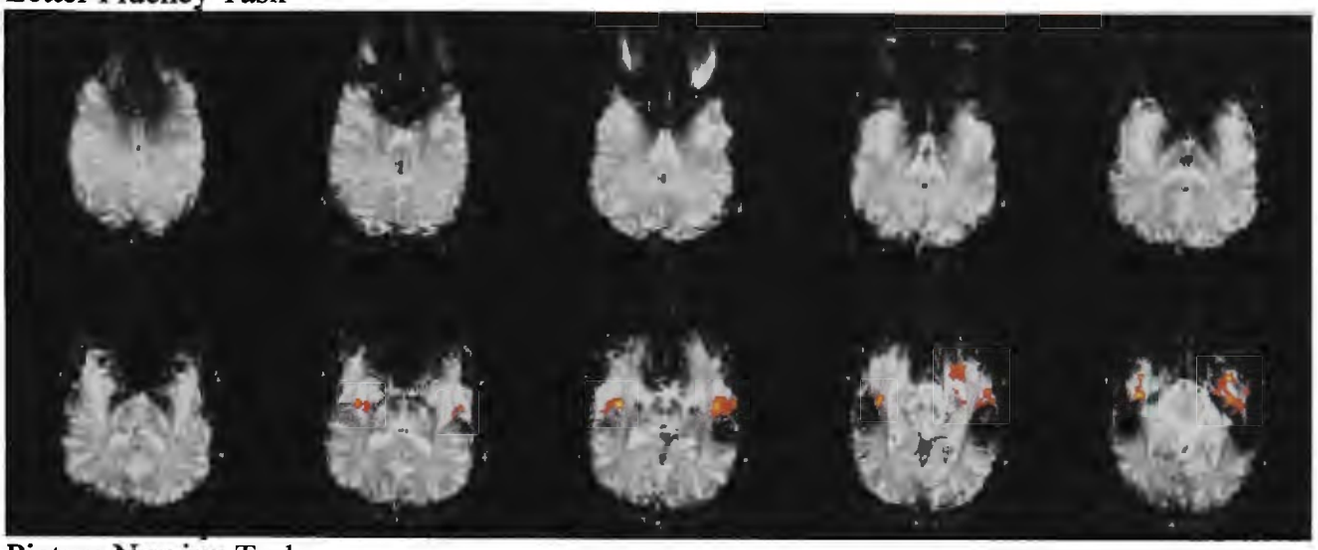
Table 32

Language task results for C20.

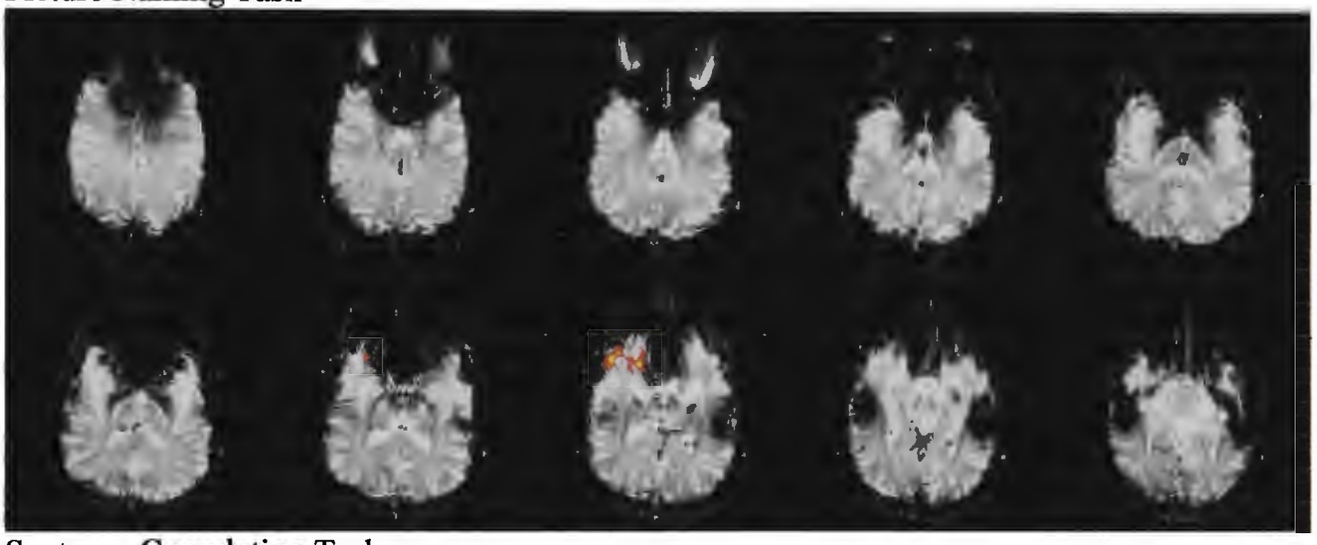
Localisation	Cluster Size	Z	x	y	z
Letter Fluency					
L MTG BA20	372	4.29	36.5	2.77	-46.9
R MTG BA21	133	4.63	-43.7	-13.5	-15.1
Category Fluency					
	Nil				
Picture Naming					
R STG BA38	133	4.3	-51.6	17.5	-37.5
Sentence Completion					
L IFG BA45	90	4.85	54.7	26	3.13

Note. Local maxima in MNI coordinates. Only the local maxima with highest Z score in each cluster are provided in the table. Cluster size is in voxels. When the cluster encompasses more than one anatomical location, the localization given corresponds to the local maxima with the highest Z score. L, left; R, right; MTG, middle temporal gyrus; STG, superior temporal gyrus; IFG, inferior frontal gyrus.

Letter Fluency Task



Picture Naming Task



Sentence Completion Task

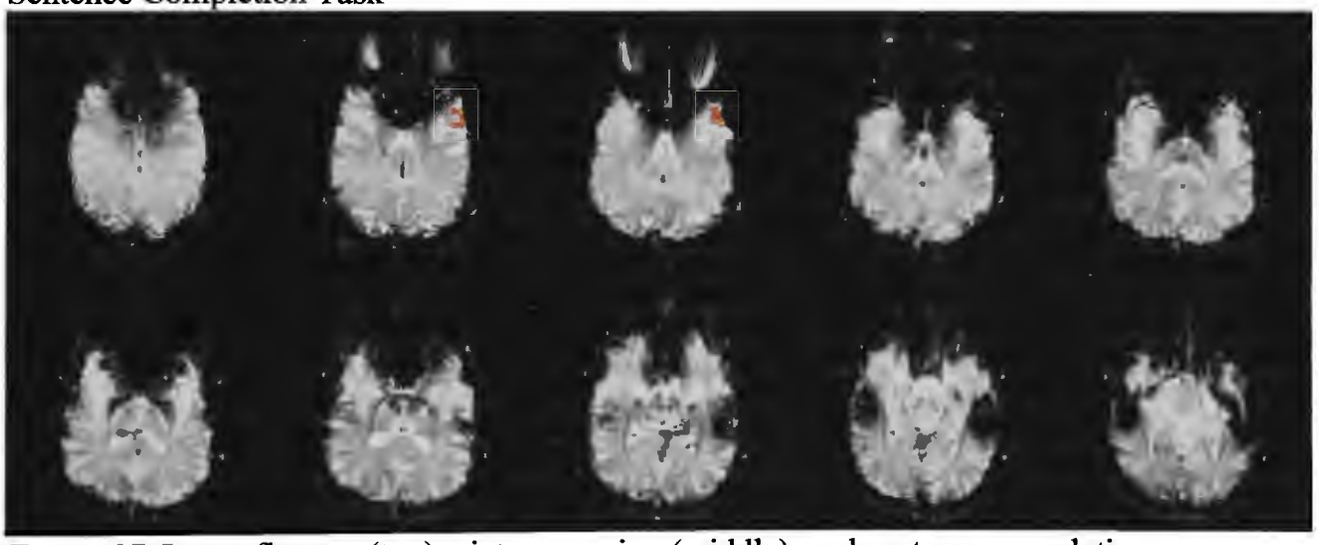


Figure 27. Letter fluency (top), picture naming (middle), and sentence completion (bottom) fMRI activation on axial slices for participant C20. Images are shown in radiological convention: the left hemisphere is displayed on the right side of the image.

APPENDIX I: Additional Tables and Figures for Original Epilepsy Patients

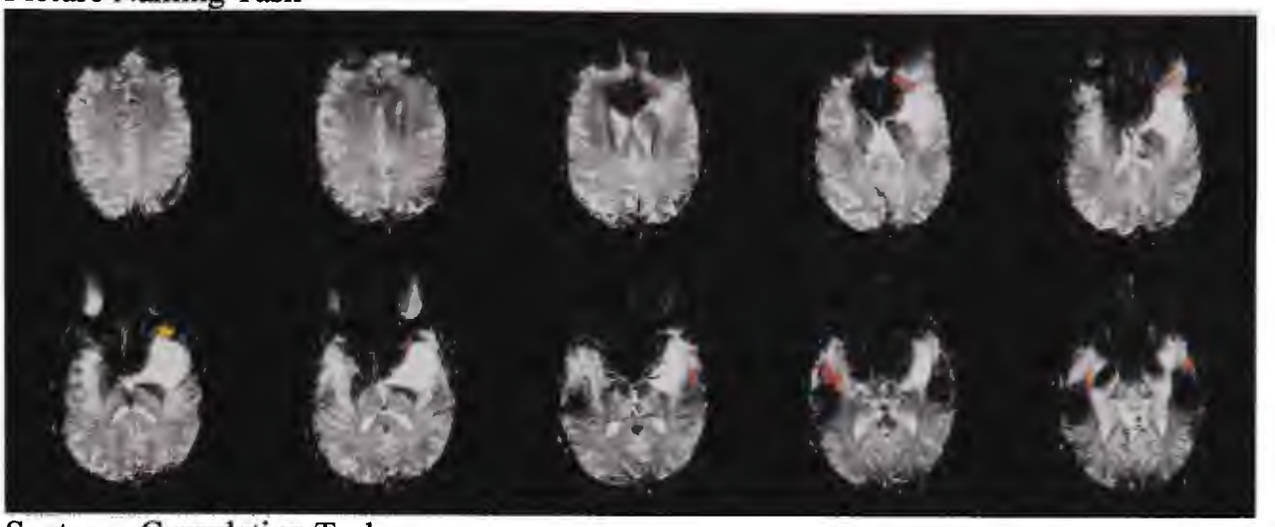
Table 33

Language task results for A1.

Localisation	Cluster Size	Z	x	y	z
Letter Fluency					
	Nil				
Category Fluency					
	Nil				
Picture Naming					
L SFG BA9	228	4.96	42.7	38.2	-8.2
R ExtraNucBA13	112	4.88	-37.8	4.18	-7.01
L MTG BA21	93	4.04	59.4	7.88	-16.3
Sentence Completion					
R ExtraNuBA13	1364	7.69	-39.7	4.4	-6.95
L MTG BA21	864	8.56	65.1	7.16	-11.8
L AntCing BA32	498	8.98	20.1	40.9	1.89
L SOG BA19	379	7.03	32.4	-86.6	23.1
L STG BA22	133	5.95	48.9	-17	36.4
R IFG BA13	114	6.32	-45.5	27.9	7.61
L PrecuneusBA7	95	5.37	19.5	-59.6	55.6

Note. Local maxima in MNI coordinates. Only the local maxima with highest Z score in each cluster are provided in the table. Cluster size is in voxels. When the cluster encompasses more than one anatomical location, the localization given corresponds to the local maxima with the highest Z score. L, left; R, right; SFG, superior frontal gyrus, ExtraNuc, extra nucleus; MTG, middle temporal gyrus; AntCing, anterior cingulate gyrus; SOG, superior occipital gyrus; STG superior temporal gyrus; IFG, inferior frontal gyrus.

Picture Naming Task



Sentence Completion Task

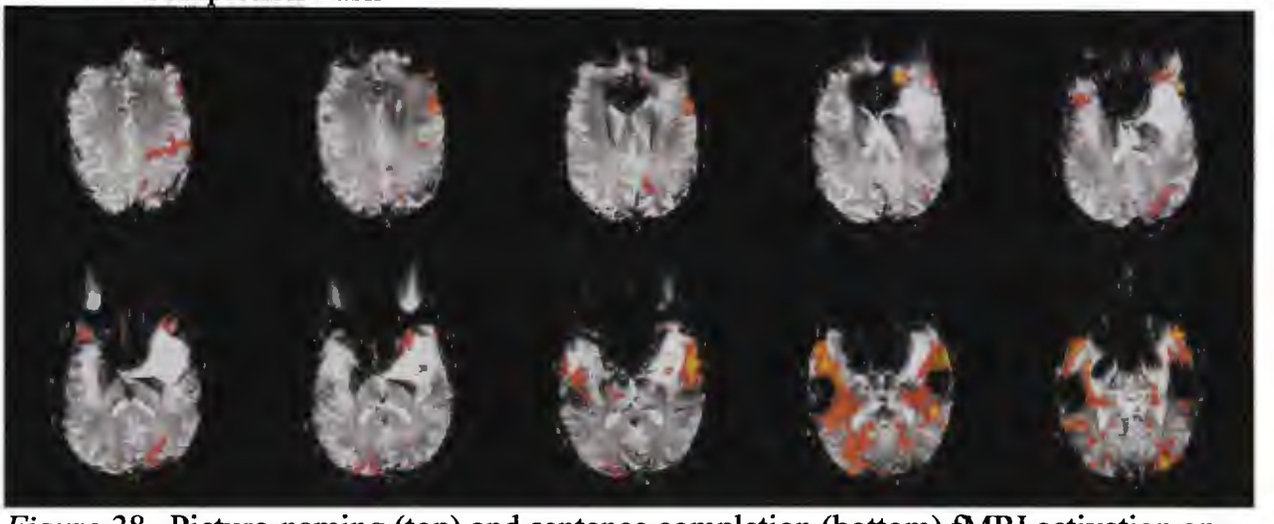


Figure 28. Picture-naming (top) and sentence completion (bottom) fMRI activation on axial slices for patient A1. Images are shown in radiological convention: the left hemisphere is displayed on the right side of the image.

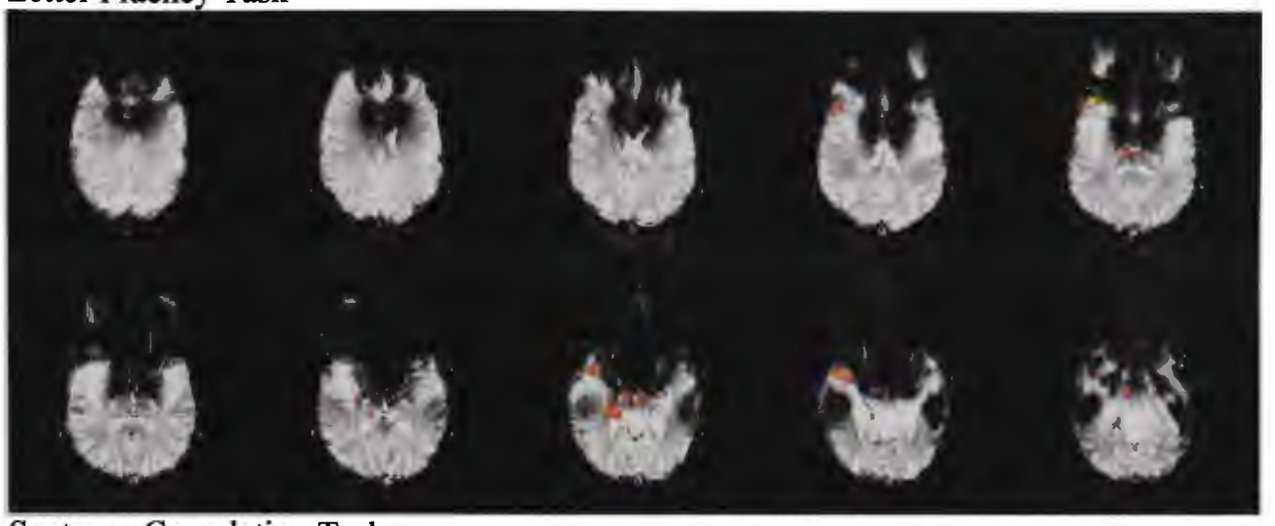
Table 34

Language task results for A2.

Localisation	Cluster Size	Z	x	y	z
Letter Fluency					
R MTG BA21	179	6.02	-44	7.78	-33.6
R ParahipG BA27	143	4.83	-22.8	-30	-5.45
L Midbrain	133	5.88	4.43	-22.6	-10.2
R MFG BA11	120	7.11	-42.3	34.5	-11.1
Category Fluency					
	Nil				
Picture Naming					
	Nil				
Sentence Completion					
R IPL	236	5.37	-33.1	-41.8	28.4
R MFG	216	5.64	-27.1	37.5	14.2
L MTG BA21	201	6.61	47.5	5.49	-35.4
R MTG BA21	158	5.35	-47.2	2.65	-40

Note. Local maxima in MNI coordinates. Only the local maxima with highest Z score in each cluster are provided in the table. Cluster size is in voxels. When the cluster encompasses more than one anatomical location, the localization given corresponds to the local maxima with the highest Z score. L, left; R, right; MTG, middle temporal gyrus; ParahipG, papahippocampal gyrus; MFG, middle frontal gyrus; IPL, inferior parietal lobule; MTG, middle temporal gyrus.

Letter Fluency Task



Sentence Completion Task

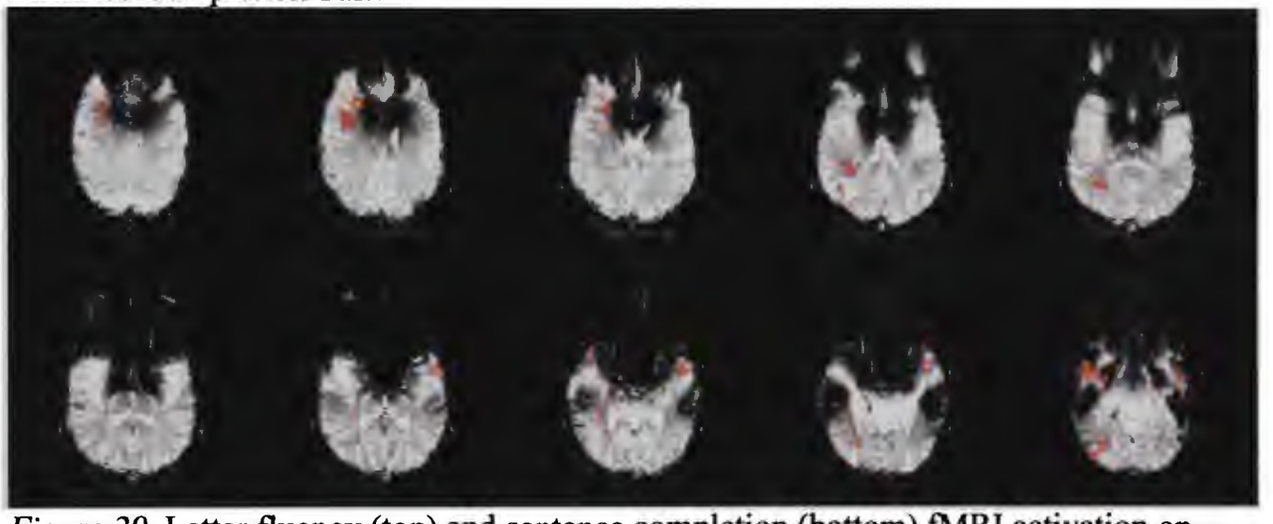


Figure 29. Letter fluency (top) and sentence completion (bottom) fMRI activation on axial slices for patient A2. Images are shown in radiological convention: the left hemisphere is displayed on the right side of the image.

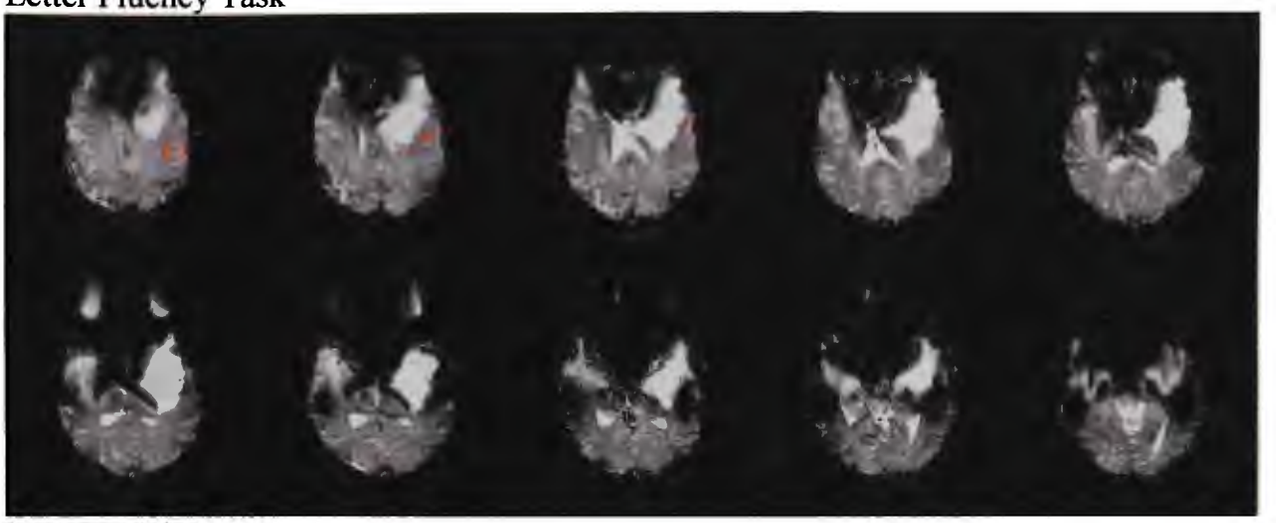
Table 35

Language task results for A3.

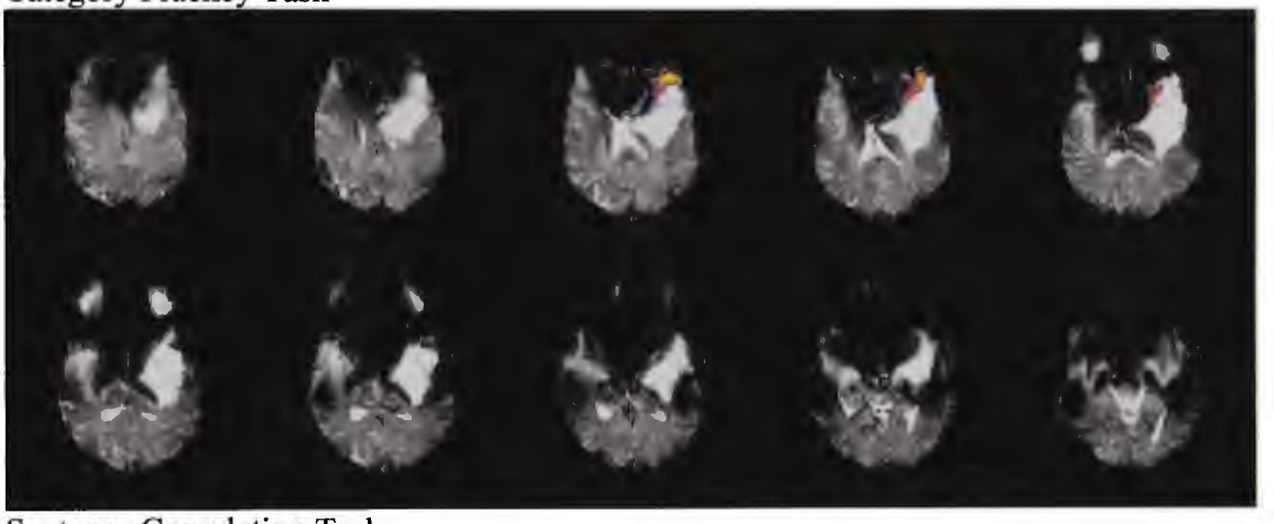
Localisation	Cluster Size	Z	x	y	z
Letter Fluency					
L IFG BA9	161	5.53	58.3	3.83	28.5
Category Fluency					
L MFG BA46	247	6.56	43.5	44.6	9.12
Sentence Completion					
L MOG BA19	337	6	29.3	-84.2	20.8
L PreCG BA6	197	6.24	59.4	3.25	36.3
L SupraMGBA40	146	5.65	62.7	-44.9	28.2

Note. Local maxima in MNI coordinates. Only the local maxima with highest Z score in each cluster are provided in the table. Cluster size is in voxels. When the cluster encompasses more than one anatomical location, the localization given corresponds to the local maxima with the highest Z score. L, left; MFG, middle frontal gyrus; IFG, inferior frontal gyrus; MOG, middle occipital gyrus; PreCG, precentral gyrus; SupraMG, supramarginal gyrus.

Letter Fluency Task



Category Fluency Task



Sentence Completion Task

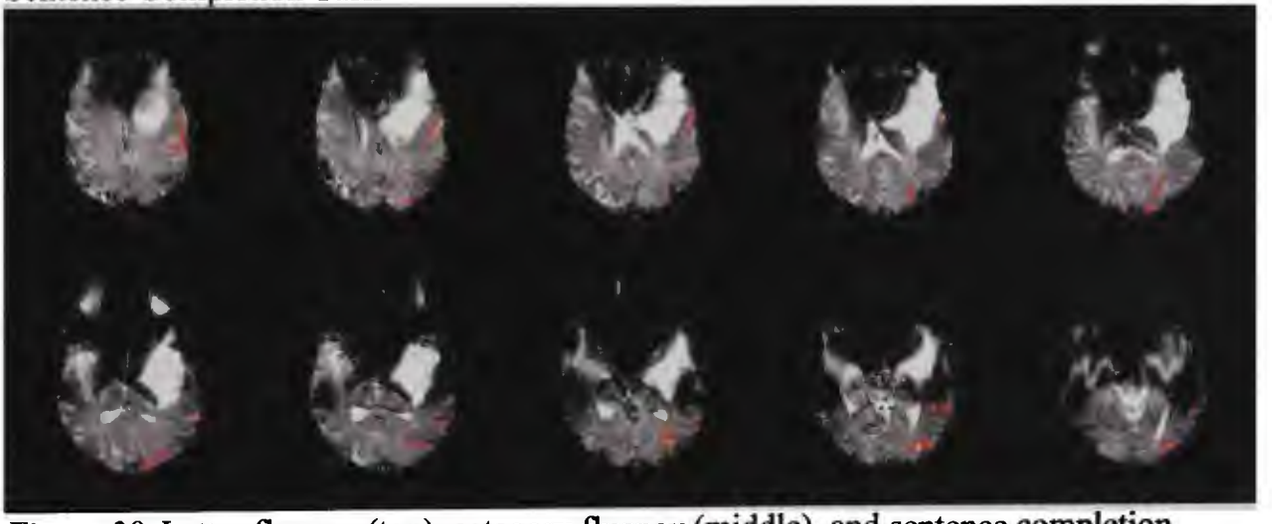


Figure 30. Letter fluency (top), category fluency (middle), and sentence completion (bottom) fMRI activation on axial slices for patient A3. Images are shown in radiological convention: the left hemisphere is displayed on the right side of the image.

Table 36

Language task results for A4.

Localisation	Cluster Size	Z	x	y	z
Letter Fluency					
	Nil				
Category Fluency					
	Nil				
Picture Naming					
	Nil				
Sentence Completion					
	Nil				

Note. Local maxima in MNI coordinates. Only the local maxima with highest Z score in each cluster are provided in the table. Cluster size is in voxels. When the cluster encompasses more than one anatomical location, the localization given corresponds to the local maxima with the highest Z score.

Table 37

Language task results for A5.

Localisation	Cluster Size	Z	x	y	z
Letter Fluency					
	Nil				
Category Fluency					
	Nil				
Picture Naming					
	Nil				
Sentence Completion					
L TL		5.25	40.3	-32	-7.73
L MFG BA46		7.04	51.1	20	30.5
L SPL BA7		6	23.2	-66.7	40.6

Note. Local maxima in MNI coordinates. Only the local maxima with highest Z score in each cluster are provided in the table. Cluster size is in voxels. When the cluster encompasses more than one anatomical location, the localization given corresponds to the local maxima with the highest Z score. L, left; TL, temporal lobe; MFG, middle frontal gyrus; SPL, superior parietal lobule.

Sentence Completion Task

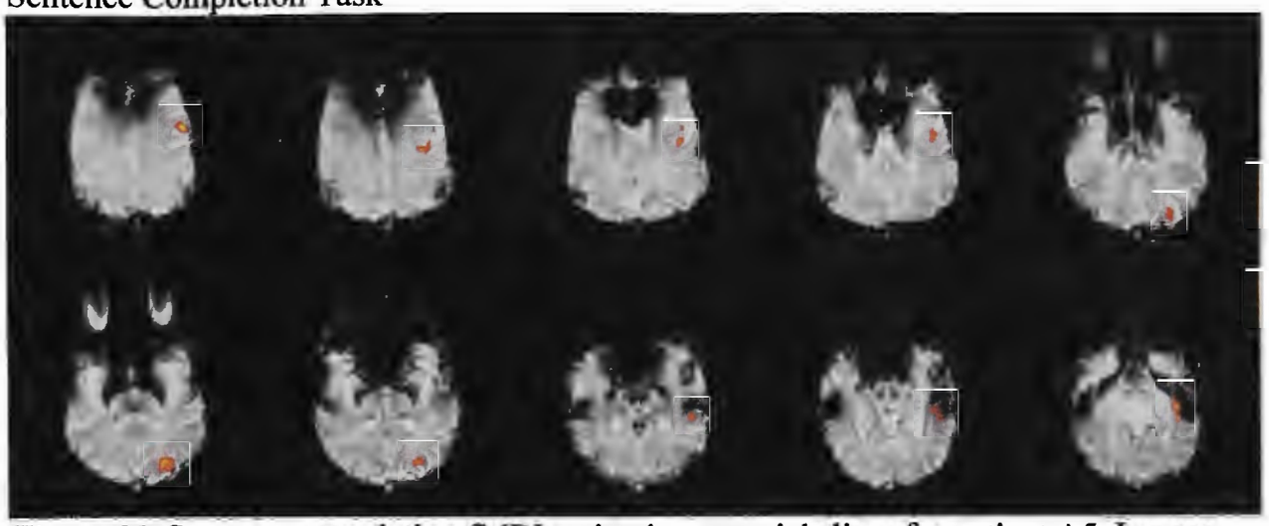


Figure 31. Sentence completion fMRI activation on axial slices for patient A5. Images are shown in radiological convention: the left hemisphere is displayed on the right side of the image.

Table 38

Language task results for A6.

Localisation	Cluster Size	Z	x	y	z
Letter Fluency					
	Nil				
Category Fluency					
	Nil				
Picture Naming					
L Brainstem	910	7.53	3.71	-29.2	-13.8
L MTG BA21	139	5.62	56	9.16	-30
L ITG BA20	121	6.12	50.5	-15.6	-35.9
L Uncus BA20	104	6.23	27.1	-1.57	-41.1

Note. Local maxima in MNI coordinates. Only the local maxima with highest Z score in each cluster are provided in the table. Cluster size is in voxels. When the cluster encompasses more than one anatomical location, the localization given corresponds to the local maxima with the highest Z score. L, left; MTL, middle temporal lobe; ITG, inferior temporal gyrus.

Picture Naming Task

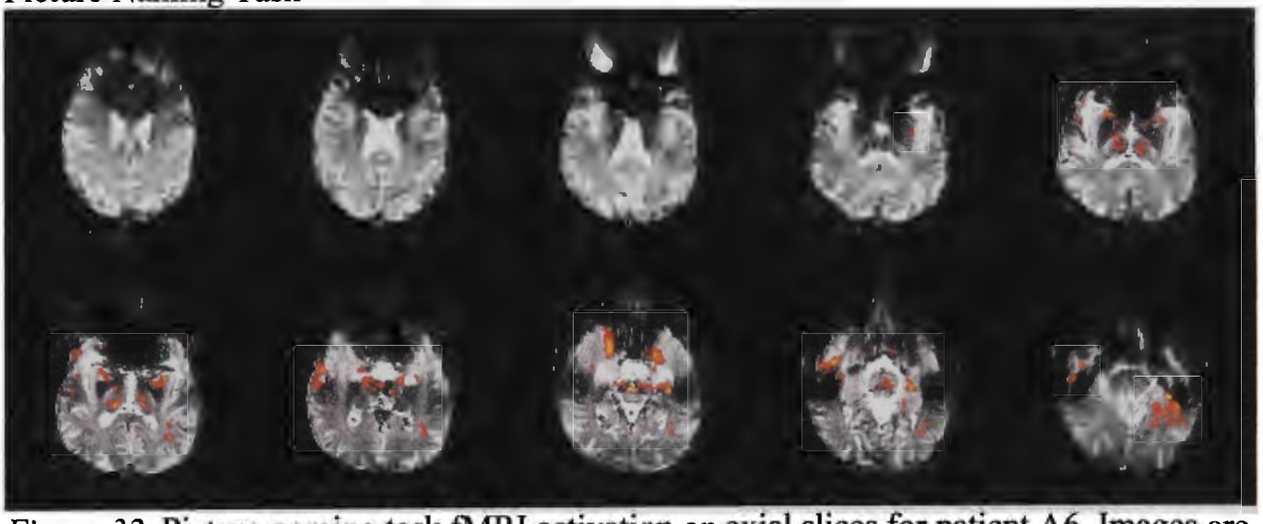


Figure 32. Picture-naming task fMRI activation on axial slices for patient A6. Images are shown in radiological convention: the left hemisphere is displayed on the right side of the image.

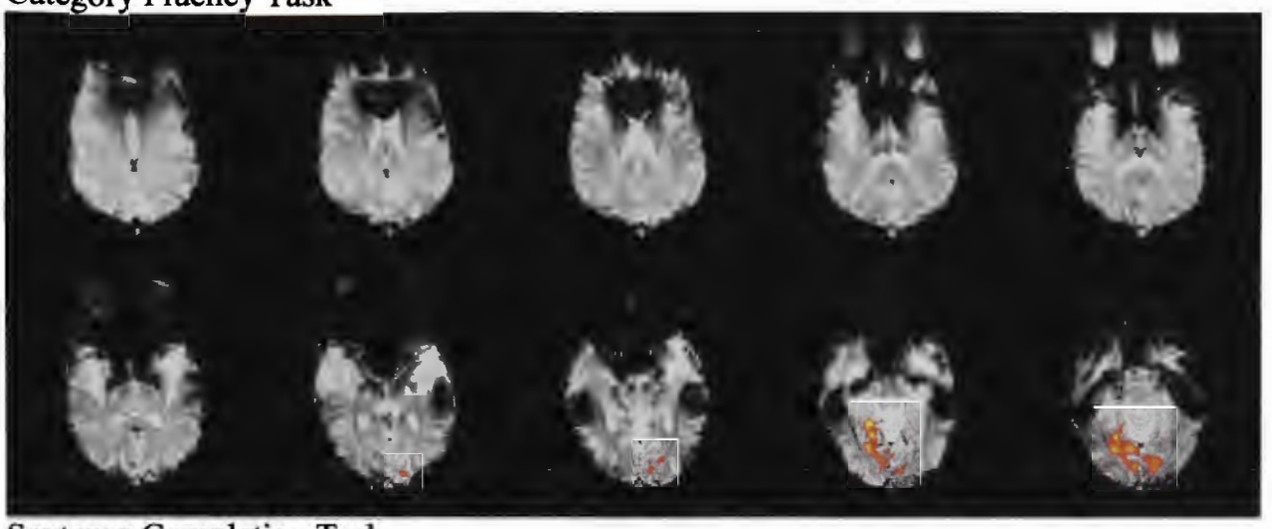
Table 39

Language task results for A7.

Localisation	Cluster Size	Z	x	y	z
Letter Fluency					
	Nil				
Category Fluency					
R ParahipG BA19	435	5.5	-20.1	-47.5	-11.3
Picture Naming					
	Nil				
Sentence Completion					
L IFG BA47	535	9.47	45.2	34.4	0.768
L ParahipG BA20	148	5.68	41.1	-24.2	-22.7
R ParahipG BA36	133	4.84	-40.7	-35.3	-16.7

Note. Local maxima in MNI coordinates. Only the local maxima with highest Z score in each cluster are provided in the table. Cluster size is in voxels. When the cluster encompasses more than one anatomical location, the localization given corresponds to the local maxima with the highest Z score. L, left; R, right; ParahipG, papahippocampal gyrus; IFG, inferior frontal gyrus.

Category Fluency Task



Sentence Completion Task

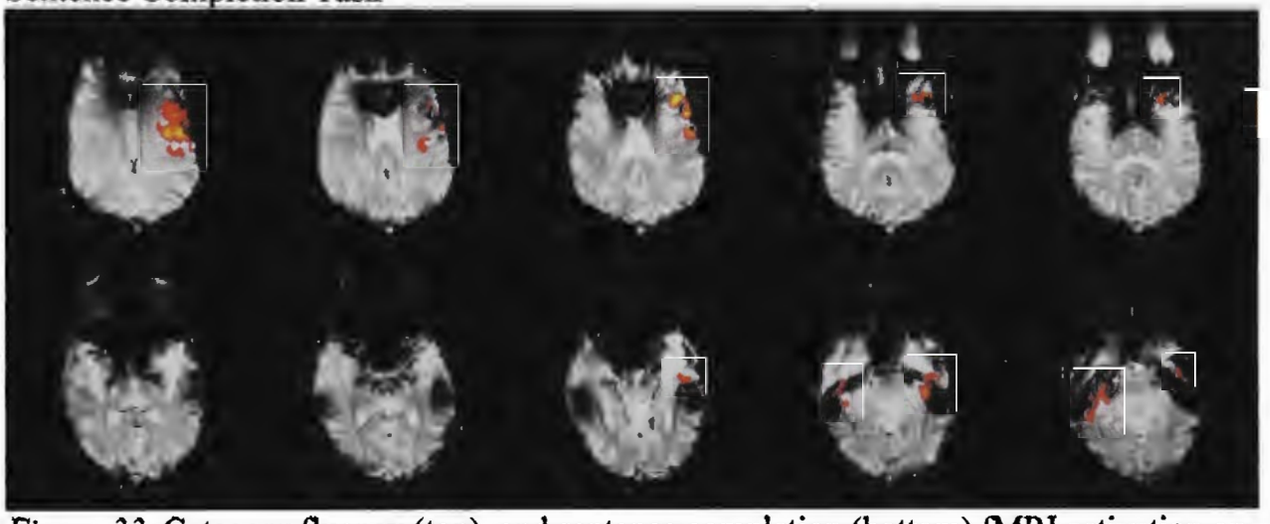


Figure 33. Category fluency (top), and sentence completion (bottom) fMRI activation on axial slices for patient A7. Images are shown in radiological convention: the left hemisphere is displayed on the right side of the image.

Table 40

Language task results for A8.

Localisation	Cluster Size	Z	x	y	z
Letter Fluency					
	Nil				
Category Fluency					
	Nil				
Sentence Completion					
L STG BA22	169	4.48	60.5	-52.4	8.19
L Caudate	156	5.52	15.4	-34.4	19.3

Note. Local maxima in MNI coordinates. Only the local maxima with highest Z score in each cluster are provided in the table. Cluster size is in voxels. When the cluster encompasses more than one anatomical location, the localization given corresponds to the local maxima with the highest Z score. L, left; STG, superior temporal gyrus.

Sentence Completion Task

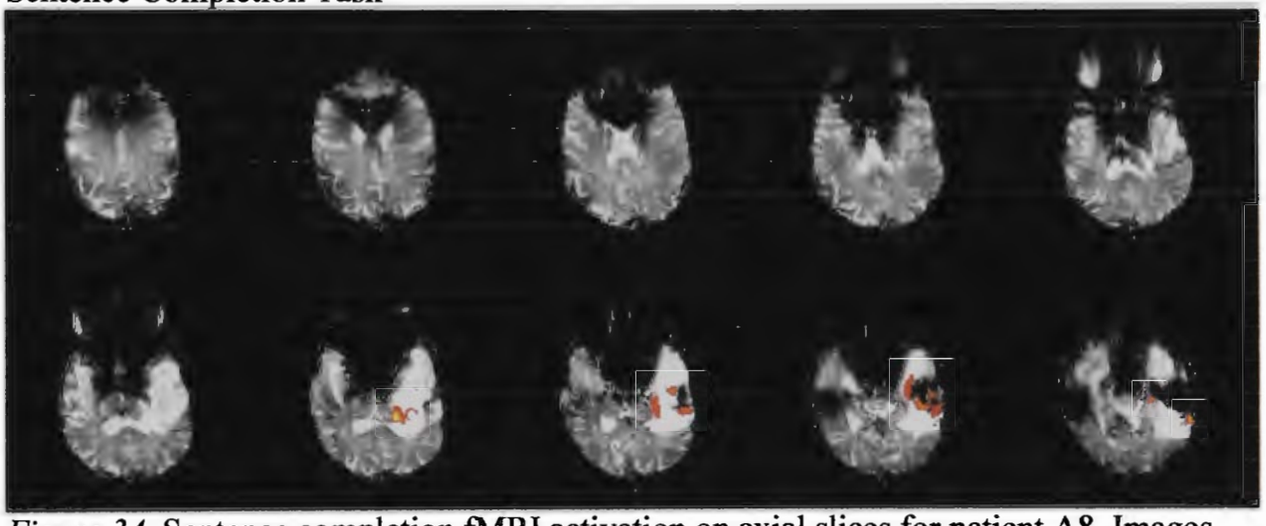


Figure 34. Sentence completion fMRI activation on axial slices for patient A8. Images are shown in radiological convention: the left hemisphere is displayed on the right side of the image.

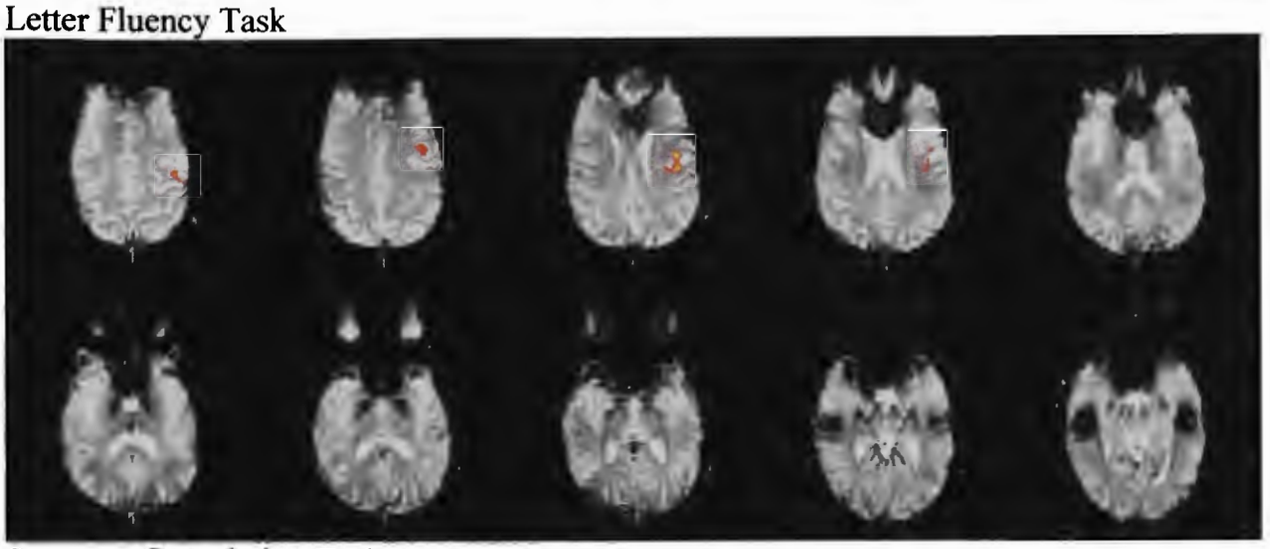
Table 41

Language task results for A9.

Localisation	Cluster Size	Z	x	y	z
Letter Fluency					
L IFG BA9	130	5.12	43.2	3.42	20.9
Category Fluency					
	Nil				
Picture Naming					
	Nil				
Sentence Completion					
L IFG BA9	298	5.82	43.4	3.47	26.6
L MTG BA21	135	5.69	60.9	-49.7	6.75
R MTG BA37	126	6.24	-55.1	-46	-9.18

Note. Local maxima in MNI coordinates. Only the local maxima with highest Z score in each cluster are provided in the table. Cluster size is in voxels. When the cluster encompasses more than one anatomical location, the localization given corresponds to the local maxima with the highest Z score. L, left; R, right; IFG, inferior frontal gyrus; MTG, middle temporal gyrus.

Letter Fluency Task



Sentence Completion Task

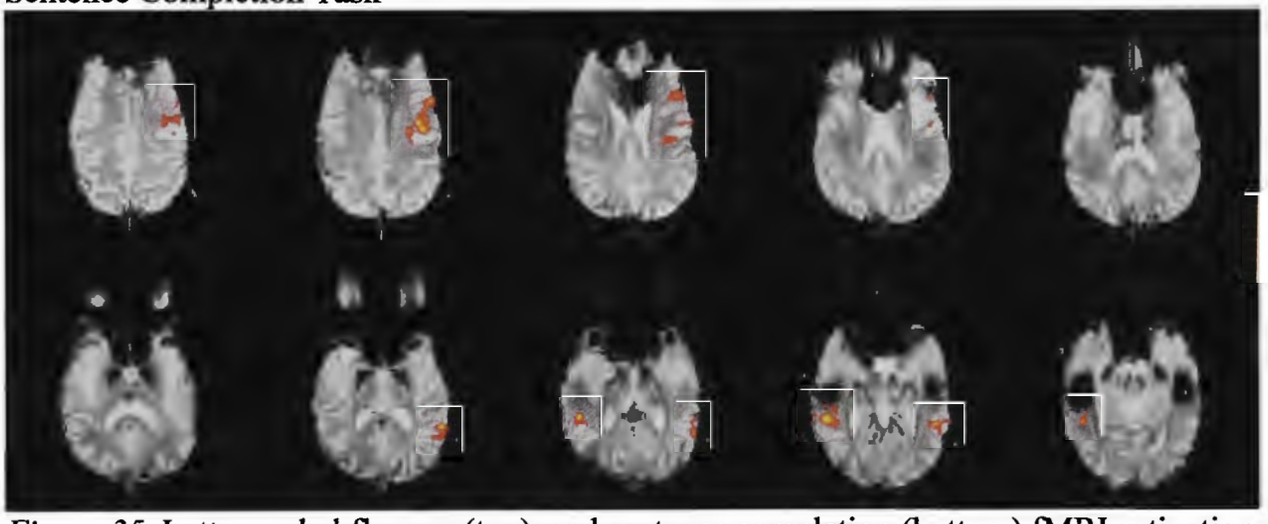


Figure 35. Letter verbal fluency (top), and sentence completion (bottom) fMRI activation on axial slices for patient A9. Images are shown in radiological convention: the left hemisphere is displayed on the right side of the image.

Table 42

Language task results for A10.

Localisation	Cluster Size	Z	x	y	z
Letter Fluency					
	Nil				
Category Fluency					
	Nil				
Picture Naming					
	Nil				
Sentence Completion					
L MTG BA37	208	7.7	51.1	-63.1	2.26

Note. Local maxima in MNI coordinates. Only the local maxima with highest Z score in each cluster are provided in the table. Cluster size is in voxels. When the cluster encompasses more than one anatomical location, the localization given corresponds to the local maxima with the highest Z score. L, left; middle temporal gyrus.

Sentence Completion Task

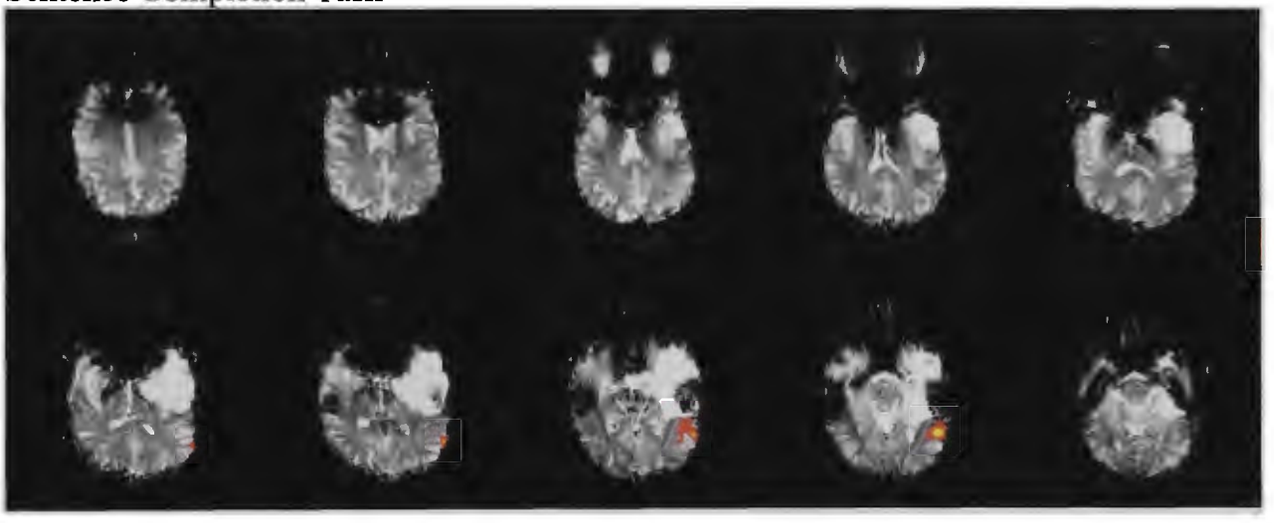


Figure 36. Sentence completion fMRI activation on axial slices for patient A10. Images are shown in radiological convention: the left hemisphere is displayed on the right side of the image.

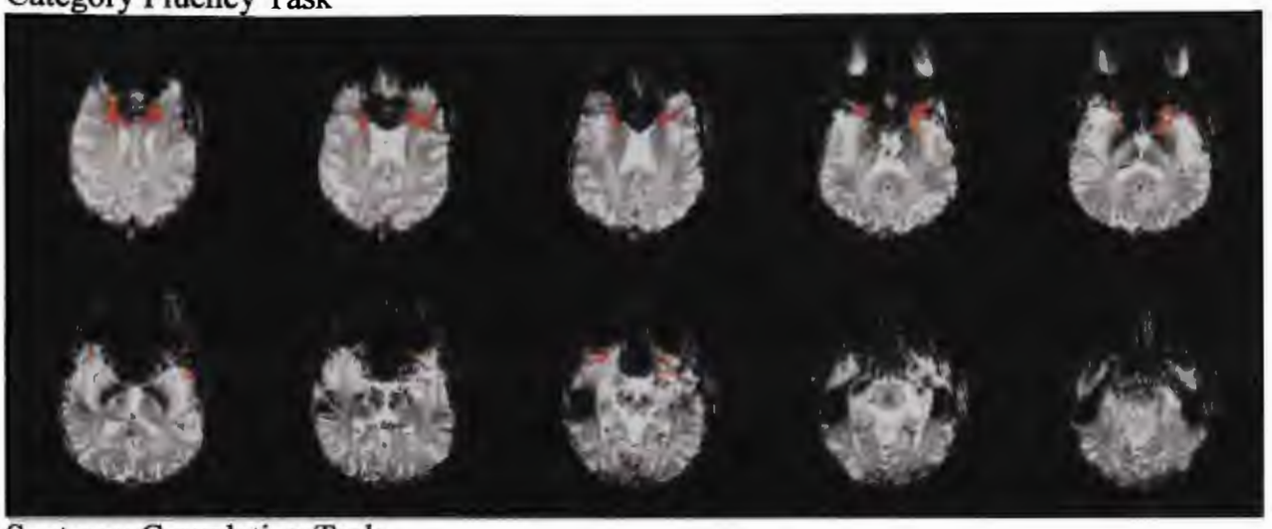
Table 43

Language task results for A11.

Localisation	Cluster Size	Z	x	y	z
Category Fluency					
LarahipG BA34	618	6.37	25.4	4.17	-18.8
R SFG BA10	285	5.18	-22.4	52	9.18
R MFG BA11	110	5.33	-42.4	35	-17.9
Picture Naming					
	Nil				
Sentence Completion					
L AntCing BA32	655	8.26	22.2	41.3	11.8
R AntCing BA32	270	7.53	-22.6	41.1	6.42

Note. Local maxima in MNI coordinates. Only the local maxima with highest Z score in each cluster are provided in the table. Cluster size is in voxels. When the cluster encompasses more than one anatomical location, the localization given corresponds to the local maxima with the highest Z score. L, left; R, right; ParahipG, papahippocampal gyrus; SFG, superior frontal gyrus; MFG, middle frontal gyrus; AntCing, anterior cingulate gyrus.

Category Fluency Task



Sentence Completion Task

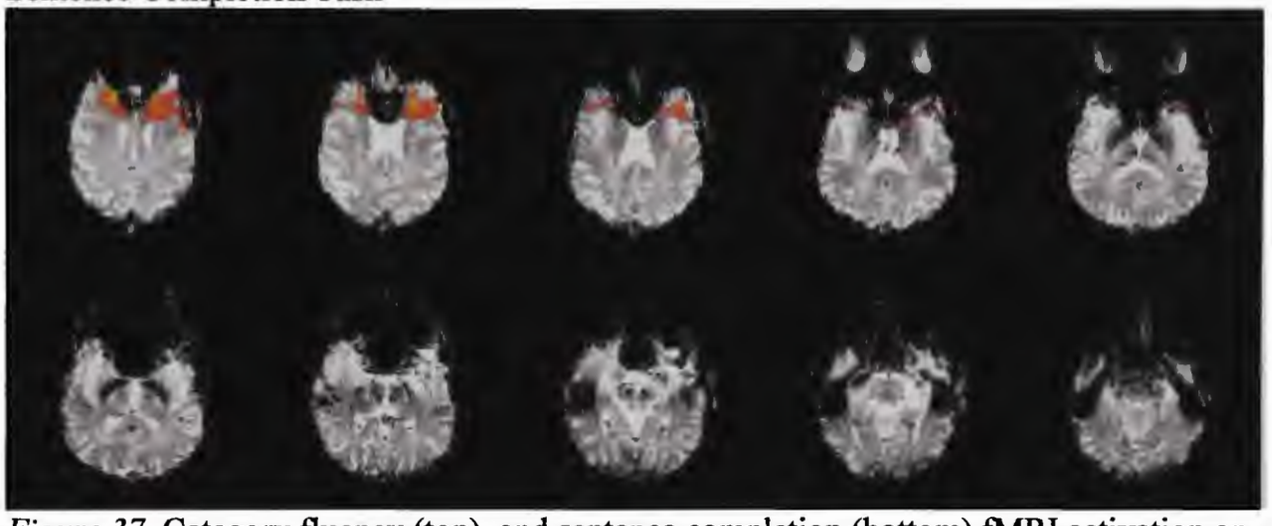


Figure 37. Category fluency (top), and sentence completion (bottom) fMRI activation on axial slices for patient A11. Images are shown in radiological convention: the left hemisphere is displayed on the right side of the image.

Table 44

Language task results for A12.

Localisation	Cluster Size	Z	x	y	z
Letter Fluency					
	Nil				
Category Fluency					
	Nil				
Picture Naming					
	Nil				
Sentence Completion					
R Precuneus BA7	407	5.33	-15.8	-61.9	44.7
L ITG BA19	335	5.18	58.4	-69.6	-6.7
L Fusiform BA19	173	5.73	43.1	-65.2	-10.4
L Precuneus BA7	102	4.5	1.53	-80.3	46.9

Note. Local maxima in MNI coordinates. Only the local maxima with highest Z score in each cluster are provided in the table. Cluster size is in voxels. When the cluster encompasses more than one anatomical location, the localization given corresponds to the local maxima with the highest Z score. L, left; R, right; ITG, inferior temporal gyrus.

Sentence Completion Task

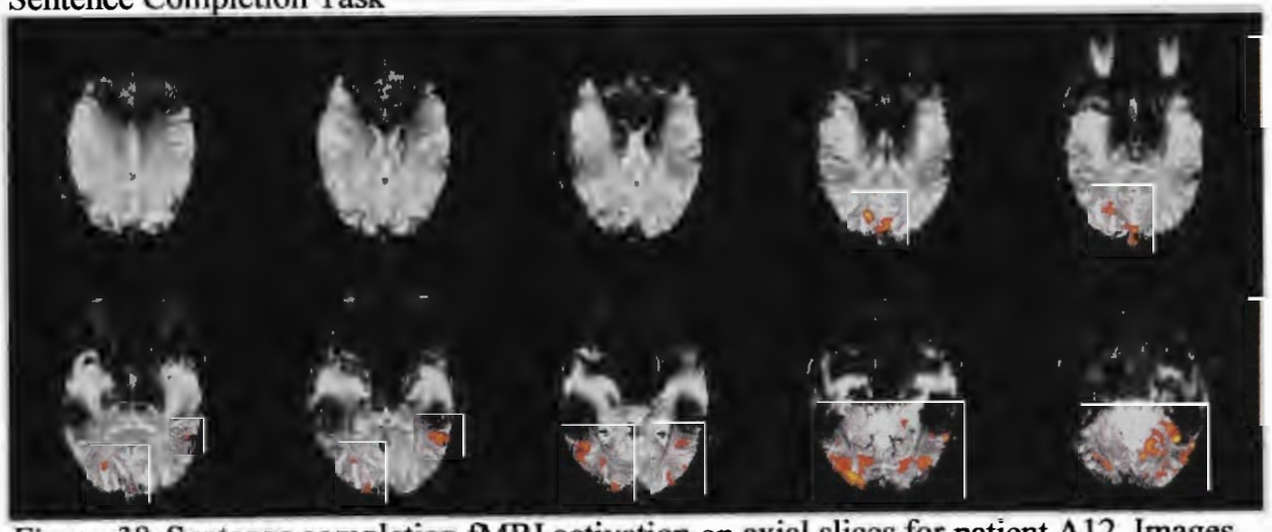


Figure 38. Sentence completion fMRI activation on axial slices for patient A12. Images are shown in radiological convention: the left hemisphere is displayed on the right side of the image.

Table 45

Language task results for B1.

Localisation	Cluster Size	Z	x	y	z
Letter Fluency					
L IFG BA45	1609	6.09	-49.6	37.5	9.36
R MFG BA 9	638	7.82	49.5	4.93	39.3
L IPL BA40	593	5.49	-44.6	-45.7	48.6
R CingG BA32	445	6.76	13	31	30.3
R SFG BA11	367	5.85	27.9	65.1	-14.3
R IFG BA47	358	6.48	37.4	30.6	0.356
R IPL BA40	262	6.22	50.8	-45	54.6
L MTG BA21	166	6.16	-54	-28.8	-4.42
L MFG BA11	156	4.98	-41.1	53.1	-11.9
R Precuneus BA7	141	5.34	28.6	-66.6	39.2
R MedFG BA10	133	4.44	14.2	44	15.9
R MFG BA6	100	5.26	34.5	4.21	60
R MFG BA10	89	4.74	48.7	52.8	-0.082
R ITG BA20	86	5.17	59.4	-46.9	-15.2
L CingG BA24	79	4.19	-1.92	7.94	26.2
L PostCG BA43	74	4.43	-58.8	-17.2	17.7
Category Fluency					
L IFG BA46	1340	7.78	-48.3	34.8	10.9
L AngG BA39	471	6.77	-36	-60.5	34.7
R MFG BA8	461	5.74	50.7	7	43.3
L CingG BA31	377	5.53	0.894	-60.5	25.2
L SFG BA6	232	6.32	0.498	12.6	58.9
L CingG BA32	215	4.6	-3.88	26.7	33
R MFG BA10	197	5.31	32.3	62.1	12.9
L STG BA39	195	5.1	-50.2	-64	16.6
R SFG BA11	160	5.13	35.6	48.7	-18.3
R MTG BA39	148	4.77	43.2	-61.9	26.9
R IFG BA47	114	4.33	54.4	16.2	-4.44
R PostCG BA2	112	3.87	49.4	-27	52.8
L Thalamus	84	4.14	-18.5	-19	4.71
L SFG BA10	79	4.62	-31.6	56.6	15.8
L FusiformG BA37	77	5	-52.7	-48.3	-20.7
Picture Naming					
R MFG BA46	416	5.31	51.7	23.5	25.7
L IFG BA46	410	5.91	-49.9	27	16.3
L MedFG BA9	99	3.75	0.112	45.2	29.5
L IFG BA47	89	4.18	-46.3	31.7	-18
L MedFG BA11	86	4.77	-4.1	33.8	-18.8
R IFG BA47	85	4.47	48.6	43.1	-19.5

Sentence Completion					
R SPL BA7	2374	7.83	28.1	-70.8	54.3
L IFG BA44	1733	8.12	-60.7	17.3	15.8
L STG BA39	1118	6.42	-52.9	-61.9	18.8
R MFG BA11	886	6.32	44.7	49	-20.7
R MFG BA8	683	5.98	50	7.89	42.1
R Uncus	432	5.63	25.1	-7.17	-25.6
L ParahipG BA35	420	5.8	-18.7	-35.6	-31.5
R MTG BA21	377	5.21	51.8	11	-43.9
L MFG BA6	320	6.5	-32.1	-5.96	50
L AntCing BA32	274	4.66	-3.2	39.9	5.57
L Claustrum	244	4.13	-21.9	18	11.2
L SFG BA6	204	8.01	0.324	0.874	61.5
R IFG BA44	155	7.14	48.8	5.99	22.6
R IPL BA40	117	5.36	40.7	-38.7	40.7
L Precuneus BA19	116	5.23	-24.1	-81.6	34.7

Note. Local maxima in MNI coordinates. Only the local maxima with highest Z score in each cluster are provided in the table. Cluster size is in voxels. When the cluster encompasses more than one anatomical location, the localization given corresponds to the local maxima with the highest Z score. L, left; R, right; IFG, inferior frontal gyrus; MFG, middle frontal gyrus; IPL, inferior parietal lobule; CingG, cingulate gyrus; SFG, superior frontal gyrus; MTG, middle temporal gyrus; MedFG, medial frontal gyrus; ITG, inferior temporal gyrus; PostCingG, postcingulate gyrus; AngG, angular gyrus; PostCG; postcentral gyrs; FusiformG, fusiform gyrus.

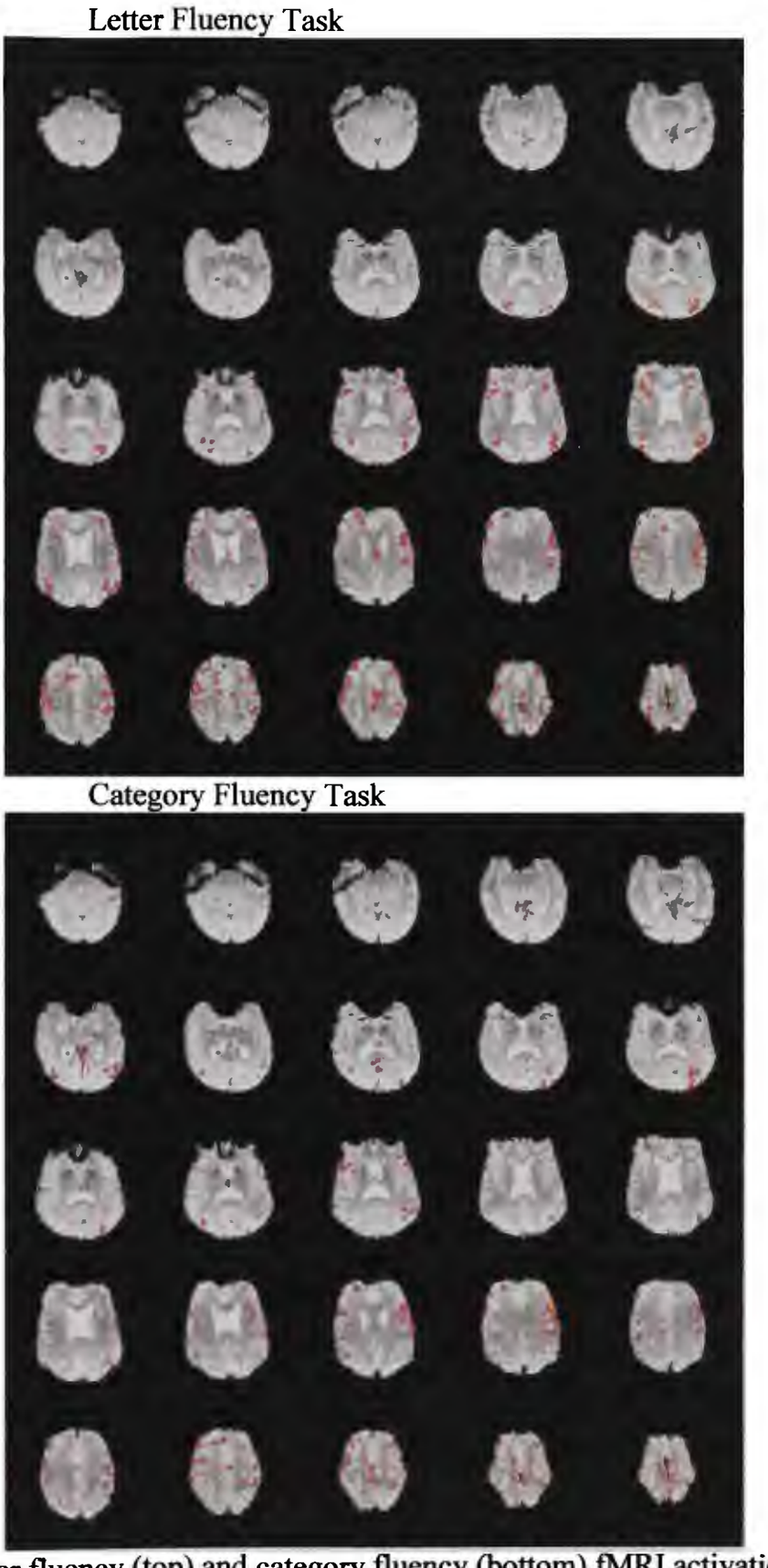


Figure 39. Letter fluency (top) and category fluency (bottom) fMRI activation on axial slices for patient B1. Images are shown in radiological convention: the left hemisphere is displayed on the right side of the image.

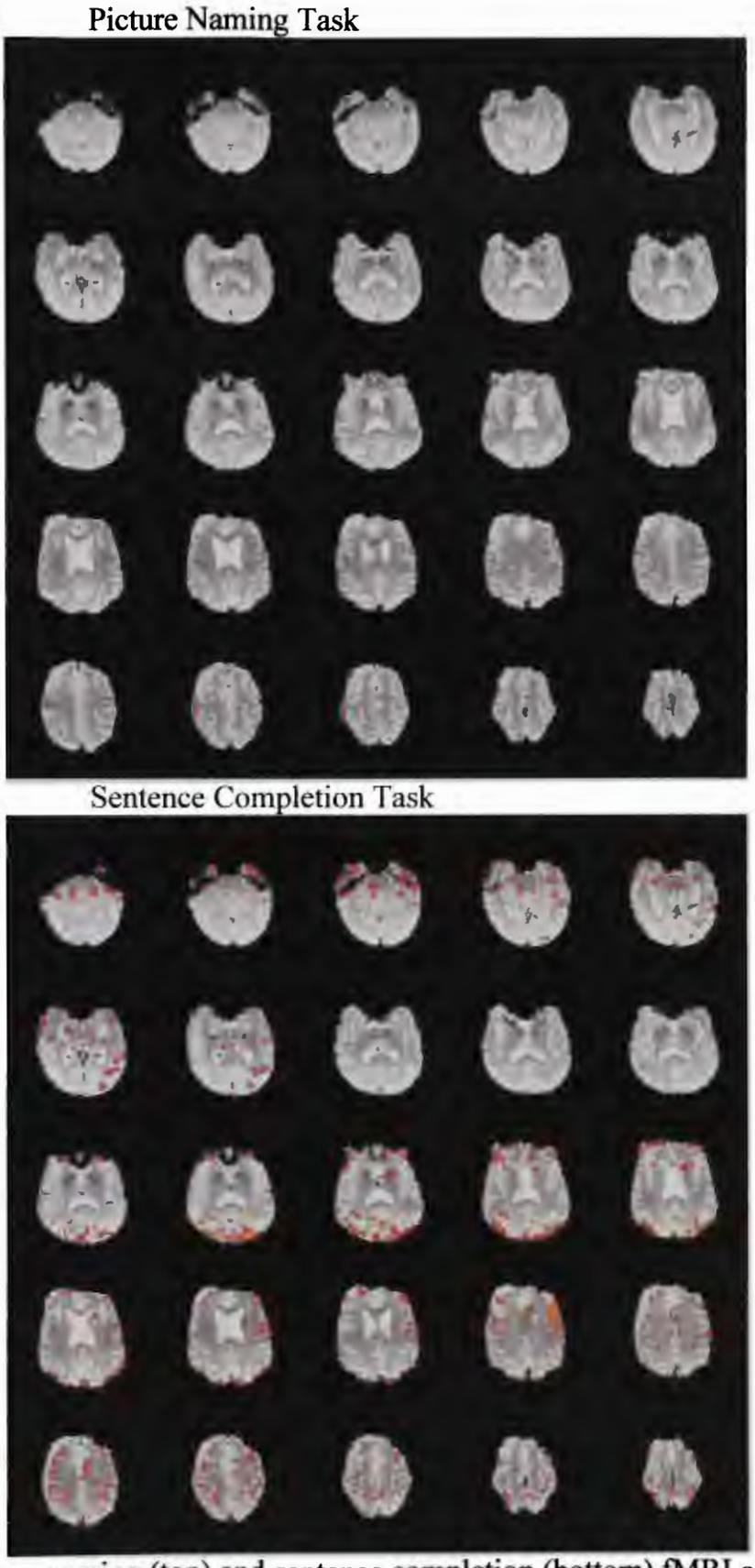


Figure 40. Picture naming (top) and sentence completion (bottom) fMRI activation on axial slices for patient B1. Images are shown in radiological convention: the left hemisphere is displayed on the right side of the image.

Table 46

Language task results for B2.

Localisation	Cluster Size	Z	x	y	z
Letter Fluency					
L PreCG BA6	2587	6.98	-47.7	-4.36	46.1
R IFG BA45	1856	5.82	60.3	20.8	22.4
L Putamen	873	5.23	-22.3	5.78	-7.68
L CingG BA24	756	7.63	-6.58	12	36.3
L STG BA13	250	7.73	-44.6	-50.5	22.9
R PostCG BA5	226	4.52	2.07	-51.8	73.8
L Precuneus BA7	171	5.11	-1.91	-80.6	56.5
L SPL BA7	163	4.79	-32.8	-76.1	41.3
R FusiformG BA20	147	4.57	42.1	-18.4	-29.5
R Sub-lobar	130	4.41	22.9	-26.3	-5.47
R SPL BA7	120	3.78	31.7	-62.5	56.1
L MFG BA9	110	5.69	-35.2	42.4	30.1
R SupraMG BA40	100	4.16	51	-47.5	30.9
L AntCingG BA32	94	4.92	-5.92	31.9	28.8
L ParaCL BA5	90	5.69	-8.4	-44.8	56.2
L MTG BA21	89	4.75	-51	2.73	-43.5
Picture Naming					
L STG BA13	7364	7.92	-45.8	-49.5	23.4
R IFG BA47	395	4.93	42	21.9	-5.59
R MFG BA8	263	4.26	47.6	13.9	42.5
R MFG BA6	222	4.48	28.5	0.024	50.2
L PostCG BA2	198	5.74	-49.9	-29.7	43.9
R SFG BA10	144	3.79	29.9	66.8	-4.22
R MTG BA21	137	4.39	70.5	-41.9	-5.32
L MFG BA8	127	3.88	-19.2	17.6	43.6
L MFG BA10	109	4.32	-43.3	49.3	6.24
L Putamen	104	3.91	-20.5	-1.02	16.1
R ParahipG	86	5.88	17.7	-4.28	-14.6
Sentence Completion					
L Precuneus BA7	19523	10.6	-18.8	-88.1	46.8
L PostCG BA40	144	5.19	64.6	-26.6	20.7
L SPL BA7	90	5.5	-34.8	-53.8	64.6

Note. Local maxima in MNI coordinates. Only the local maxima with highest Z score in each cluster are provided in the table. Cluster size is in voxels. When the cluster encompasses more than one anatomical location, the localization given corresponds to the local maxima with the highest Z score. L, left; R, right; IFG, inferior frontal gyrus; MFG, middle frontal gyrus; IPL, inferior parietal lobule; CingG, cingulate gyrus; SFG, superior frontal gyrus; MTG, middle temporal gyrus; MedFG, medial frontal gyrus; ITG, inferior temporal gyrus; PostCingG, postcingulate gyrus; AngG, angular gyrus; PostCG; postcentral gyrs; Fusiform G, fusiform gyrus; PreCingG, precingulate gyrus; STG, superior temporal gyrus; SupraMG, supramarginal gyrus; AntCingG, anterior cingulated gyrus; ParaCL, paracentral lobule.

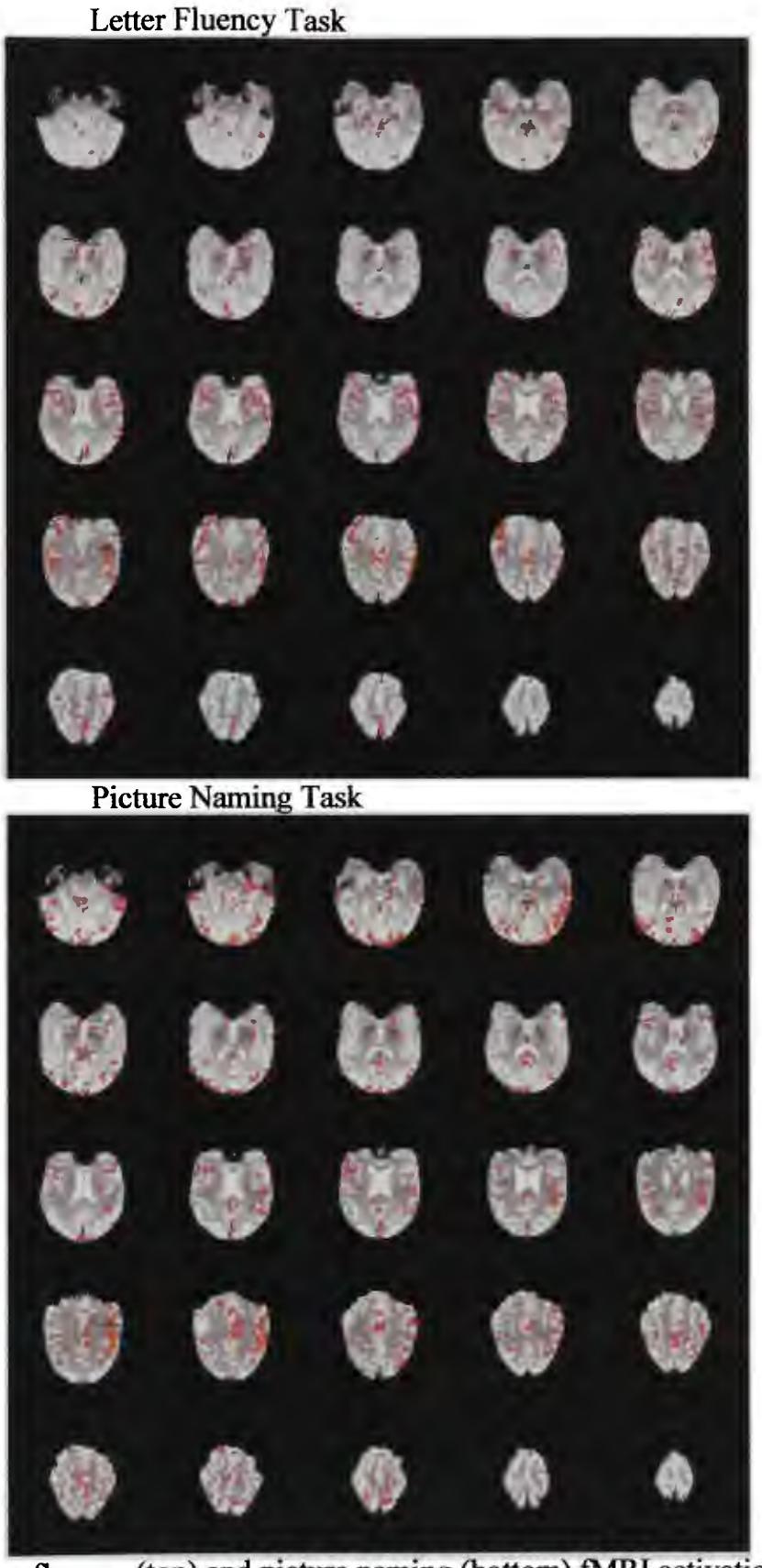


Figure 41. Letter fluency (top) and picture naming (bottom) fMRI activation on axial slices for patient B2. Images are shown in radiological convention: the left hemisphere is displayed on the right side of the image.

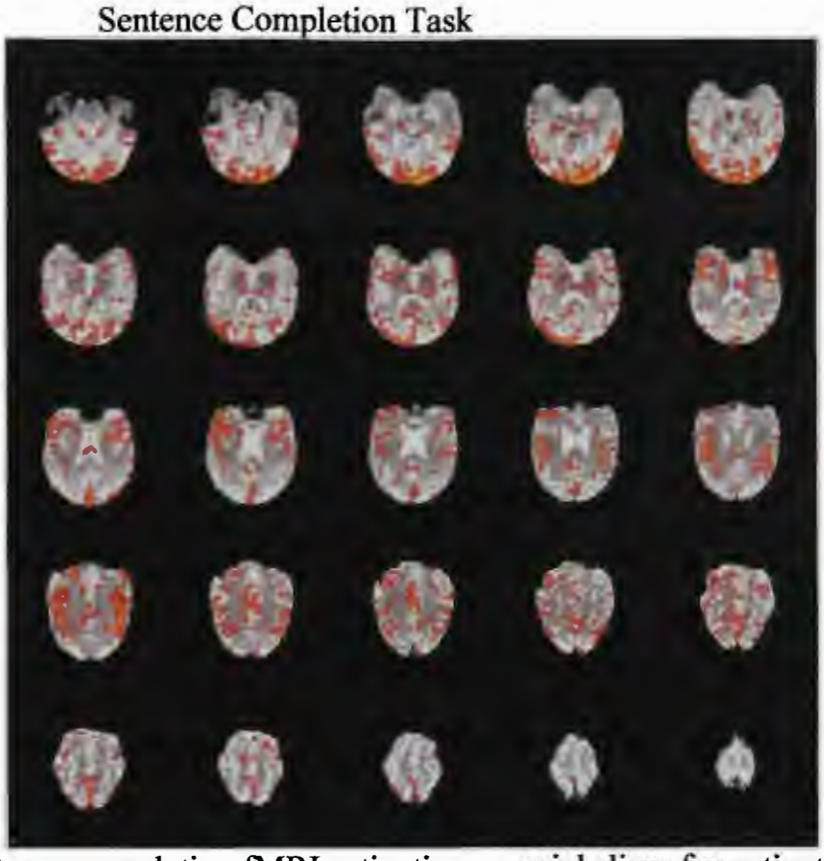


Figure 42. Sentence completion fMRI activation on axial slices for patient B2. Images are shown in radiological convention: the left hemisphere is displayed on the right side of the image.

Table 47

Language task results for B3.

Localisation	Cluster Size	Z	x	y	z
Letter Fluency					
L MFG BA9	381	6.91	-51.6	11.8	36.9
L IFG BA47	182	5.11	-43.9	28.8	-6.44
R Caudate	157	4.32	38.4	-39.4	0.197
R PostCG BA3	122	4.1	40.8	-34.6	69.3
Precuneus BA19	117	5.33	-6.86	-100	40.6
L SFG BA6	116	5.12	-1.21	7.08	59.8
L PostCG BA7	99	5.29	-13.7	-57.5	74.7
L Occipital Lobe BA18	88	4.02	-1.13	-97	17.9
R Lingual Gyrus BA17	81	4.59	6.64	-87.3	-1.89
Picture Naming					
L Sub-lobar	84	4.34	-17.7	29.8	14.3
Sentence Completion					
L IFG BA47	1329	6.84	-47.2	23.4	1.9
L MTG BA19	1221	6.51	-45.2	-65.6	11.6
L MFG BA8	952	4.65	-4.97	25.9	45
L SPL BA7	841	6	-9.13	-79.6	62.8
L MOG BA18	506	5.95	-24.6	-93.9	9.27
R FusiformG BA19	159	4.57	20.4	-64.5	-12.6
L CingG BA31	156	4.1	-22.9	-42.5	22.9
L CingG BA23	155	5.36	-4.31	-36.2	56.2
L ParahipG BA30	145	4.65	-9.95	-34	-10.6
R MTG BA39	137	4.79	38.6	-72.1	19.8
L Midbrain	126	3.69	0.392	-7.51	-13.1
R Precuneus BA7	115	5.69	21.9	-79.6	57.5
L ParahipG BA19	107	5.91	-33.9	-58.2	-8.3
R Sub-lobar	96	4.4	14.5	9.6	-13.4
R PostCG BA3	88	3.6	58.3	-15.9	49.4

Note. Local maxima in MNI coordinates. Only the local maxima with highest Z score in each cluster are provided in the table. Cluster size is in voxels. When the cluster encompasses more than one anatomical location, the localization given corresponds to the local maxima with the highest Z score. L, left; R, right; MFG, middle frontal gyrus; IFG, inferior frontal gyrus; PostCG; postcentral gyrus; SFG, superior frontal gyrus; MTG, middle CingG, cingulate gyrus; temporal gyrus; SPL, superior parietal lobule; MOG, middle occipital lobule; FusiformG, fusiform gyrus; ParahipG, parahippocamal gyrus.

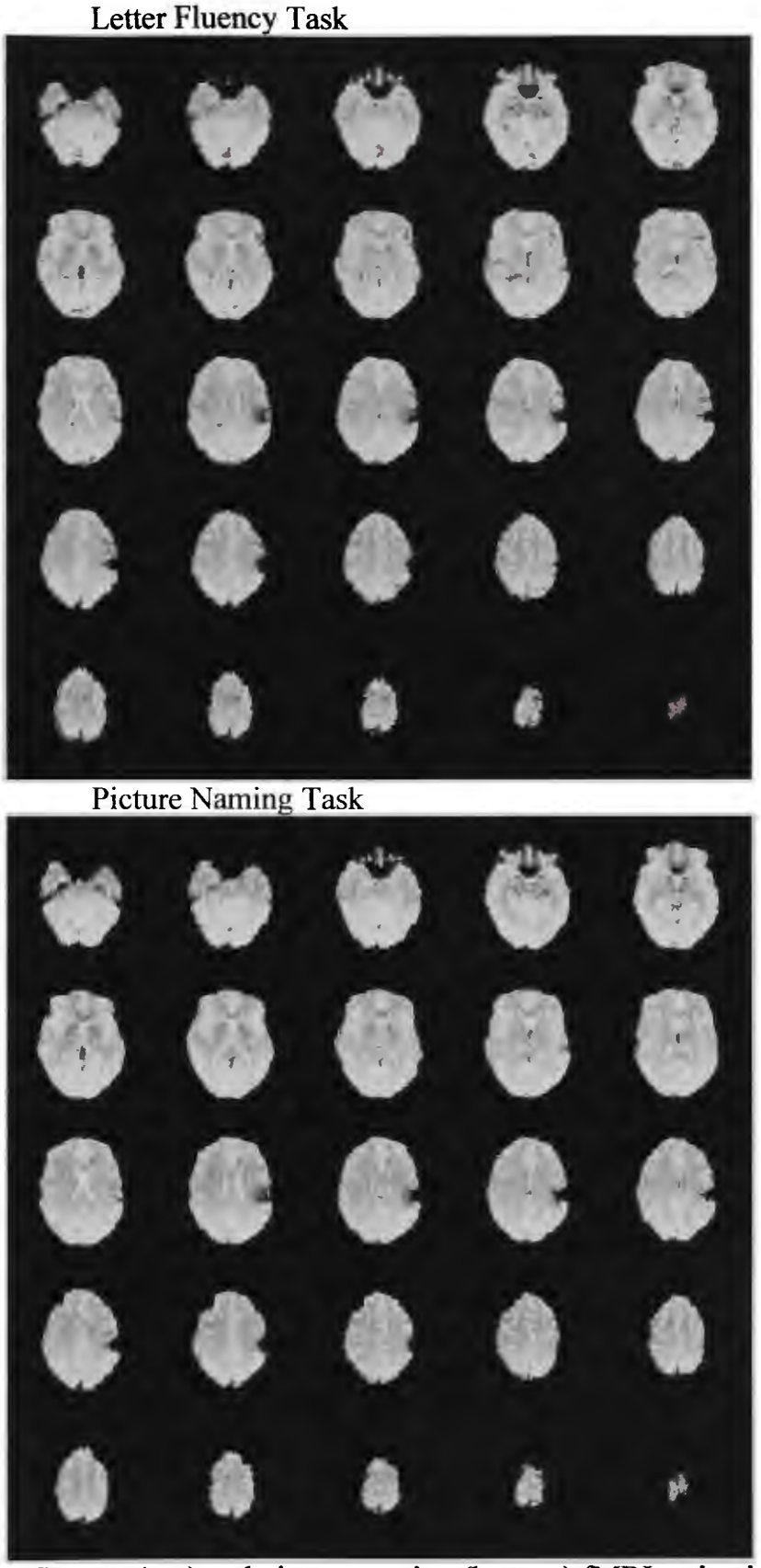


Figure 43. Letter fluency (top) and picture naming (bottom) fMRI activation on axial slices for patient B3. Images are shown in radiological convention: the left hemisphere is displayed on the right side of the image.

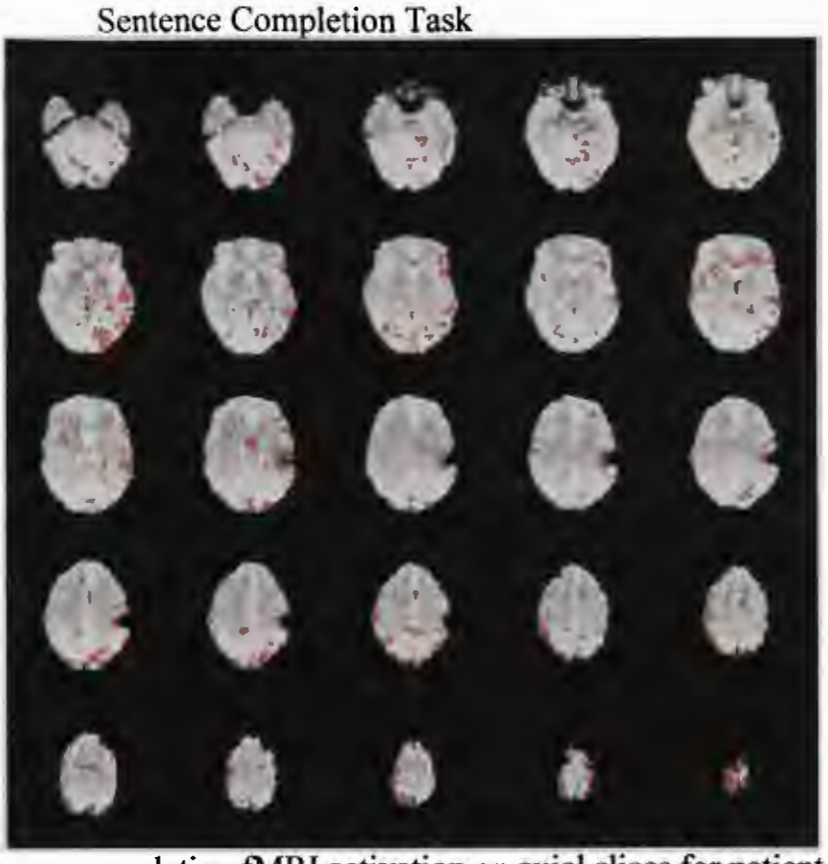


Figure 44. Sentence completion fMRI activation on axial slices for patient B3.

Table 48

Language task results for B4.

Localisation	Cluster Size	Z	x	y	z
Letter Fluency					
L IFG BA44	1218	7.03	-52.6	8.09	25
L PostCingG BA29	345	5.17	-5.73	-43.2	7.79
L AntCing BA24	191	6.59	-2.48	27.3	23.5
R IFG BA47	137	4.83	36	30.4	-16.4
L SPL BA7	136	5.16	-31.8	-60.5	49.6
R PostCing BA30	88	3.76	17.6	-56.5	7.59
R Fusiform BA36	86	5.19	39.5	-57	-32.7
L MTG BA20	82	5.72	-52.6	-44.4	-11.6
Category Fluency					
L Sub-lobar	289	6.54	-34	16.9	25.4
L PostCingG BA30	279	5.47	-14.9	-55.6	9.55
L IFG BA47	236	4.77	-52	22.3	-4.61
L Sub-lobar	168	4.61	-22.3	-12.3	-13.2
L CingG BA32	158	6.85	-3.7	17.2	41.2
R IFG BA47	141	4.36	36.3	33.9	-7.9
L Orbital Gyrus BA11	116	4.52	-8.73	47.4	-31.4
L SPL BA7	108	4.55	-25.7	-71.8	55
R IFG BA9	101	5.23	59.3	2.17	25.9
L Sub-lobar	80	4.97	-38.6	34.1	-32.4
R STG BA21	77	4.74	49.1	-29	-8.22
Picture Naming					
L SPL BA7	283	5.72	-30.3	-59	55.5
R ParahipG BA19	265	4.77	31	-58.6	-13.9
R Midbrain	189	4.12	5.98	-5.99	-29.8
R ParahipG BA36	183	4.65	16.1	-40.8	-14.9
L FusiformG BA20	151	4.31	-35.8	-41.2	-25.3
R PrarhipG BA36	148	5.65	30.1	-34.9	-29.2
L MFG BA11	134	4.02	-26.4	40.4	-4.73
L FusiformG BA19	132	5.28	-20.4	-57.9	-12.5
R Cuneus BA17	132	4.68	4.47	-84	4.47
R SPL BA7	115	4.98	29.9	-63.2	44.6
L CingG BA31	137	3.99	-12.9	-28.2	37.5
L STG BA38	98	3.79	-49.5	20.8	-33
R Sub-lobar	85	3.87	28.9	1.97	-7.33
L STG BA38	75	3.78	-53.9	17.3	-8.73
Sentence Completion					
R MTG BA 21	1027	5.34	61.5	-46.6	0.027
L Precuneus BA19	853	6.07	-28.4	-62.9	39.4
L IFG BA47	830	5.47	-49.3	23.5	-5.75

R IFG BA47	432	4.46	29.4	16.2	-13
L MTG BA22	324	5.88	-56.3	-41.5	1.41
R SPL BA7	303	5.67	33.4	-54.9	49
L PreCingG BA31	178	4.73	-22	-62.6	13.6
R FusiformG BA37	176	4.65	38.4	-54.2	-14.4
R PreCG BA6	145	4.7	51.6	-2.32	16.5
R IFG BA46	105	3.43	46.3	39.7	10.1

Note. Local maxima in MNI coordinates. Only the local maxima with highest Z score in each cluster are provided in the table. Cluster size is in voxels. When the cluster encompasses more than one anatomical location, the localization given corresponds to the local maxima with the highest Z score. L, left; R, right; IFG, inferior frontal gyrus; PostCingG, postcingulate gyrus; AntCingG, anterior cingulate gyrus; SPL, superior parietal lobule; MTG, middle temporal gyrus; CingG, cingulate gyrus; SPL, superior parietal lobule; STG, superior temporal gyrus; ParahipG, parahippocamal gyrus; FusiformG, fusiform gyrus; MFG, middle frontal gyrus; PreCingG, precingulate gyrus.

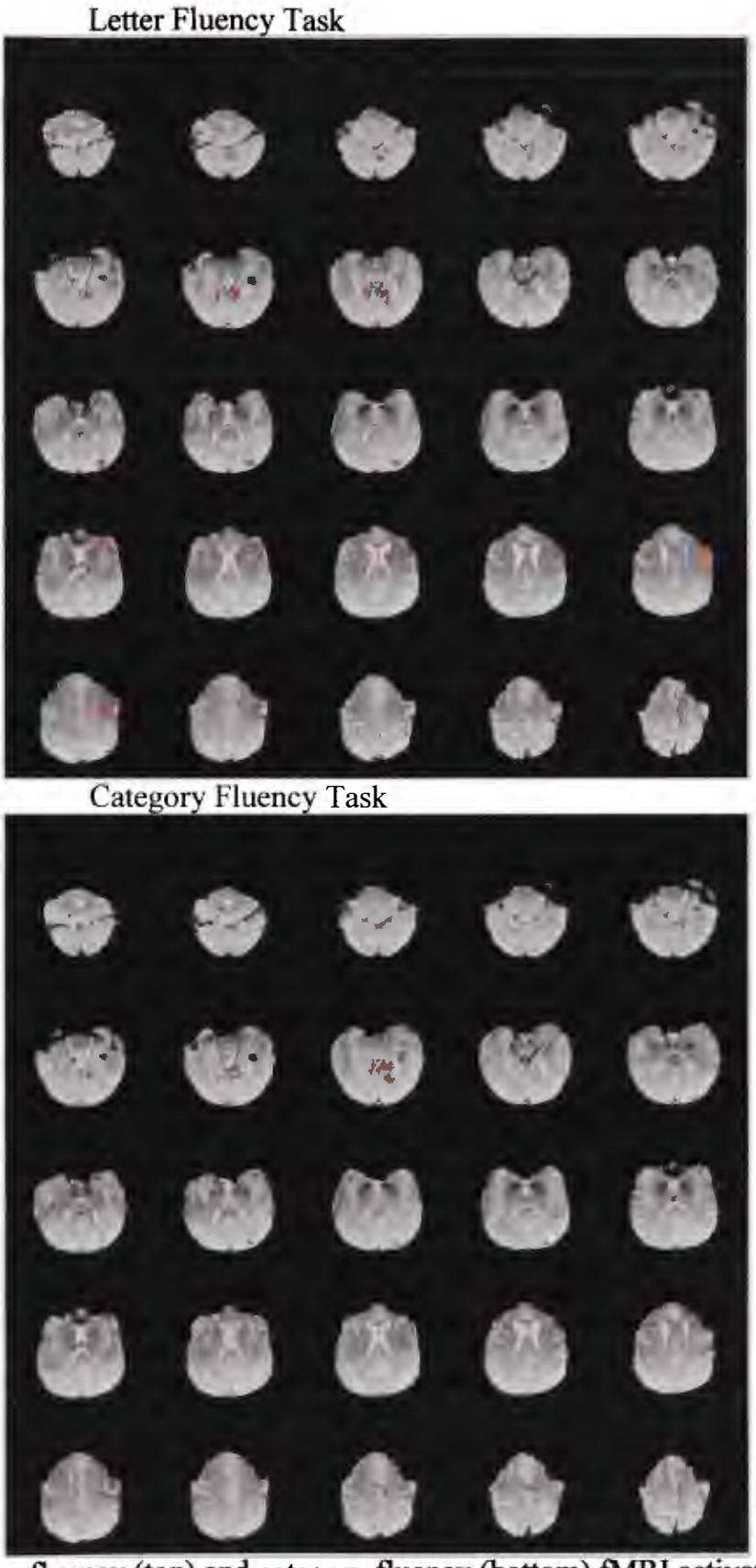


Figure 45. Letter fluency (top) and category fluency (bottom) fMRI activation on axial slices for patient B4. Images are shown in radiological convention: the left hemisphere is displayed on the right side of the image.

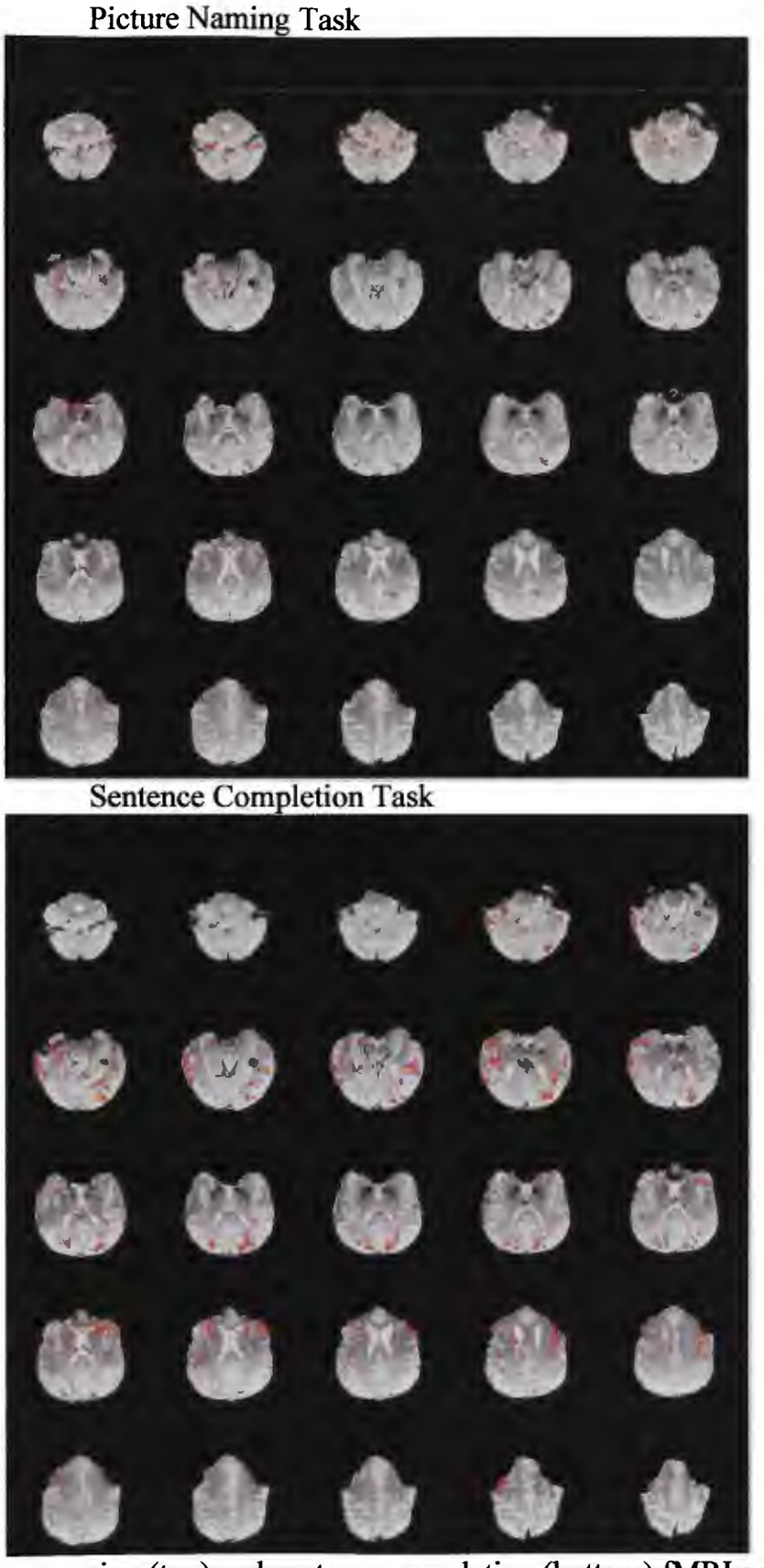


Figure 46. Picture naming (top) and sentence completion (bottom) fMRI activation on axial slices for patient B4. Images are shown in radiological convention: the left hemisphere is displayed on the right side of the image.

Table 49

Language task results for B5.

Localisation	Cluster Size	Z	x	y	z
Letter Fluency					
R MedFG BA10	180	4.33	1.59	65.7	23.9
Category Fluency					
R PreCG BA6	1118	4.75	68.3	8.33	8.13
R Temporal Lobe	293	4.65	35	-28.8	-11
R CingG BA32	130	4.33	10.1	18.4	37.9
L PreCG BA4	130	3.91	-16.3	-26.4	59.3
L CingG BA6	127	4.58	-15.3	25	38.9
Picture Naming					
L IOG BA18	2148	6.41	-51.8	-82.2	-5.43
R IFG BA45	1677	6.84	63.5	31.9	9.74
R MedFG BA10	1526	6.03	12.8	54.9	-3.98
R STG BA38	509	4.91	56.9	28	-32
L Lingual Gyrus BA18	371	6.56	-26.1	-79.6	-2.1
R PreCG BA6	286	5.89	26.9	-21.2	56.1
R Occipital Lobe	230	4.94	1.78	-57.7	-5.36
L PostCG BA3	212	5.01	-39.2	-25.3	58.5
L PostCG BA3	173	5.29	-26.4	-40.8	48.2
L Precuneus BA19	150	3.83	-34.2	-75.1	39.2
L Frontal Lobe	100	4.54	-20.5	-6.5	57
R Insula BA13	97	4.78	47.8	-13.3	22
Sentence Completion					
R PreCG BA6	2743	6.99	68.8	-8.56	37.7
L MTG BA21	1314	7.09	-72	-22.5	-24.4
L SFG BA10	683	7.78	-7.28	75.7	-5.07
R CingG BA24	369	5.23	15.6	-6.48	36.2
L SFG BA8	308	4.97	-23.3	13.5	47.8
L STG BA38	252	5.1	-54.1	17.1	-26.1
R Insula BA13	236	6.15	43.7	-46.4	12.5
R IFG BA 47	136	6.69	63	29.8	-3.95
L Parietal Lobe	106	4.49	-22.6	-41.9	55.3

Note. Local maxima in MNI coordinates. Only the local maxima with highest Z score in each cluster are provided in the table. Cluster size is in voxels. When the cluster encompasses more than one anatomical location, the localization given corresponds to the local maxima with the highest Z score. L, left; R, right; MedFG, medial frontal gyrus; PreCG, precentral gyrus; CingG, cingulated gyrus, IOG, inferior occipital lobe; IFG, inferior frontal lobe; STG, superior temporal gyrus; PostCG, postcentral gyrus; SFG, superior frontal gyrus,

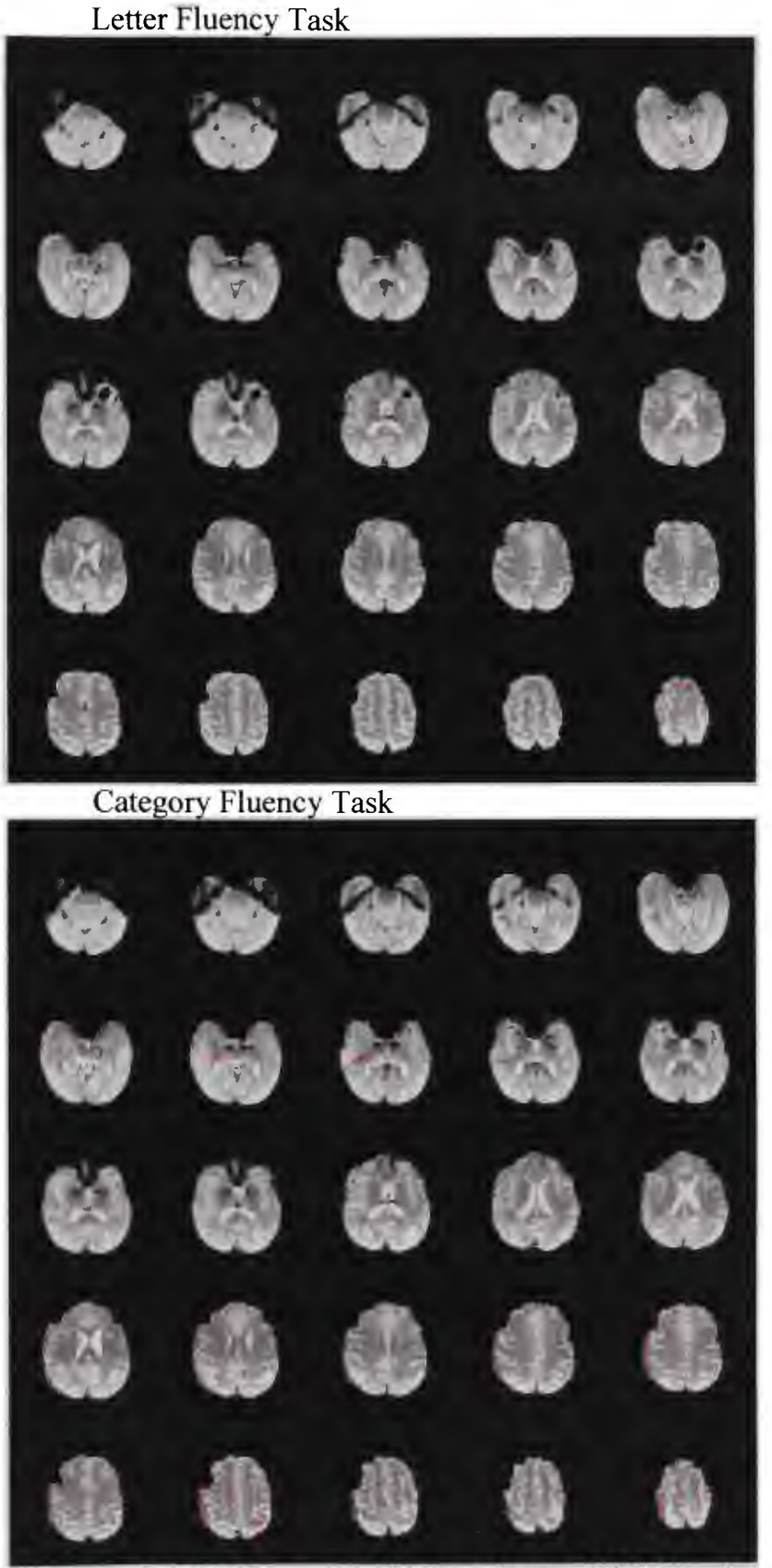


Figure 47. Letter fluency (top) and category fluency (bottom) fMRI activation on axial slices for patient B5. Images are shown in radiological convention: the left hemisphere is displayed on the right side of the image.

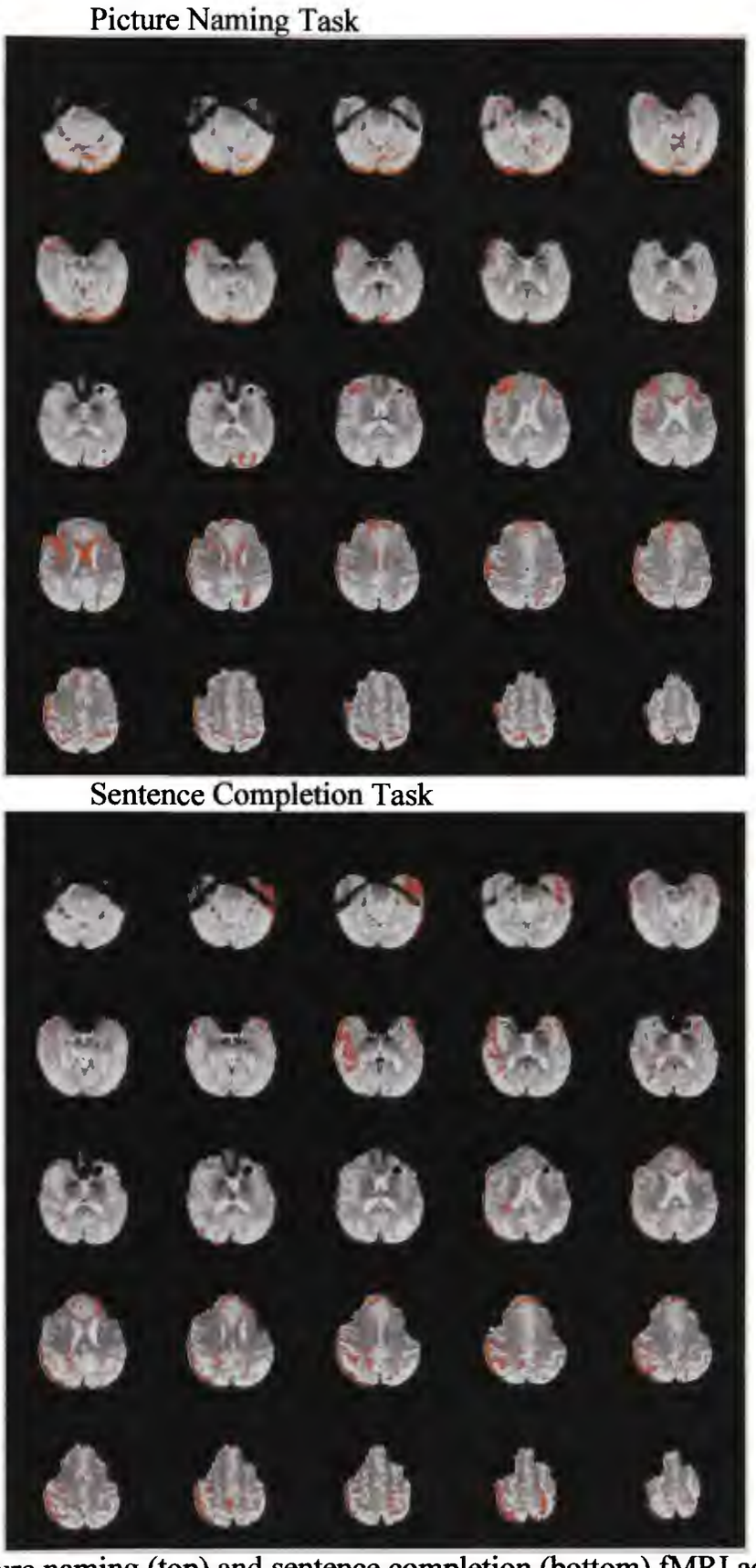


Figure 48. Picture naming (top) and sentence completion (bottom) fMRI activation on axial slices for patient B5. Images are shown in radiological convention: the left hemisphere is displayed on the right side of the image.

Table 50

Language task results for B6.

Localisation	Cluster Size	Z	x	y	z
Letter Fluency					
L PreCG BA6	892	7.73	-51	-0.47	38.1
L CingG BA32	694	6.94	-5.26	15.3	39.6
L PostCG BA5	344	6.49	-39.1	-48.7	60.4
R Sub-lobar	181	4.06	23	5.5	-4.14
L STG BA22	175	5.6	-52.6	13.7	-4.55
L MTG BA21	113	4.51	-67.8	-36.5	-1.18
R MFG BA47	89	4.75	37.5	38.1	-2.55
R MTG	77	5.17	48.3	-32.9	-2.11
Category Fluency					
L STG BA22	904	6.58	-50.5	9.76	-3.03
L PreCG BA6	666	7.12	-51.3	-0.75	37.8
L CingG BA32	614	7.73	-0.14	13.7	40.5
R Insula BA13	216	5.24	31.3	17.7	-5.89
L SPL BA7	180	4.92	-33	-76.5	46.7
R SFG BA11	139	5.42	16.8	55.2	-12.7
R MFG BA10	117	5.62	38.6	49.9	-4.27
Picture Naming					
L ParahipG BA36	387	5.02	-30.7	-29.2	-29.8
L IFG BA47	386	6.82	-55.6	25.4	-6.8
L SPL BA7	323	5.94	-22.1	-66.7	61.5
L ITG BA37	272	7.41	-56	-55.1	-4.92
L PreCG BA6	241	6.03	-51.9	-0.41	38
L IFG BA45	169	5	-51.5	24	13.9
L ParahipG BA30	82	4.63	-9.85	-45.2	-0.53
L CingG BA24	79	3.84	-14.5	1.92	36.8
L PreCG BA6	78	4.46	-21.8	-22.8	71
L MTG BA39	78	5.26	-45.6	-77.1	22.7
L MFG BA6	76	4.25	-41.1	5.61	54.4
Sentence Completion					
L Cuneus BA19	1210	5.68	-27	-86.2	24.2
L PreCG BA6	689	9.37	-51.4	1.42	36.3
L MTG BA21	687	9.36	-61.9	-42.2	-2.99
L SPL BA7	528	6.39	-13.4	-66.9	63
L IFG BA47	527	7.48	-53.2	25	-7.8
R MFG BA8	351	5	32.5	36.5	42.8
L MedFG BA6	200	5.64	-4.83	2.01	52.3
R SFG BA11	155	3.47	16.5	57	-9.93
R CingG BA32	131	5.98	12.1	15.3	29.8
L MFG BA10	118	5.12	-30.9	48.6	28.8
R Sub-lobar	110	4.41	24.6	8.63	-5.91

L MFG BA6	95	3.55	-22.5	-1.16	53.7
R MTG BA 22	89	4.83	52.3	-38.2	-2.31
R Sub-lobar	80	3.88	13.6	16.8	8.95
R Frontal Lobe	79	3.64	21.9	4.27	56.6
L SFG BA11	75	4.93	-10.5	58.1	-21.3

Note. Local maxima in MNI coordinates. Only the local maxima with highest Z score in each cluster are provided in the table. Cluster size is in voxels. When the cluster encompasses more than one anatomical location, the localization given corresponds to the local maxima with the highest Z score. L, left; R, right; PreCG, precentral gyrus; CingG, cingulate gyrus; PostCingG, postcingulate gyrus; , superior temporal gyrus; MTG, middle temporal gyrus; MFG, middle temporal gyrus; STG, superior temporal gyrus; SPL, superior parietal lobule; SFG, superior frontal gyrus; ParahipG, parahippocamal gyrus; IFG, inferior frontal lobe; ITG, inferior temporal gyrus; MedFG, medial frontal gyrus; CingG, cingulated gyrus.

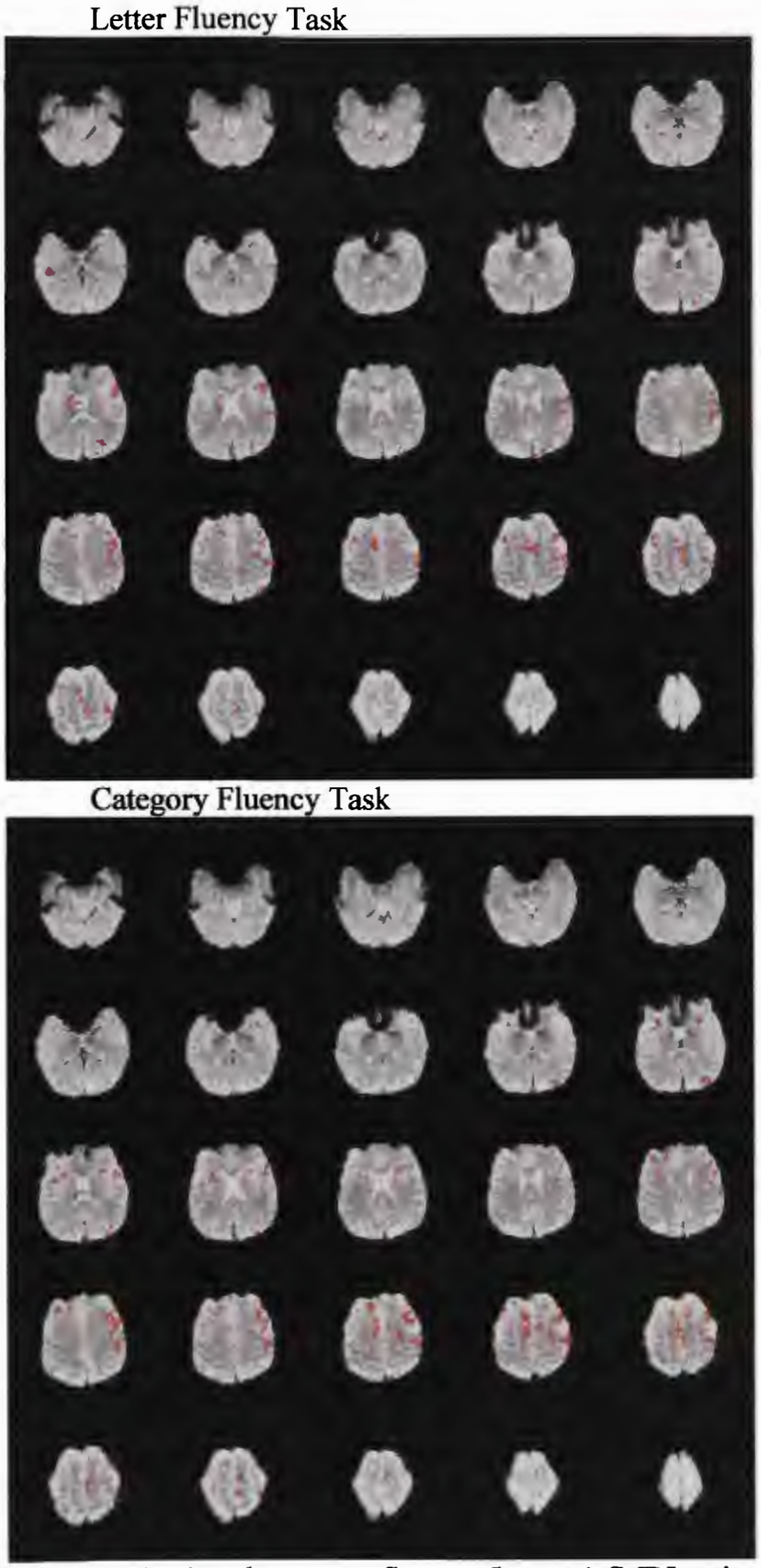


Figure 49. Letter fluency (top) and category fluency (bottom) fMRI activation on axial slices for patient B6. Images are shown in radiological convention: the left hemisphere is displayed on the right side of the image.

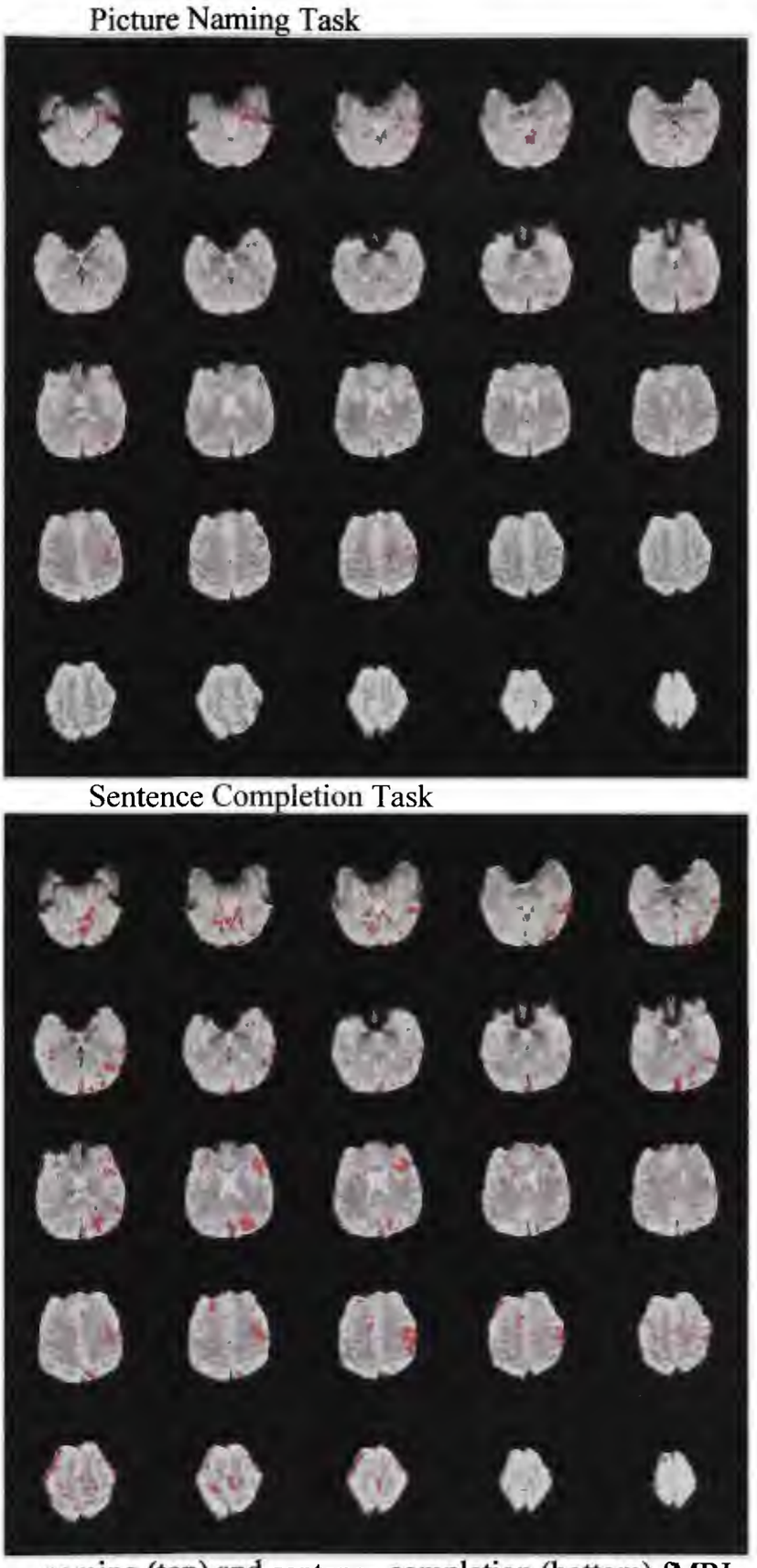


Figure 50. Picture naming (top) and sentence completion (bottom) fMRI activation on axial slices for patient B6. Images are shown in radiological convention: the left hemisphere is displayed on the right side of the image.

APPENDIX J: Additional Tables and Figures for New Healthy Controls

Table 51

Reading and semantic decision task results for NC1.

Localisation	Cluster Size	Z	x	y	z
Reading task					
L MTG BA21	148	5.08	59.2	-5.18	-8.56
L MTG BA21	127	4.89	55	-47.6	3.85
Decision task					
R IFG BA45	621	5.5	-54.6	18.6	21.6
L IFG BA46	350	6.35	43.1	32.6	9.01
R Cuneus BA18	342	4.54	-26.1	-71.5	14.1
R Cuneus BA30	249	4.21	-2.67	-65.2	2.06
L Caudate	178	4.54	13.7	9.32	10.6
L MTG BA21	176	4.1	62.3	-40	-13.4
L PreCG BA6	147	4.97	34	4.02	34
L MTG BA21	114	4.69	56.3	-46.7	4.6
R ParrhipG	13	4.31	-27.3	-8.69	-15.6
L MFG BA11	102	3.77	40.4	40.2	-14.7
L Insula BA13	101	4.49	26.6	-36.6	26.8
R Insula BA13	93	3.73	-38.3	-4.3	25.2
L Precuneus BA7	93	3.62	10	-43.4	49.1

Note. Local maxima in MNI coordinates. Only the local maxima with highest Z score in each cluster are provided in the table. Cluster size is in voxels. When the cluster encompasses more than one anatomical location, the localization given corresponds to the local maxima with the highest Z score. L, left; R, right; MTG, middle temporal gyrus; IFG, inferior frontal gyrus; PreCG, precentral gyrus; ParrhipG, parahippocampal gyrus; MFG, middle frontal gyrus.

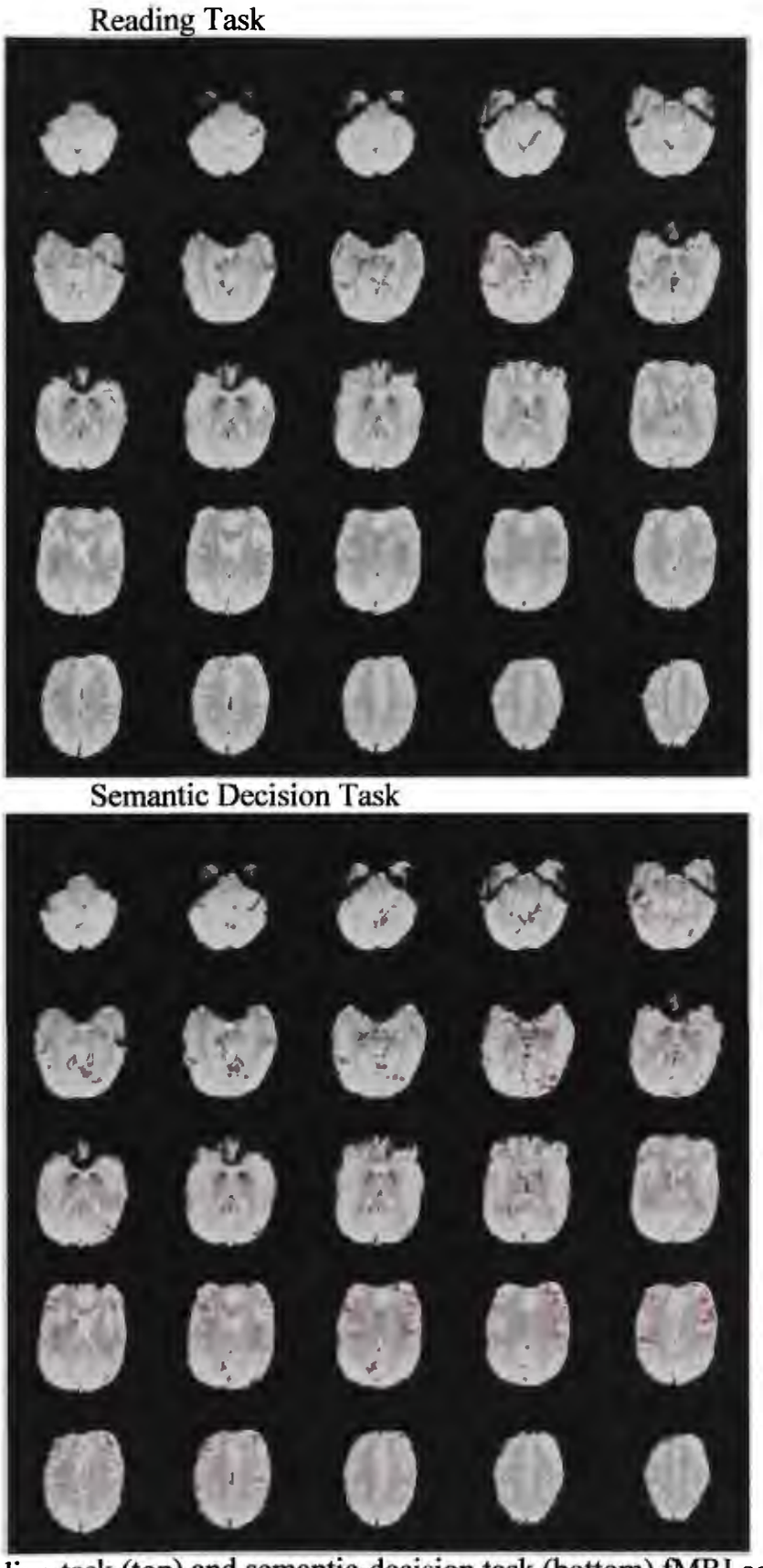


Figure 51. Reading task (top) and semantic-decision task (bottom) fMRI activation on axial slices for patient NC1. Images are shown in radiological convention: the left hemisphere is displayed on the right side of the image.

Table 52

Reading and semantic decision task results for NC2.

Localisation	Cluster Size	Z	x	y	z
Reading task					
L MTG BA21	449	7.35	48.7	-33.3	-3.93
L IFG BA45	379	5.8	55.8	24.6	13
L MFG BA8	347	8.34	53.3	6.03	42.2
L IFG BA47	170	5.19	34.4	30.4	-0.394
R STG BA38	165	4.62	-47.1	16.9	-29.1
L MFG BA6	108	6.76	2.52	0.678	53.2
R STG BA22	106	5.45	-47	-32	2.14
R STG BA22	86	4.4	-53.5	-10.4	-9.78
Decision task					
	Nil				

Note. Local maxima in MNI coordinates. Only the local maxima with highest Z score in each cluster are provided in the table. Cluster size is in voxels. When the cluster encompasses more than one anatomical location, the localization given corresponds to the local maxima with the highest Z score. L, left; R, right; MTG, middle temporal gyrus; IFG, inferior frontal gyrus; MFG, middle frontal gyrus; STG, superior temporal gyrus.

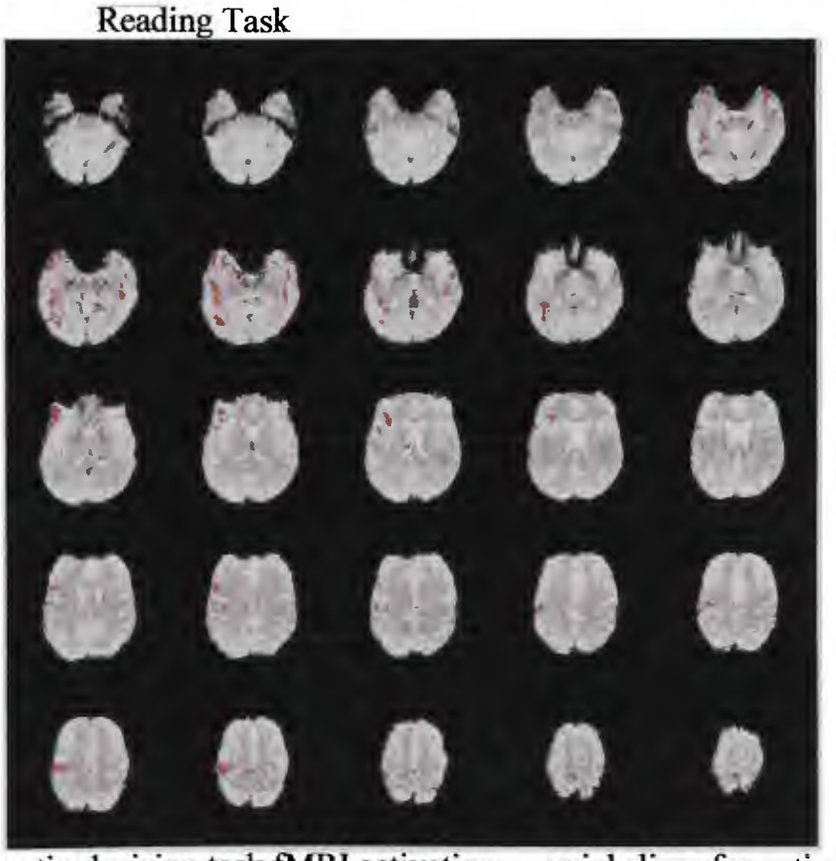


Figure 52. Semantic-decision task fMRI activation on axial slices for patient NC2. Images are shown in radiological convention: the left hemisphere is displayed on the right side of the image.

Table 53

Reading and semantic decision task results for NC3.

Localisation	Cluster Size	Z	x	y	z
Reading task					
L STG BA22	3916	7.66	72.1	-15.6	1.36
R MTG BA21	728	6.21	-63.8	-7.24	-15.6
L PreCG BA6	527	4.64	-34.4	-12.2	68.3
L SFG BA6	451	5.49	3.56	17.2	58.6
L PostCing BA23	403	4.69	3.18	-55.4	13
L PostCG BA3	119	4.91	54.8	-17.4	50.9
R IFG BA45	116	4.56	-49.6	23.5	10.9
R CingG BA32	106	4.52	-5.43	20.6	34.6
R MedFG BA6	103	3.81	-2.53	-13.8	80.4
Decision task					
L IFG BA47	2457	7.76	45.6	32.3	-0.795
L IPL BA40	995	6.61	42	-56.8	53.6
R MFG BA9	388	6.41	-40.4	12.2	30.1
L MTG BA37	282	4.89	56.3	-45.6	-8.86
R IFG BA47	170	5.7	-32.6	25	-6.38
R AngG BA39	145	4.86	-42.9	-63.4	31.2
R MFG BA10	125	4.88	-40.7	55.2	-1.32
R IFG BA47	119	4.06	43.8	-24.9	-18.6

Note. Local maxima in MNI coordinates. Only the local maxima with highest Z score in each cluster are provided in the table. Cluster size is in voxels. When the cluster encompasses more than one anatomical location, the localization given corresponds to the local maxima with the highest Z score. L, left; R, right; STG, superior temporal gyrus; MTG, middle temporal gyrus; PreCG, precenral gyrus; PostCing, postcingualte gyrus; IFG, inferior frontal gyrus; CingG, cingulate gyrus; MedFG, medial frontal gyrus; IPL, inferior parietal lobule; MFG, middle frontal gyrusl AngG, angular gyrus.

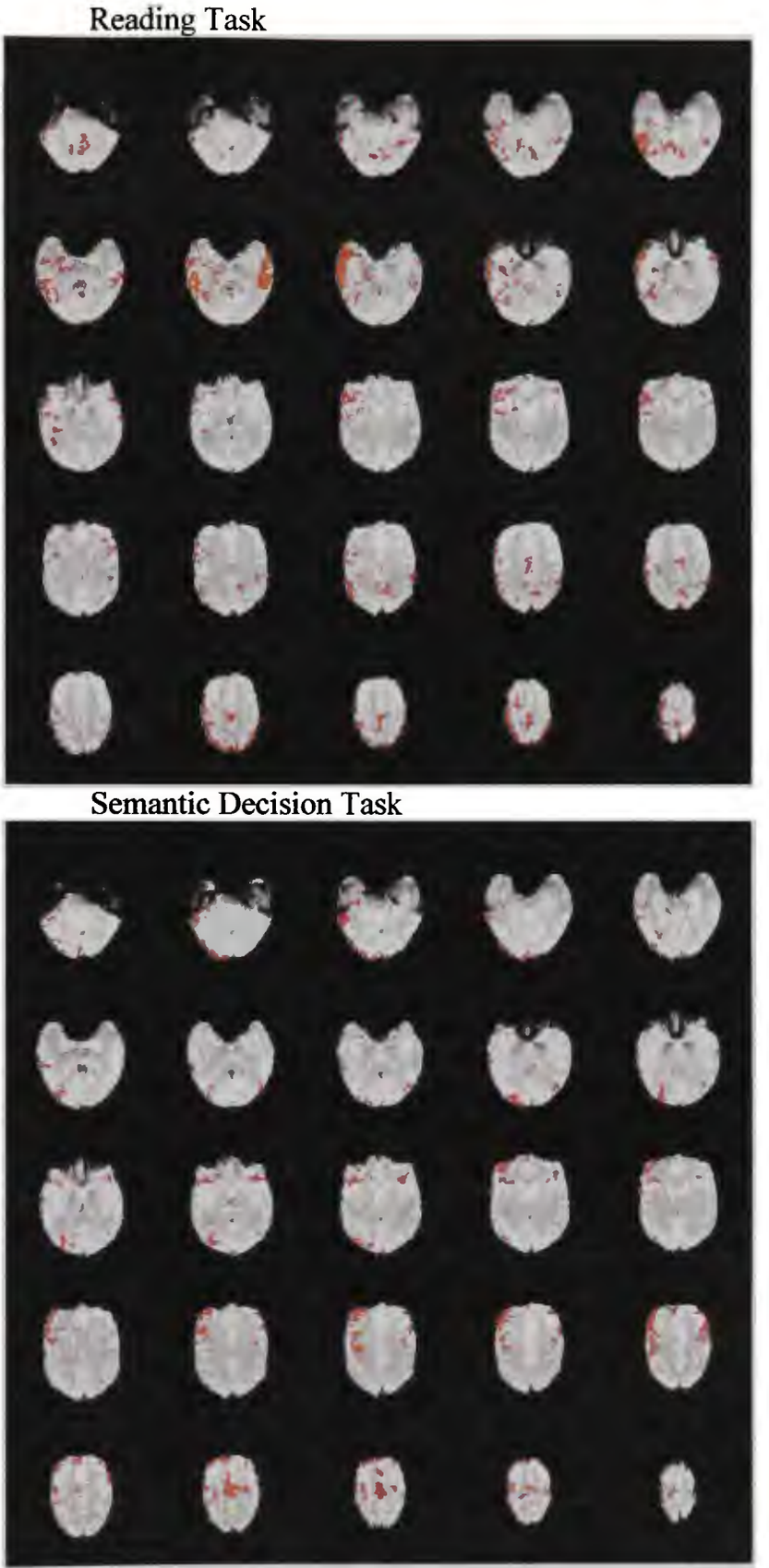


Figure 53. Reading task (top) and semantic-decision task (bottom) fMRI activation on axial slices for patient NC3. Images are shown in radiological convention: the left hemisphere is displayed on the right side of the image.

Table 54

Reading and semantic decision task results for NC4.

Localisation	Cluster Size	Z	x	y	z
Reading task					
L LingualG BA19	449	4.72	9.92	-61.2	-3.65
R MTG BA21	292	8.64	-47.4	-33.1	-5.8
R Uncus BA36	248	5.54	-20.2	-5.23	-39.7
L MTG BA22	223	7.03	51.3	-36.3	-2.47
R IFG BA45	156	4.43	-52.3	21.3	14
L PostCG BA3	122	3.57	28.2	-27.9	42.5
L ParahippG	120	4.86	21	-8.59	-22.3
L ITG BA20	100	4.04	43.4	2.03	-48.3
L STG BA38	99	4.09	42.5	12.5	-34
R Hippocampus	99	4.84	-45.6	-38.4	13.5
R Brainstem	97	5.18	-6.52	-25.1	-13.9
R MFG BA6	8	4.83	-47.5	4.75	48.9
Decision task					
L IFG BA47	1977	8.85	37.8	32.6	-17
R MFG BA8	1002	6.75	-40.3	22	46.1
L MTG BA20	687	6.56	54.2	-36.9	-13.6
R CingG BA32	462	6.18	-7.45	24.3	31.4
R MFG BA11	408	8.07	-32.3	37.9	-17.7
L IPL BA40	254	5.47	43.9	-53.9	45.6
L MFG BA8	175	6.75	29.8	16.8	46.8
L PosCingG BA23	129	6.02	3.68	-55.6	15.1
R STG BA38	123	5.03	-57.6	16.8	-5.44
R IPL BA40	121	5.95	-48.5	-64.3	47.1
R MTG BA21	99	4.66	-68.7	-20.3	-9.38
R STG BA38	99	5.48	-25.6	8.68	-57.1
L Precuneus BA19	78	5.2	28.7	-82.1	10.5

Note. Local maxima in MNI coordinates. Only the local maxima with highest Z score in each cluster are provided in the table. Cluster size is in voxels. When the cluster encompasses more than one anatomical location, the localization given corresponds to the local maxima with the highest Z score. L, left; R, right; LingualG, lingual gyrus; MTG, middle temporal gyrus; IFG, inferior frontal gyrus; PostCG, postcentral gyrus; ParahippG, parahippocampal gyrus; ITG, inferior frontal gyrus; STG, superior temporal gyrus; MFG, middle frontal gyrus; CingG, cingulate gyrus; IPL, inferior parietal lobule; STG, superior temporal gyrus.

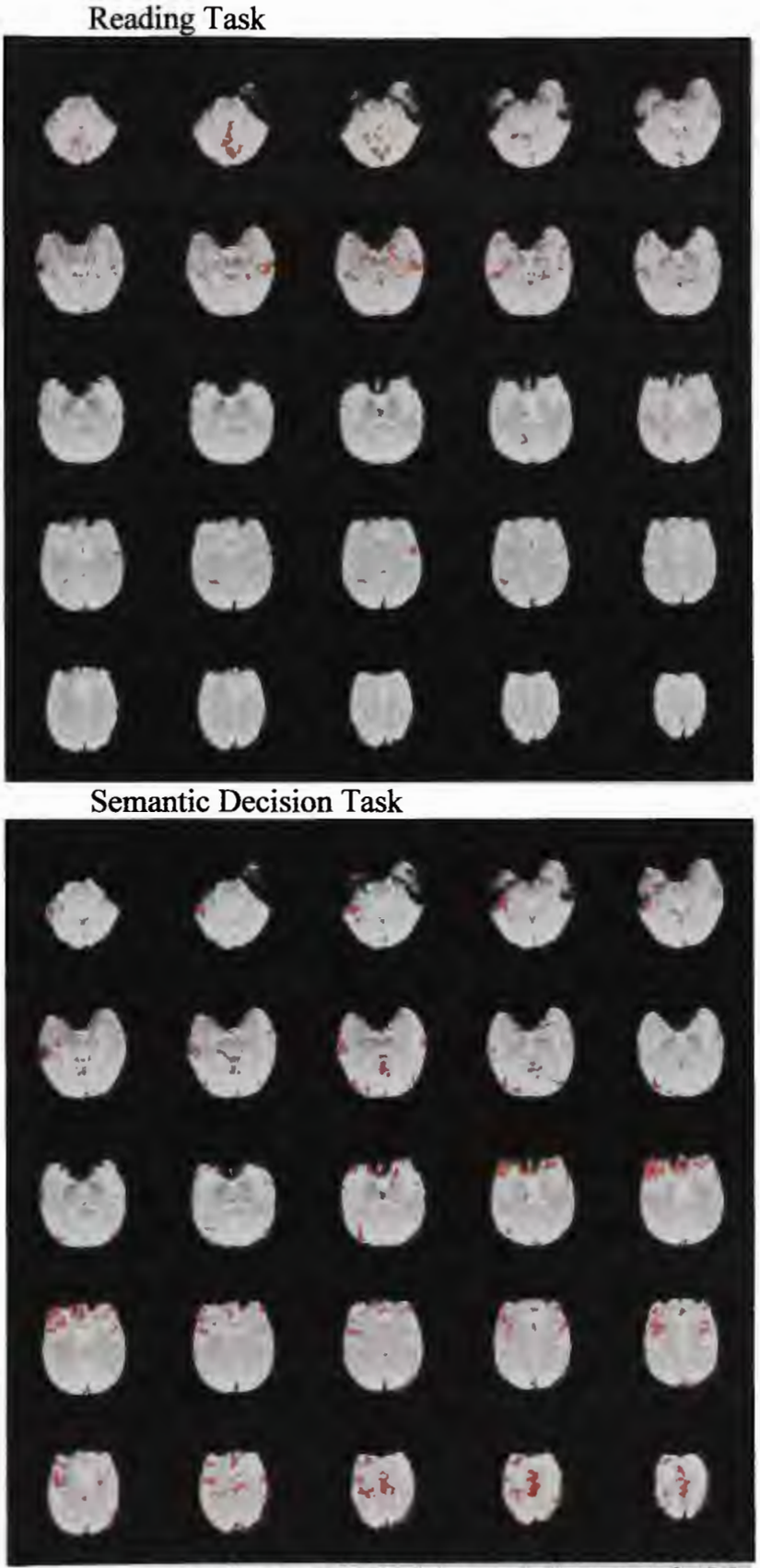


Figure 54. Reading task (top) and semantic-decision task (bottom) fMRI activation on axial slices for patient NC4. Images are shown in radiological convention: the left hemisphere is displayed on the right side of the image.

Table 55

Reading and semantic decision task results for NC5.

Localisation	Cluster Size	Z	x	y	z
Reading task					
L MTG BA21	281	4.86	66.5	-18.6	-4.68
R IFG BA9	155	4.63	-56	14.5	32.7
Decision task					
R Uncus BA20	165	3.89	-33.1	-14.8	-38.4
L IFG BA9	133	4.39	34.4	8.6	30.2
L MFG BA10	97	3.51	48.6	56.8	-3.07
R ParahipG BA34	76	3.73	-18.7	3.96	-18.5

Note. Local maxima in MNI coordinates. Only the local maxima with highest Z score in each cluster are provided in the table. Cluster size is in voxels. When the cluster encompasses more than one anatomical location, the localization given corresponds to the local maxima with the highest Z score. L, left; R, right; MTG, middle temporal gyrus; IFG, inferior frontal gyrus; MFG, middle frontal gyrus; ParahippG, parahippocampal gyrus.

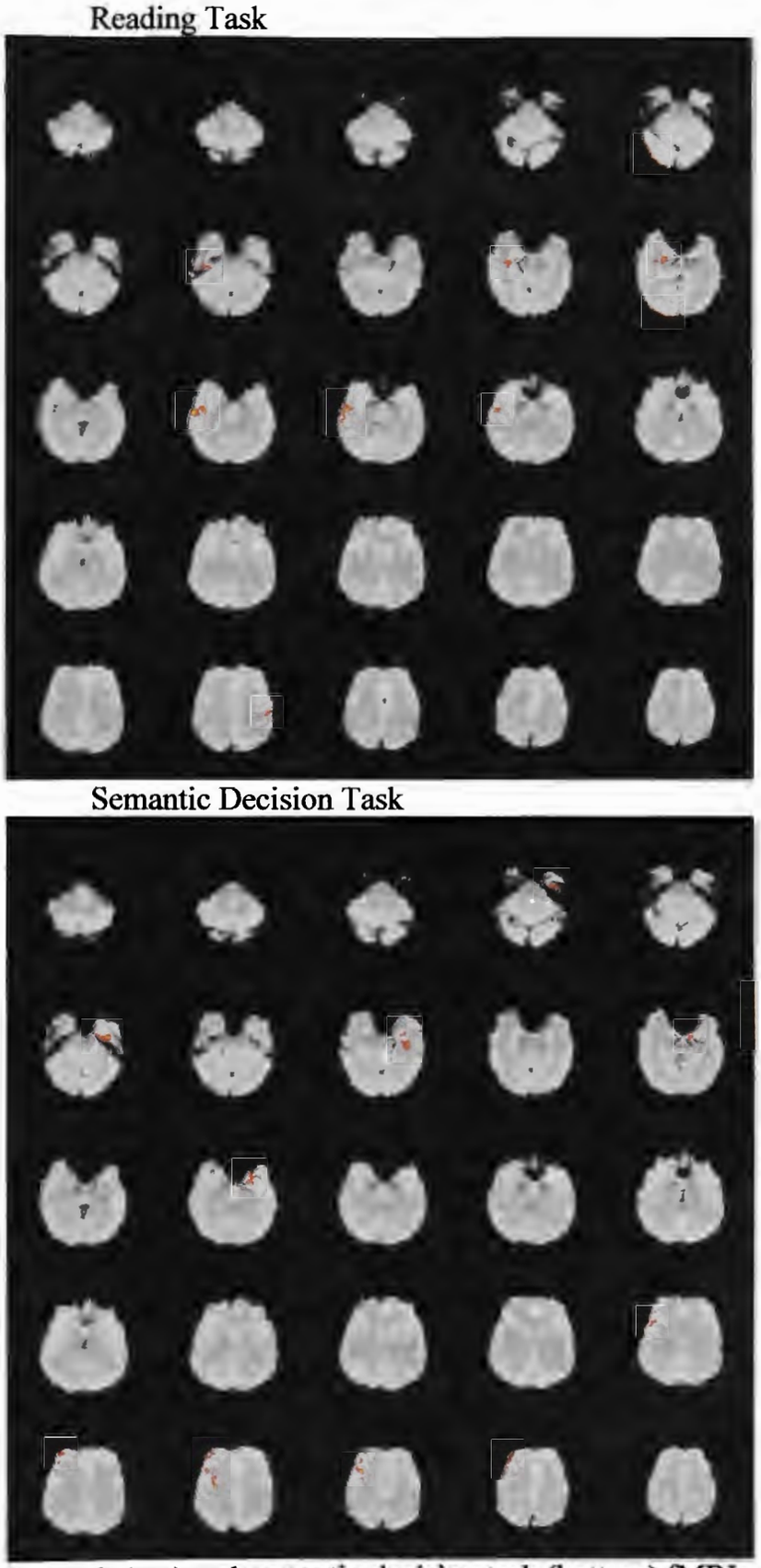


Figure 55. Reading task (top) and semantic-decision task (bottom) fMRI activation on axial slices for patient NC5. Images are shown in radiological convention: the left hemisphere is displayed on the right side of the image.

Table 56

Reading and semantic decision task results for NC6.

Localisation	Cluster Size	Z	x	y	z
Reading task					
L ITG BA20	129	4.24	62.3	-38.7	-24.9
R PostCG BA2	112	4.53	-61.2	-28.2	50
R PostCG BA5	84	3.98	-21.9	-44.3	75
Decision task					
R MFG BA9	5219	7.25	-49.9	15.6	36.6
R CingG BA32	448	6.22	0.974	27.4	37.3
L ITG BA20	234	4.57	45.2	-3.22	-39.2
R Caudate	214	4.49	-13.1	-1.36	13.8
L MTG BA21	181	6.76	63.8	-42.4	-10.7
R IPL BA40	150	4.73	-49.3	-62	47.9
L IPL BA40	111	5.38	37.9	-59.4	14.7
R MFG BA6	101	5.05	-24.1	13	61.4
L MFG BA	85	4.18	2.3	12.3	49.6

Note. Local maxima in MNI coordinates. Only the local maxima with highest Z score in each cluster are provided in the table. Cluster size is in voxels. When the cluster encompasses more than one anatomical location, the localization given corresponds to the local maxima with the highest Z score. L, left; R, right; ITG, inferior temporal gyrus; PostCG, postcentral gyrus; MFG, middle frontal gyrus; CingG, cingulate gyrus; MTG, middle temporal gyrus; IPG, inferior parietal lobule.

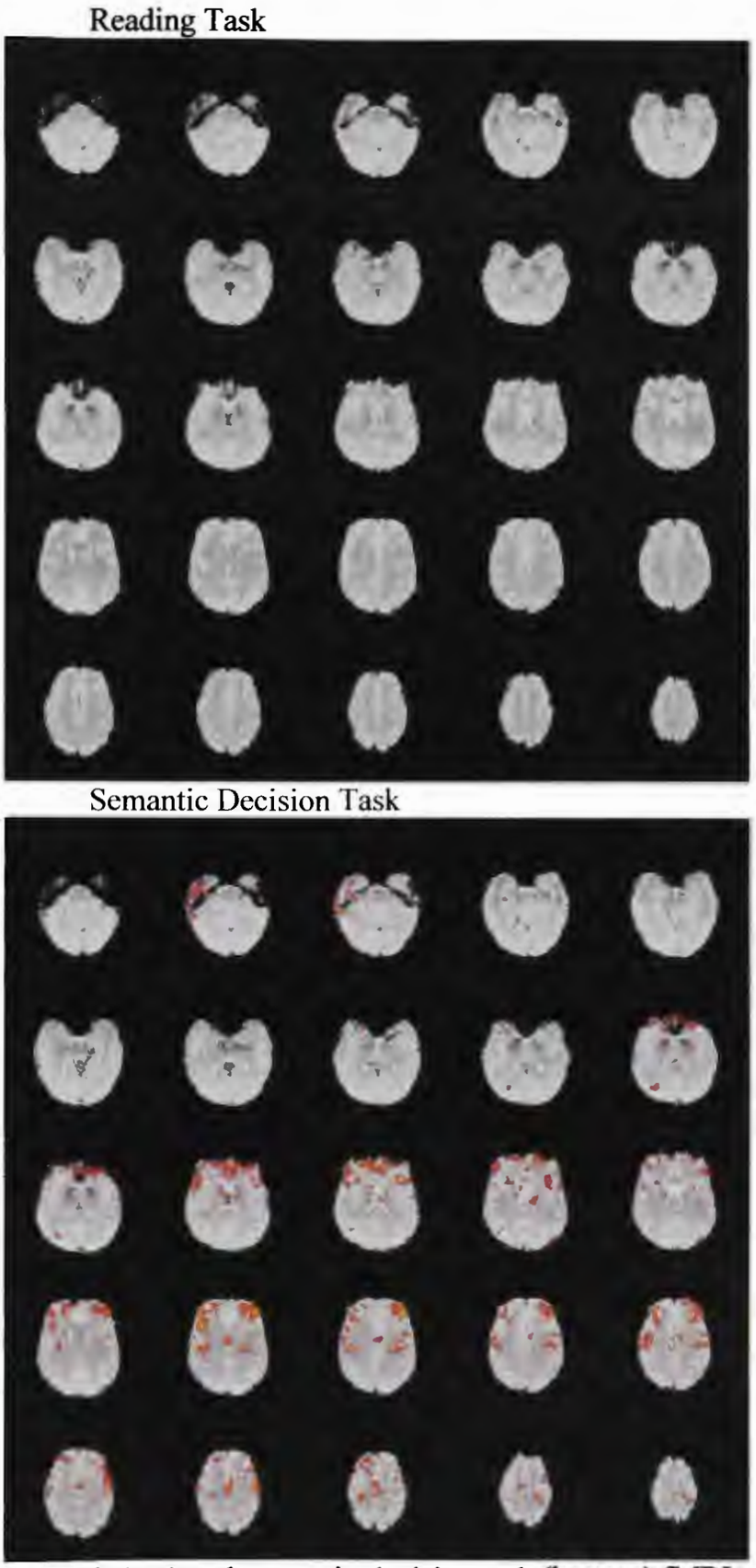


Figure 56. Reading task (top) and semantic-decision task (bottom) fMRI activation on axial slices for patient NC6. Images are shown in radiological convention: the left hemisphere is displayed on the right side of the image.

Table 57

Reading and semantic decision task results for NC7.

Localisation	Cluster Size	Z	x	y	z
Reading task					
L IFG BA47	3121	8.18	55.6	40.2	-9.16
L STG BA38	1590	6.41	52.9	22.2	-29.8
L IFG BA46	321	6.3	54.4	42.7	9.87
L MTG BA21	240	7.05	62.3	-37.6	0.425
L MFG BA10	150	4.66	13.3	59.2	17.5
R STG BA39	131	4.6	-54.9	-49.7	13.2
R CingG BA24	120	4.18	-7.94	-18.5	40.2
LParaCenLobBA5	98	4.36	5.84	-42.6	65.6
R SFG BA11	94	4.69	-33.2	53.5	-13.9
L IParLobBA40	94	5.58	51.1	-35.1	23.8
L CingG BA24	89	4.5	6.12	10.5	34.9
L PreCG BA6	83	4.08	33	-16.4	68.1
Decision task					
L MFG BA9	1643	6.2	46.9	33.9	32.4
L MTG BA38	387	4.62	16.2	-6.45	-44.4
R ParahipGBAS35	150	4.6	-21.5	-13.6	-27.7

Note. Local maxima in MNI coordinates. Only the local maxima with highest Z score in each cluster are provided in the table. Cluster size is in voxels. When the cluster encompasses more than one anatomical location, the localization given corresponds to the local maxima with the highest Z score. L, left; R, right; IFG, inferior frontal gyrus; STG, superior temporal gyrus; MTG, middle temporal gyrus; CingG, cingulate gyrus; ParaCenLob, paracentral lobule; SFG, superior frontal gyrus; IParLob, inferior parietal lobule; PreCG, precentral gyrus; MFG, middle frontal gyrus; ParahipG, parahippocampal gyrus.

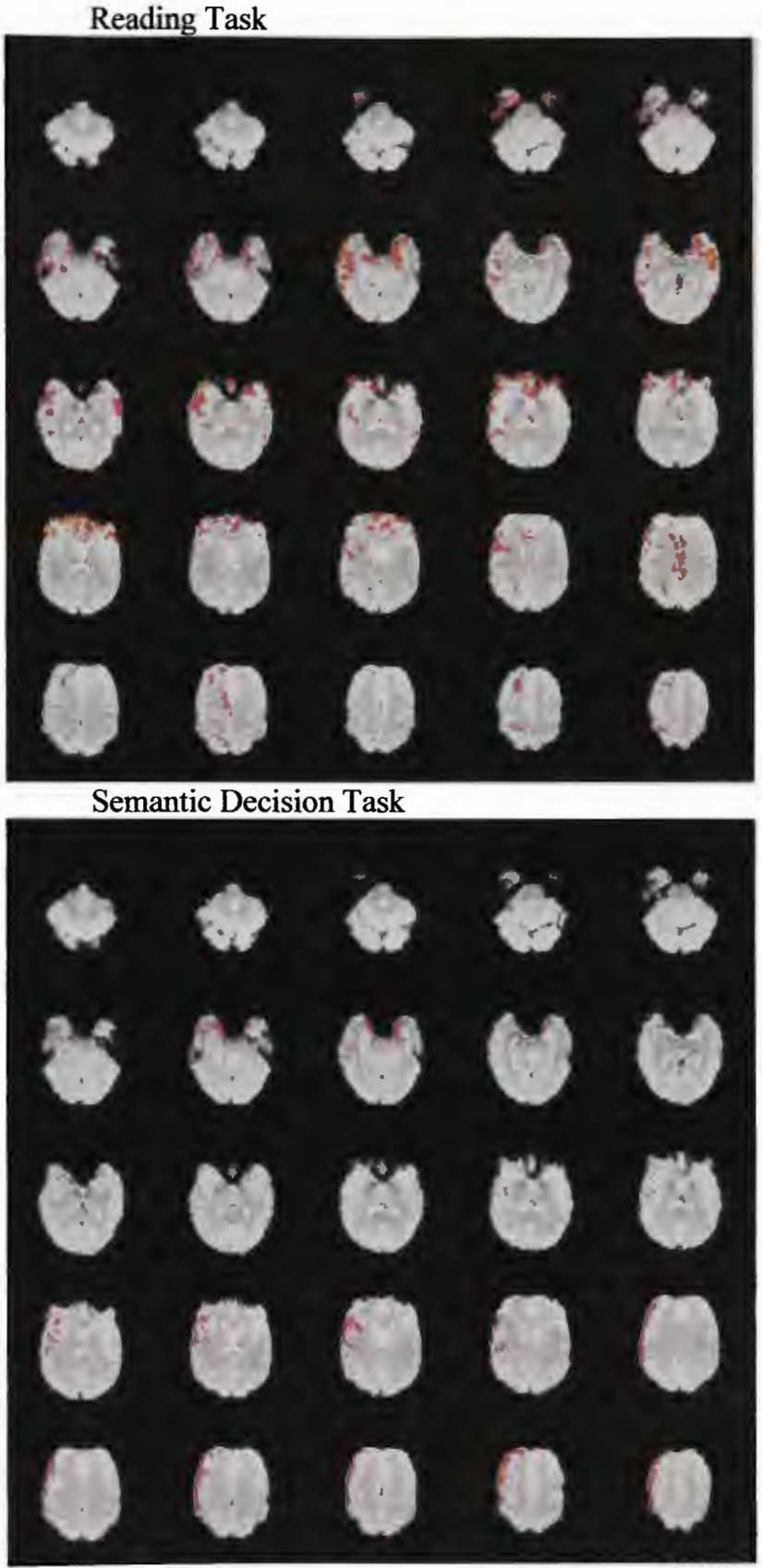


Figure 57. Reading task (top) and semantic-decision task (bottom) fMRI activation on axial slices for patient NC7. Images are shown in radiological convention: the left hemisphere is displayed on the right side of the image.

Table 58

Reading and semantic decision task results for NC8.

Localisation	Cluster Size	Z	x	y	z
Reading task					
L MFG BA11	796	5.85	6.47	36.3	-17.1
L MTG BA21	670	6.81	51	-43.8	8.38
R STG BA22	256	4.48	-47.4	-11	-8.53
R FusiforG BA20	176	4.69	-43.2	-20.8	-28.5
L MTG BA39	139	5.1	10.3	-71.5	21.7
L PreCG BA6	116	5.14	42	-1.42	37.7
L STG BA38	90	6.3	41.9	11.9	-41.5
L IFG BA47	82	4.5	59.9	39.4	-5.83
Decision task					
R IFG BA47	797	4.82	-52.2	17.5	-11.9
L IFG BA46	481	4.98	51.6	41.3	8.04
L MedialGlobPal	198	3.85	8.34	.0.755	-8.93
L MFG BA11	168	5.56	29.9	38.6	-12.3
L IPL BA40	154	5.17	36.9	-47.5	46.1
R CingG BA32	152	4.75	-9.06	22.6	39.6
R IFG BA46	147	4.35	-48.7	36.3	12.9
R MedialGlobPal	110	4.27	-12.1	-1	-8.53
L STG BA22	102	4.18	68.5	-21.7	3.25

Note. Local maxima in MNI coordinates. Only the local maxima with highest Z score in each cluster are provided in the table. Cluster size is in voxels. When the cluster encompasses more than one anatomical location, the localization given corresponds to the local maxima with the highest Z score. L, left; R, right; MFG, middle frontal gyrus; MTG, middle temporal gyrus; STG, superior temporal gyrus; FusiforG, fusiform gyrus; PreCG, precentral gyrus; IFG, inferior frontal gyrus; MedGlobPal, medial globus pallidus; IPL, inferior parietal lobule; CingG, cingulate gyrus.

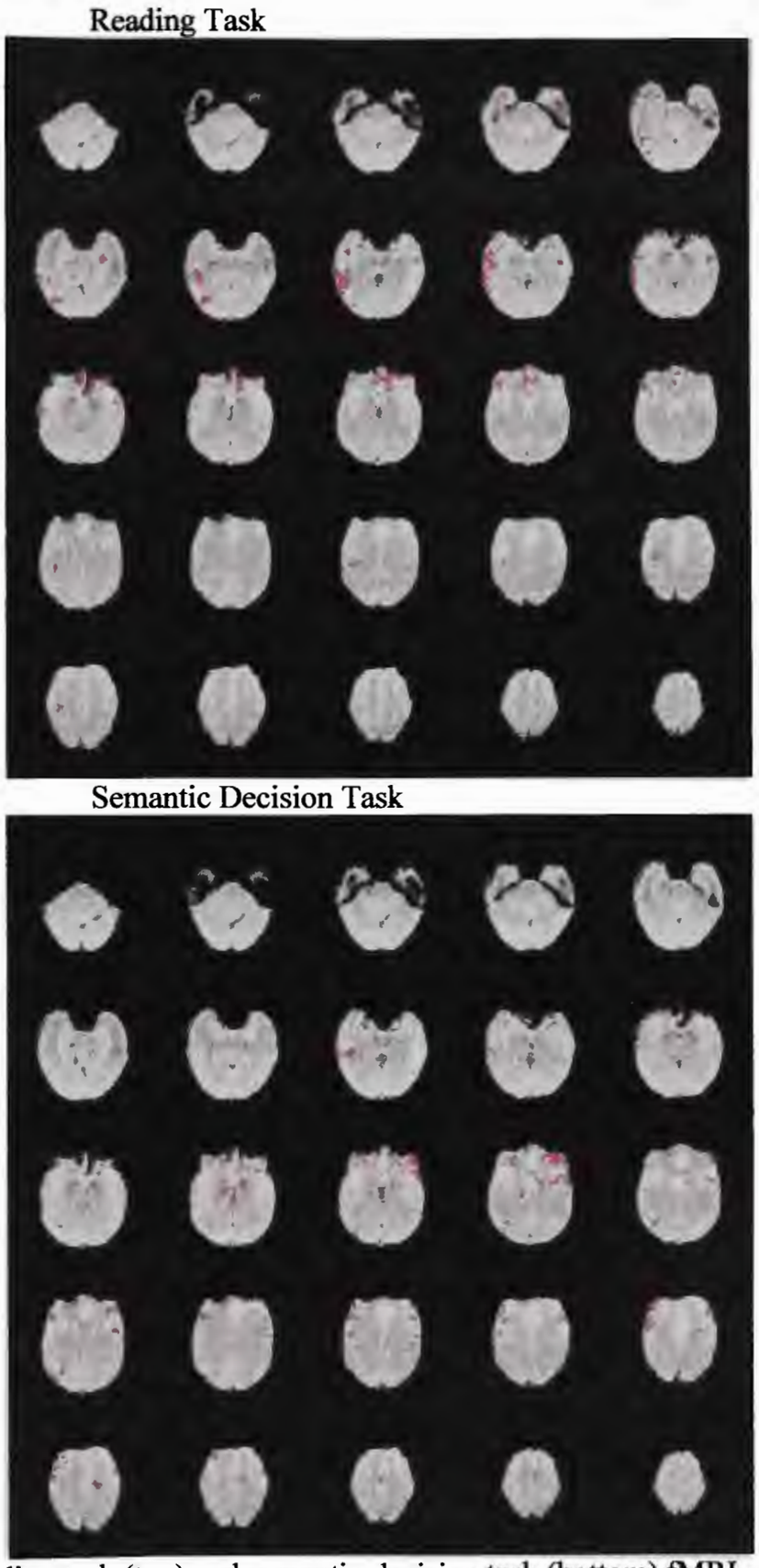


Figure 58. Reading task (top) and semantic-decision task (bottom) fMRI activation on axial slices for patient NC8. Images are shown in radiological convention: the left hemisphere is displayed on the right side of the image.

Table 59

Reading and semantic decision task results for NC9.

Localisation	Cluster Size	Z	x	y	z
Reading task					
L IFG BA47	497	5.96	45.3	38.2	-4.86
L CingG BA24	144	5.19	3.98	-0.309	50.8
L PreCG BA6	139	7.09	53.5	-4.42	38.4
L MTG BA22	127	4.75	67.1	-40.4	3.02
R PreCG BA6	125	6.26	-59.3	-3.5	43.5
R MFG BA9	103	4.14	-32.7	16	25.3
L MTG BA20	90	4.4	50.7	9.04	-54.6
R IFG BA47	89	3.96	-39.6	31.9	-0.0808
R STG BA22	79	4.5	-54.5	12.4	-6.7
Decision task					
R IFG BA10	228	6.15	45.4	47.8	-1.37
L MedFG BA10	103	4.34	10.2	60	0.567

Note. Local maxima in MNI coordinates. Only the local maxima with highest Z score in each cluster are provided in the table. Cluster size is in voxels. When the cluster encompasses more than one anatomical location, the localization given corresponds to the local maxima with the highest Z score. L, left; R, right; IFG, inferior frontal gyrus; CingG, cingulate gyrus; PreCG, precentral gyrus; MFG, middle frontal gyrus; MTG, middle temporal gyrus; STG, superior temporal gyrus; MedFG, medial frontal gyrus.

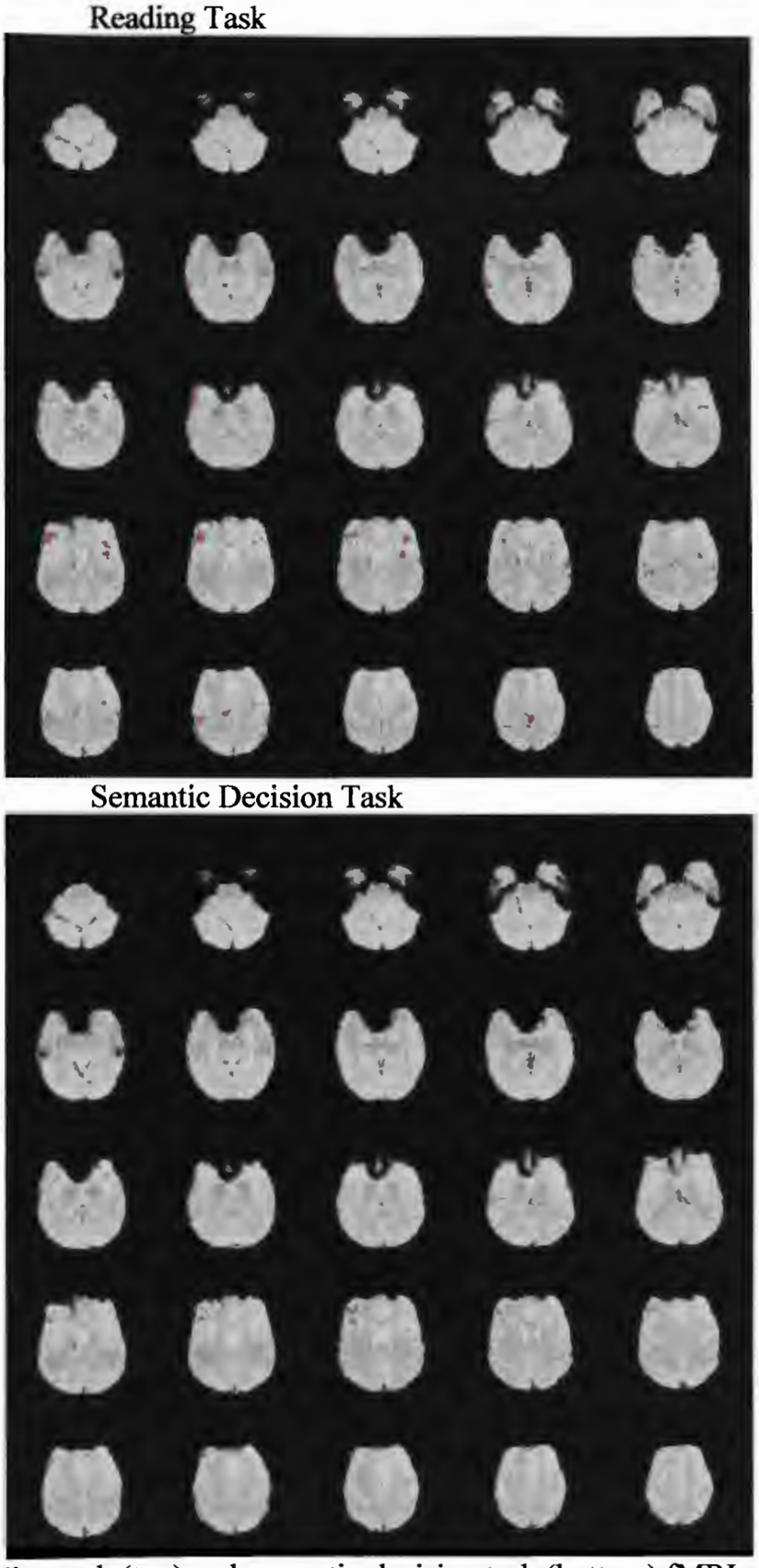


Figure 59. Reading task (top) and semantic-decision task (bottom) fMRI activation on axial slices for patient NC9. Images are shown in radiological convention: the left hemisphere is displayed on the right side of the image.

Table 60

Reading and semantic decision task results for NC10.

Localisation	Cluster Size	Z	x	y	z
Reading task					
R FL BA11	787	6.05	-12.6	51.3	-23
L MTG BA20	500	6.04	60.5	18.8	-42
L IFG BA47	494	5.74	39.4	28.7	-24.8
R MTG BA38	330	5.98	-43.4	14.8	-55.6
R PostCG BA3	299	4.83	-13.5	-37.8	81.5
L STG BA22	228	5.86	64.6	-24.4	2.07
L Caudate	220	4.66	15.3	26.7	15.1
R MFG BA10	195	5.27	-18	52.6	15.8
L MFG BA9	163	4.91	26.2	36.6	19.1
R FusiforG BA19	143	4.12	-30.4	-62.2	-18.4
L MFG BA9	138	5.44	38.3	21.7	29.8
L IPL BA40	130	7.58	52.1	-37	24.8
L PrecCG BA6	124	6.74	52.8	-6.68	39.6
R STG BA38	104	5.51	-47.9	-3.8	-13.4
R MFG BA10	103	4.62	-3.64	67.5	-3.28
L Putamen	98	3.52	23.8	2.46	1.74
L MTG BA20	97	4.63	44.9	-9.85	-23.8
Decision task					
L SFG BA10	177	4.52	31.1	51	19.8
LParietalLobeBA7	141	4.71	22.9	-53.3	59
R Caudate	127	4.78	-10.4	8.44	25.6
R Putamen	118	4.04	-26.7	-10.2	6.93
L PreCG BA4	115	3.93	19.8	-26.2	60.8
R Insula BA 13	93	4.3	-23	31.3	9.51
RParietalLobeBA40	92	3.59	-60.9	-45	33.1
R PreCG BA4	89	5.21	-27.4	-26.6	68
L IFG BA46	82	4.76	56.5	30.4	10.2

Note. Local maxima in MNI coordinates. Only the local maxima with highest Z score in each cluster are provided in the table. Cluster size is in voxels. When the cluster encompasses more than one anatomical location, the localization given corresponds to the local maxima with the highest Z score. L, left; R, right; MTG, middle temporal gyrus; IFG, inferior frontal gyrus; PostCG, postcentral gyrus; STG, superior temporal gyrus; MFG, middle frontal gyrus; FusiforG, fusiform gyrus; IPL, inferior parietal lobule; PreCG, precentral gyrus.

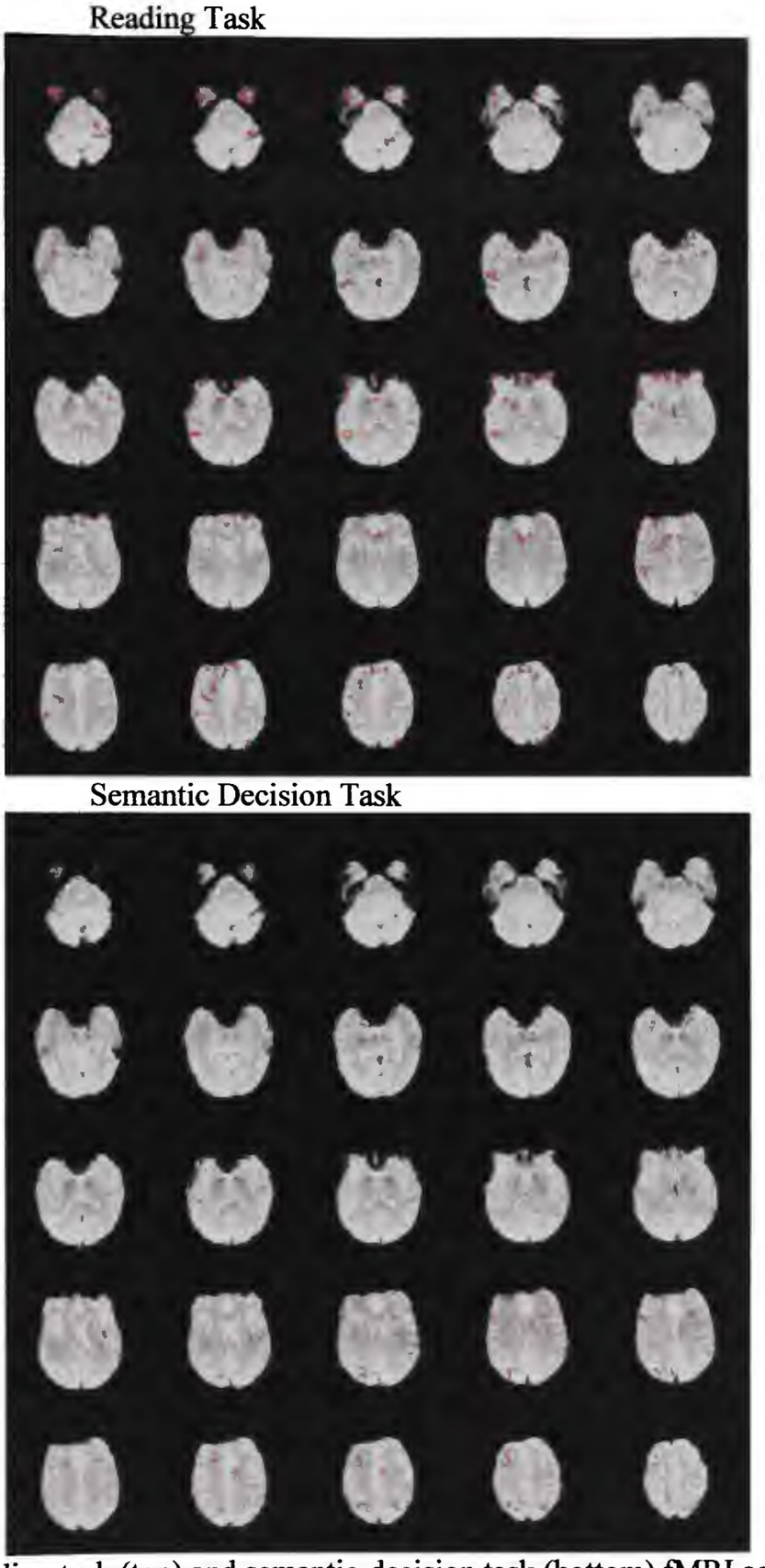


Figure 60. Reading task (top) and semantic-decision task (bottom) fMRI activation on axial slices for patient NC10. Images are shown in radiological convention: the left hemisphere is displayed on the right side of the image.

Table 61

Reading and semantic decision task results for NC11.

Localisation	Cluster Size	Z	x	y	z
Reading task					
L IFG BA 9	140	4.88	41.6	9.55	27.4
Decision task					
R SFG BA11	3231	7.01	-24.3	45.7	-15.2
R IPL BA40	414	5.17	-52.1	-40.4	52.3
R IFG BA47	376	6.18	-39.7	27.3	-9.24
R MFG BA6	193	4.65	4.7	-16.8	79
R PreCG BA6	189	4.88	-31.3	-23.1	72.0
L MTG BA21	131	5.69	73.4	-43.7	-8.72
R MTG BA21	103	5.93	-60.9	-26.2	-16.9
L MFG BA8	94	4.36	39.4	19.9	47
R IFG BA9	81	5.64	-49.6	12	30.2

Note. Local maxima in MNI coordinates. Only the local maxima with highest Z score in each cluster are provided in the table. Cluster size is in voxels. When the cluster encompasses more than one anatomical location, the localization given corresponds to the local maxima with the highest Z score. L, left; R, right; MTG, middle temporal gyrus; IFG, inferior frontal gyrus; STG, superior temporal gyrus; IPL, inferior parietal lobule; MFG, middle frontal gyrus; PreCG, precentral gyrus.

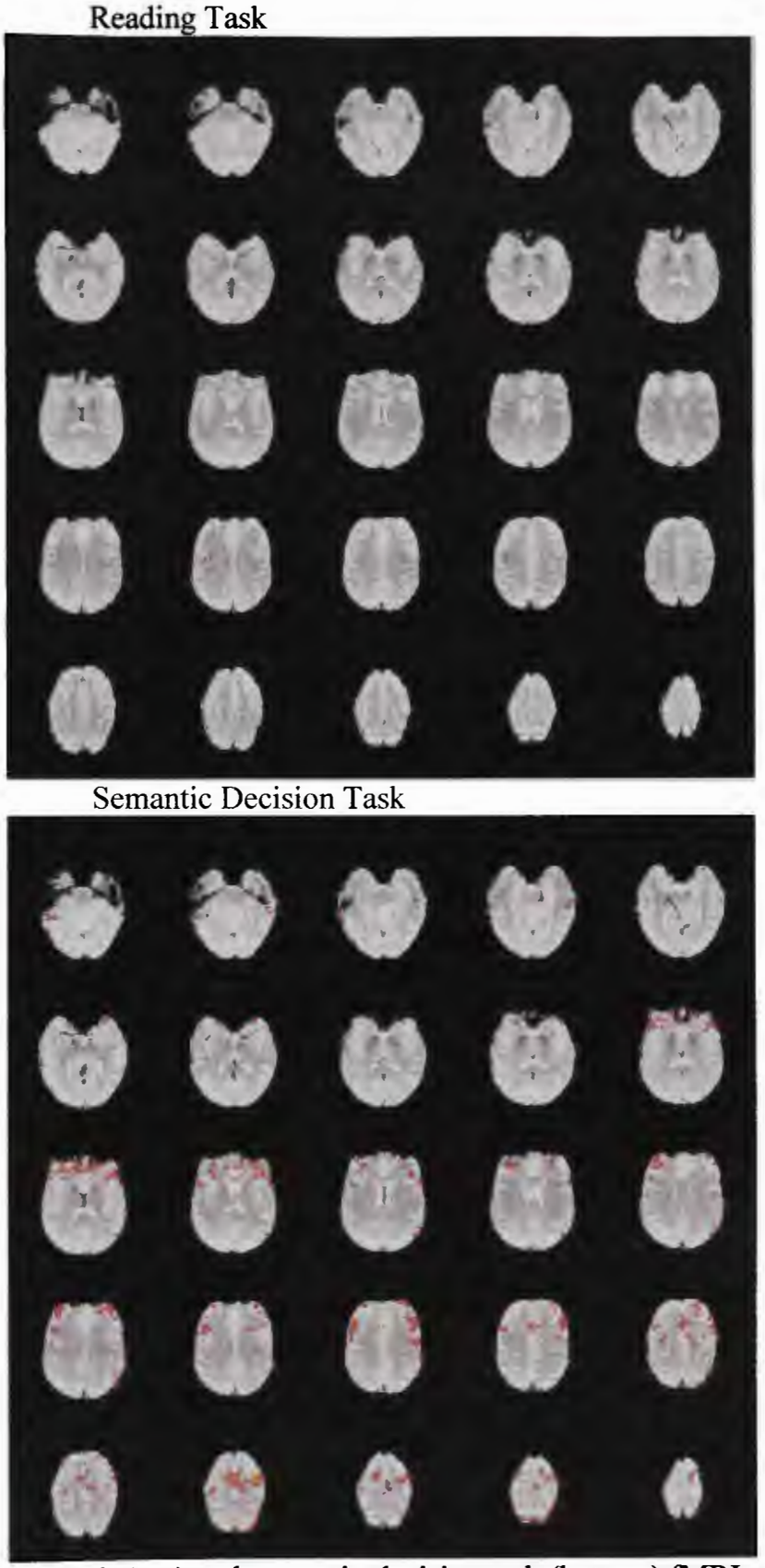


Figure 61. Reading task (top) and semantic-decision task (bottom) fMRI activation on axial slices for patient NC11. Images are shown in radiological convention: the left hemisphere is displayed on the right side of the image.

APPENDIX K: Additional Tables and Figures for New Epilepsy Patients

Table 62

Language task results for NP1.

Localisation	Cluster Size	Z	x	y	z
Reading Task					
L MTG BA22	984	8.68	-58.3	-50.9	1.44
L PreCG BA6	302	7.42	-48.7	-3.01	5.8
L STG BA38	272	6.23	-52.7	16.9	-5.74
L IFG BA9	226	6.1	-61.5	15.4	30.3
L PostCG BA3	130	4.14	-43.4	-22.2	66.6
R IFG BA47	119	3.92	62.1	35.8	-4.42
L Fusiform BA37	94	3.68	-37.8	-43.7	-27.5
L SFG BA9	85	5.23	-13.1	54.2	24.7
R STG BA41	74	4.05	50.4	-33.5	8.51
Semantic Decision					
R PostCG BA5	4140	6.69	26.8	-48.1	72.4
L ParahipG BA36	1173	5.9	-35.4	-22.1	-29.5
R Insula BA13	743	5.48	49.2	10.1	4.25
L IFG BA47	581	6.09	-46.2	39.4	-23.9
R Caudate	544	6.01	5.28	-1.11	20.1
R STG BA38	311	6.04	34.4	18.7	-31.2
L MFG BA9	261	6.54	-40.3	7.65	39.8
R SFG BA8	203	4.83	6.81	17.3	55.3
L Precuneus BA7	202	5.22	-28.4	-74.3	51
R PostCG BA 43	120	4.16	52.5	14.4	13.2
L IFG BA46	118	6.57	-49.2	31.3	16.1
R MedTG BA20	118	4.9	43.4	-16.6	-21.2
L STG BA38	106	6.22	-46.8	7.29	-20.9
L IPL BA40	82	4.9	-39.5	-45.9	44.8
R STG BA13	79	5.18	41.7	-49.6	22.8

Note. Local maxima in MNI coordinates. Only the local maxima with highest Z score in each cluster are provided in the table. Cluster size is in voxels. When the cluster encompasses more than one anatomical location, the localization given corresponds to the local maxima with the highest Z score. L, left; R, right; MTG, middle temporal gyrus; PreCG, precentral gyrus; STG, superior temporal gyrus; IFG, inferior frontal gyrus; PostCG, postcentral gyrus; SFG, superior frontal gyrus; ParahipG, parahippocampal gyrus; MFG, middle frontal gyrus; MedTg, medial temporal gyrus; IPL, inferior parietal lobule.

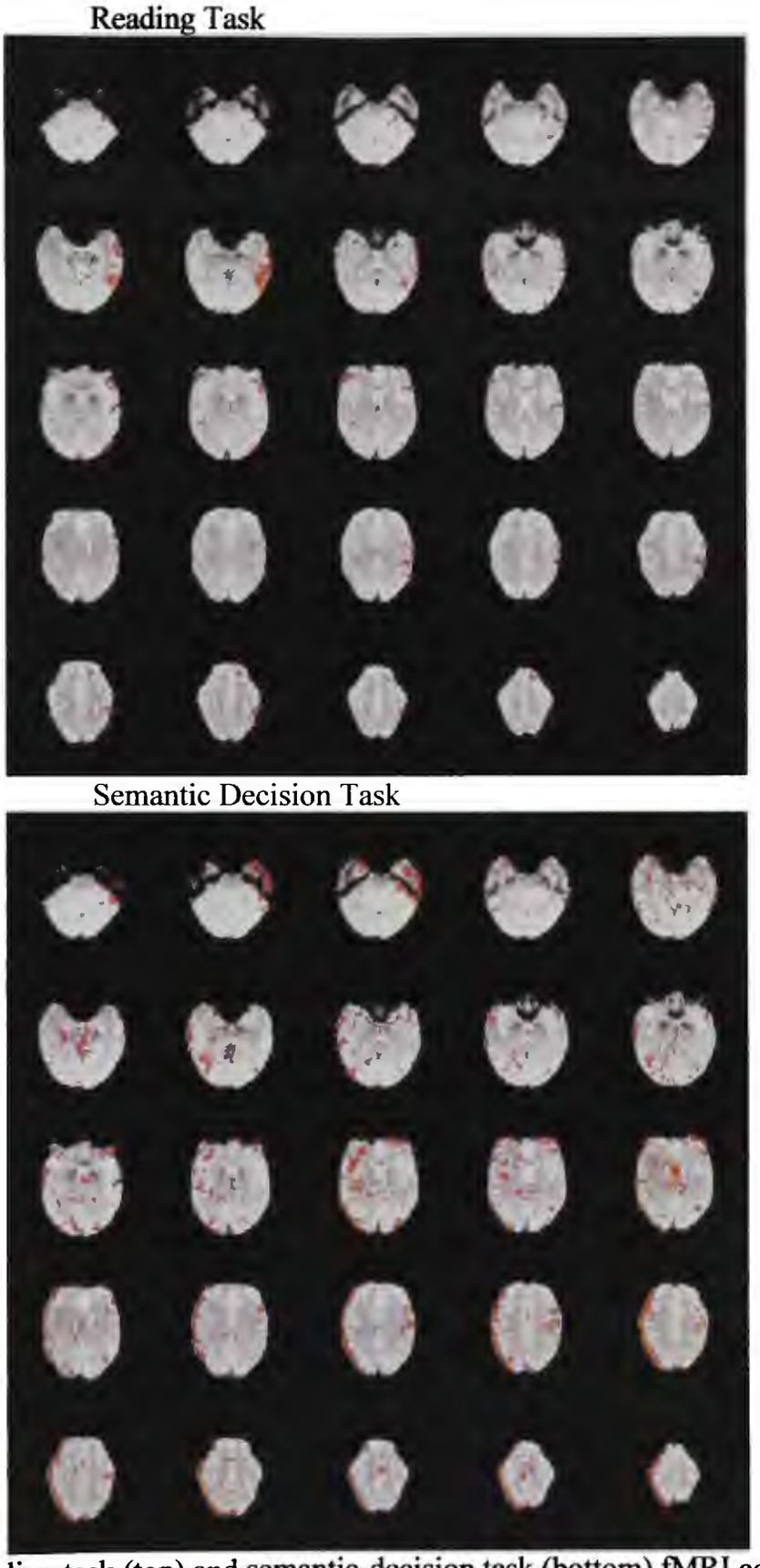


Figure 62. Reading task (top) and semantic-decision task (bottom) fMRI activation on axial slices for patient NP1. Images are shown in radiological convention: the left hemisphere is displayed on the right side of the image.

Table 63

Language task results for NP2.

Localisation	Cluster Size	Z	x	y	z
Reading Task					
L IFG BA47	650	5.34	-47.1	20.3	-11.3
R PreCG BA6	446	5.33	59.6	-9.01	43.7
L PreCG BA4	406	6.99	-57.5	-4.92	25
L MTG BA21	377	4.8	-64.1	-55.7	3.53
R PreCG BA6	235	6.42	56.3	-2.67	19.6
L Cerebellum	134	4.57	-1.84	-41	-25.5
L Cerebellum	113	4	-22.2	-37.4	-28
R Caudate	111	4.12	20.2	-32.4	18.9
R PreCG BA6	103	5.41	34.7	-23.2	67.8
R IPL BA40	97	5.3	49	-57.2	50.3
L MTG BA21	94	4.05	-63	-23.8	-17.4
R Precuneus BA31	93	4.22	24.7	-76.4	18
Semantic Decision					
R MTG BA39	2499	6.71	56.3	-70.4	26.6
L PreCG BA6	2381	6.92	-63.1	-2.81	21.8
L Brainstem	680	4.97	-4.64	-12.4	-20.8
L SFG BA6	604	6.62	-8.54	-9.98	68.7
L PreCG BA4	412	7.74	-31.2	-26.4	69.6
R ITG BA20	359	6.4	54.5	-32.1	-20.7
R ParaCenLobBA4	341	6.5	9.34	-42.1	71.5
L Uncus BA20	231	5.95	-35.9	-12.1	-36.9
L ParahipG BA37	223	5.47	-42.6	-39.5	-12.7
L PreCG BA6	204	5.69	-45.1	-11.3	38.4
R PostCing BA30	196	5.52	1.22	-62	4.18
L STG BA21	121	4.77	-48.1	-26.3	-1.86
L MFG BA9	114	6.21	-8.35	46.1	29.1
R MFG BA6	108	5.5	38.8	8.47	46.6
L ParahipG BA34	108	4.64	-28.5	5.2	-18.5

Note. Local maxima in MNI coordinates. Only the local maxima with highest Z score in each cluster are provided in the table. Cluster size is in voxels. When the cluster encompasses more than one anatomical location, the localization given corresponds to the local maxima with the highest Z score. L, left; R, right; IFG, inferior frontal gyrus; PreCG, precentral gyrus; MTG, middle temporal gyrus; IPL, inferior parietal lobule; SFG, superior frontal gyrus; ITG, inferior temporal gyrus; ParaCenLob, paracentral lobule; ParahipG, parahippocampal gyrus; PostCG, postcentral gyrus; STG, superior temporal gyrus; MFG, middle frontal gyrus.

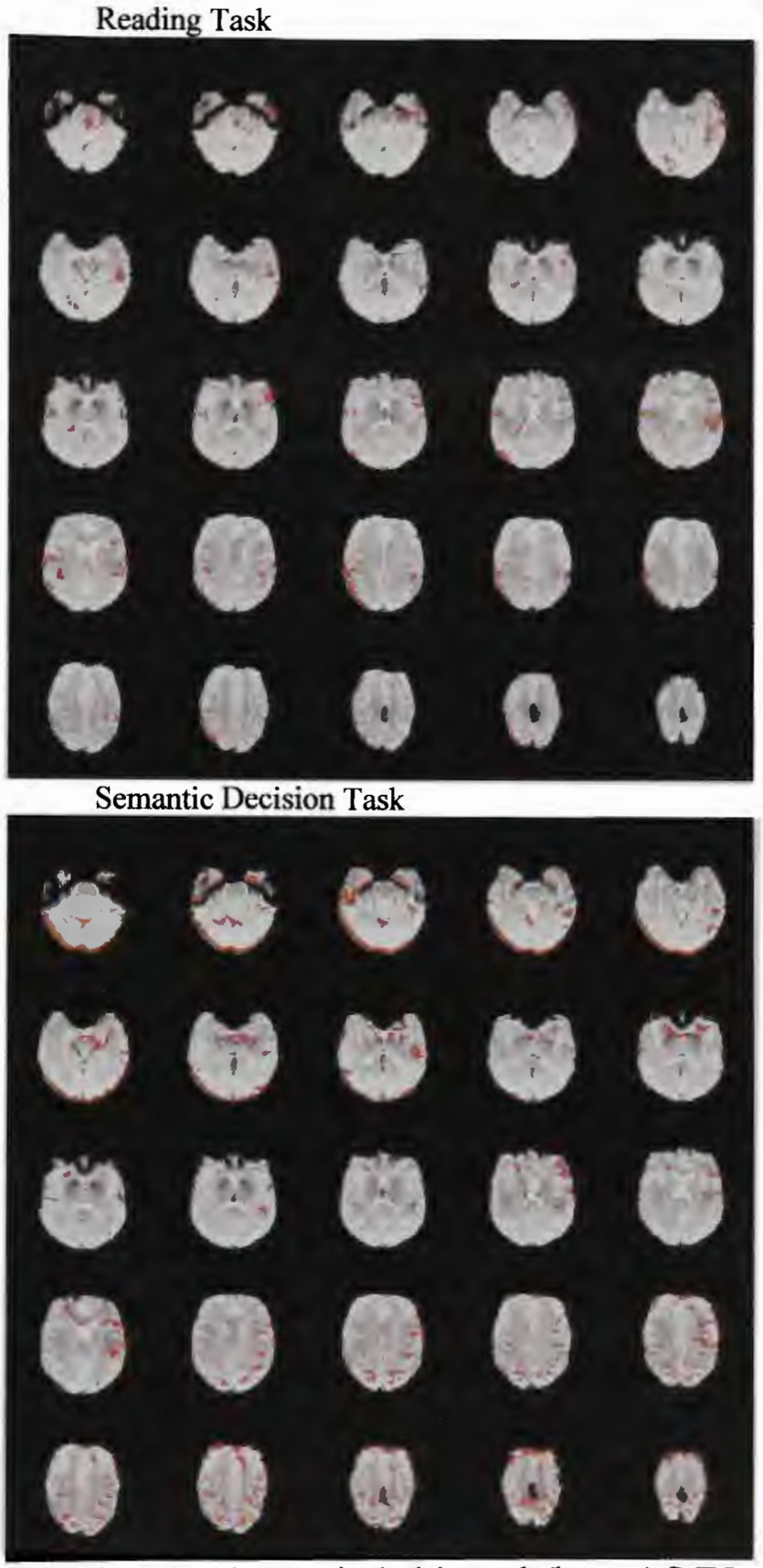


Figure 63. Reading task (top) and semantic-decision task (bottom) fMRI activation on axial slices for patient NP2. Images are shown in radiological convention: the left hemisphere is displayed on the right side of the image.

Table 64

Language task results for NP3.

Localisation	Cluster Size	Z	x	y	z
Reading Task					
	Nil				
Semantic Decision					
L IFG BA47	459	7.27	-34.6	30.3	-21

Note. Local maxima in MNI coordinates. Only the local maxima with highest Z score in each cluster are provided in the table. Cluster size is in voxels. When the cluster encompasses more than one anatomical location, the localization given corresponds to the local maxima with the highest Z score. L, left; IFG, inferior frontal gyrus.

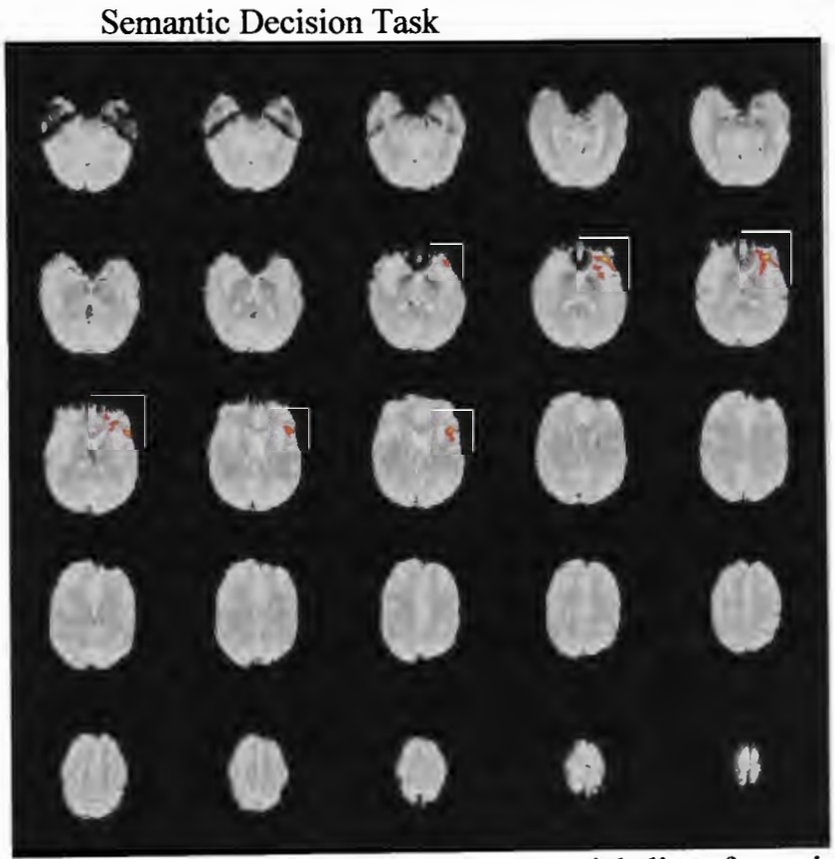


Figure 64. Semantic-decision task fMRI activation on axial slices for patient NP3. Images are shown in radiological convention: the left hemisphere is displayed on the right side of the image.

Table 65

Language task results for NP4.

Localisation	Cluster Size	Z	x	y	z
Reading Task					
L IFG BA47	288	5.86	-45.6	27.6	-10.1
L MTG BA22	232	6.45	-53.5	-35.8	5.48
L PreCG BA6	88	4.95	-52.7	-0.791	37.8
R LentiformN	86	4.16	19.8	9.56	-8.98
R PreCG BA4	83	3.88	21.5	-27	73.8
Semantic Decision					
R PostCG BA5	1061	4.5	8.27	-28.4	75
L MedFG BA25	334	5.81	-9.94	24.8	-18.6
R AntCing BA 24	151	4.12	6.87	32	16.6
R MTG BA38	134	4.71	37.3	12.8	-46
R PreCG BA4	116	4.39	44.8	-15.8	46.9

Note. Local maxima in MNI coordinates. Only the local maxima with highest Z score in each cluster are provided in the table. Cluster size is in voxels. When the cluster encompasses more than one anatomical location, the localization given corresponds to the local maxima with the highest Z score. L, left; R, right; IFG, inferior frontal gyrus; PreCG, precentral gyrus; MTG, middle temporal gyrus; LentiformN, lentiformm nucleus; PostCG, postcentral gyrus; MedFG, medial frontal gyrus; AntCing, anterior cingulate.

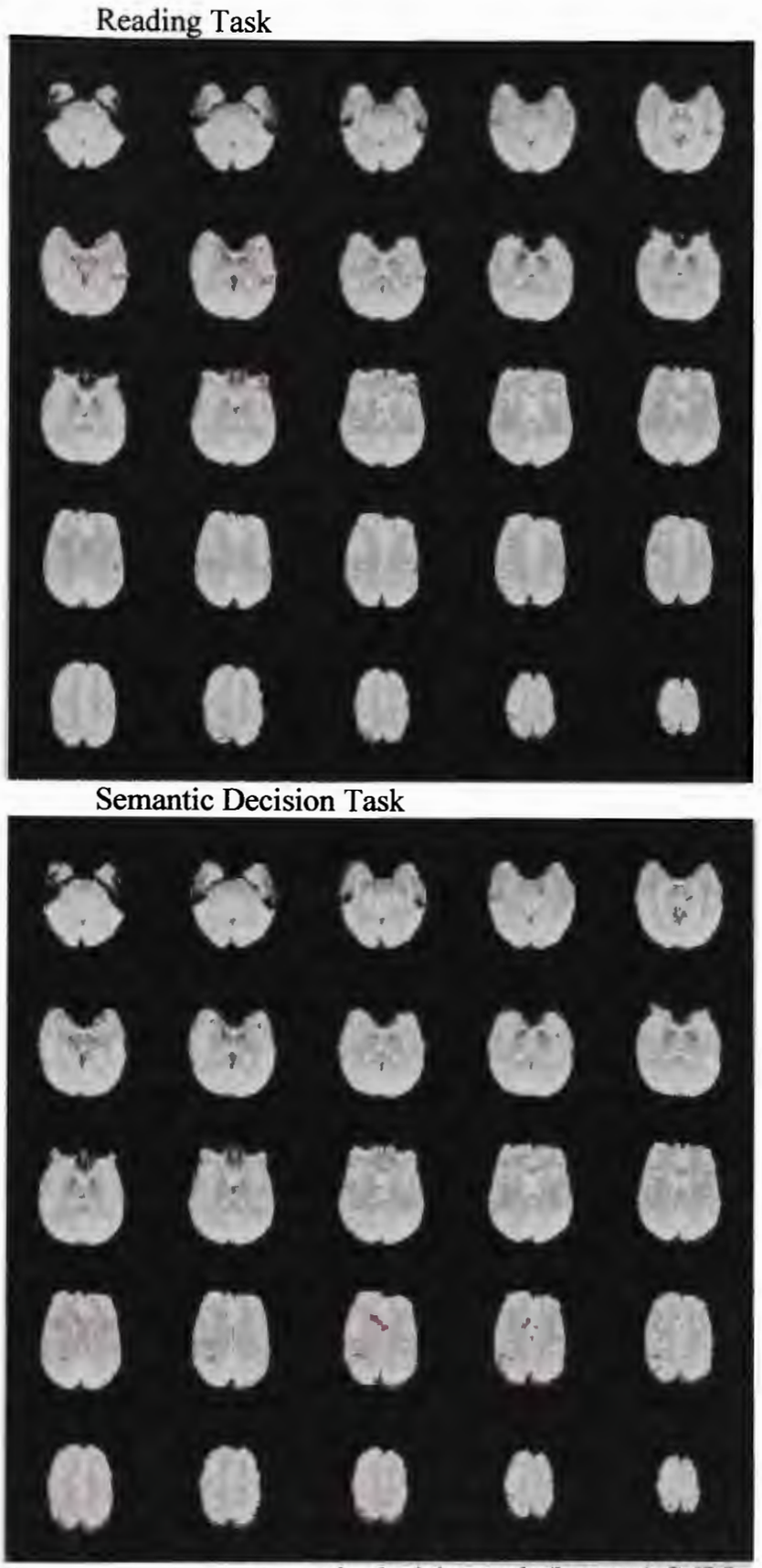


Figure 65. Reading task (top) and semantic-decision task (bottom) fMRI activation on axial slices for patient NP4. Images are shown in radiological convention: the left hemisphere is displayed on the right side of the image.

Table 66

Language task results for NP5.

Localisation	Cluster Size	Z	x	y	z
Reading Task					
L MTG BA21	2167	7.14	-56.6	-1.48	-13.2
R MTG BA21	1398	6.45	62.6	-14.8	-8.93
L MedFG BA6	286	5.55	-3.37	-4.16	68.3
L ParahipG BA19	282	5.24	-26.9	-51	-4.31
L SFG BA10	274	5.49	-20.1	62.7	18
L MFG BA6	206	6.55	-50.7	1.58	48.5
L PreCG BA6	173	4.43	-33.4	-22.9	72.4
R PostCing BA29	164	4.07	11.9	-46.4	9.67
L Cuneus BA7	129	3.63	-2.06	-67.9	29
R MedFG BA11	107	4.17	4.65	61.4	-12.6
L Insula BA13	104	4.58	-39.1	15.1	19.5
L MFG BA8	88	4.49	-22.3	25.3	41.5
Semantic Decision					
L MFG BA11	1474	5.2	-33.9	40.3	-15.1
L PreCG BA4	1265	6.09	-22.5	-25.8	74
L IFG BA47	629	6.2	-41.8	24.7	1
L Fusiform BA37	495	5.3	-28.6	-42	-13.8
L LingualG BA18	423	6.19	-6.51	-56.5	-1.88
L Insula BA13	229	4.68	-34.5	13.6	11.3
R IFG BA13	157	4.85	37	22.8	8.9
L CingG BA31	120	6.7	-.48	-38	40.6
R MFG BA11	100	4.73	31.8	36.4	-13.8
L MedFG BA6	85	4.35	-9.27	3.99	54.4

Note. Local maxima in MNI coordinates. Only the local maxima with highest Z score in each cluster are provided in the table. Cluster size is in voxels. When the cluster encompasses more than one anatomical location, the localization given corresponds to the local maxima with the highest Z score. L, left; R, right; MTG, middle temporal gyrus; MedFG, medial fronal gyrus; ParahipG, parahippocampal gyrus; SFG, superior frontal gyrus; MFG, middle frontal gyrus; PreCG, precentral gyrus; Post Cing, postcingulate gyrus; MFG, middle frontal gyrus; IFG, inferior frontal gyrus; LingualG, lingual gyrus; CingG, cingulate gyrus.

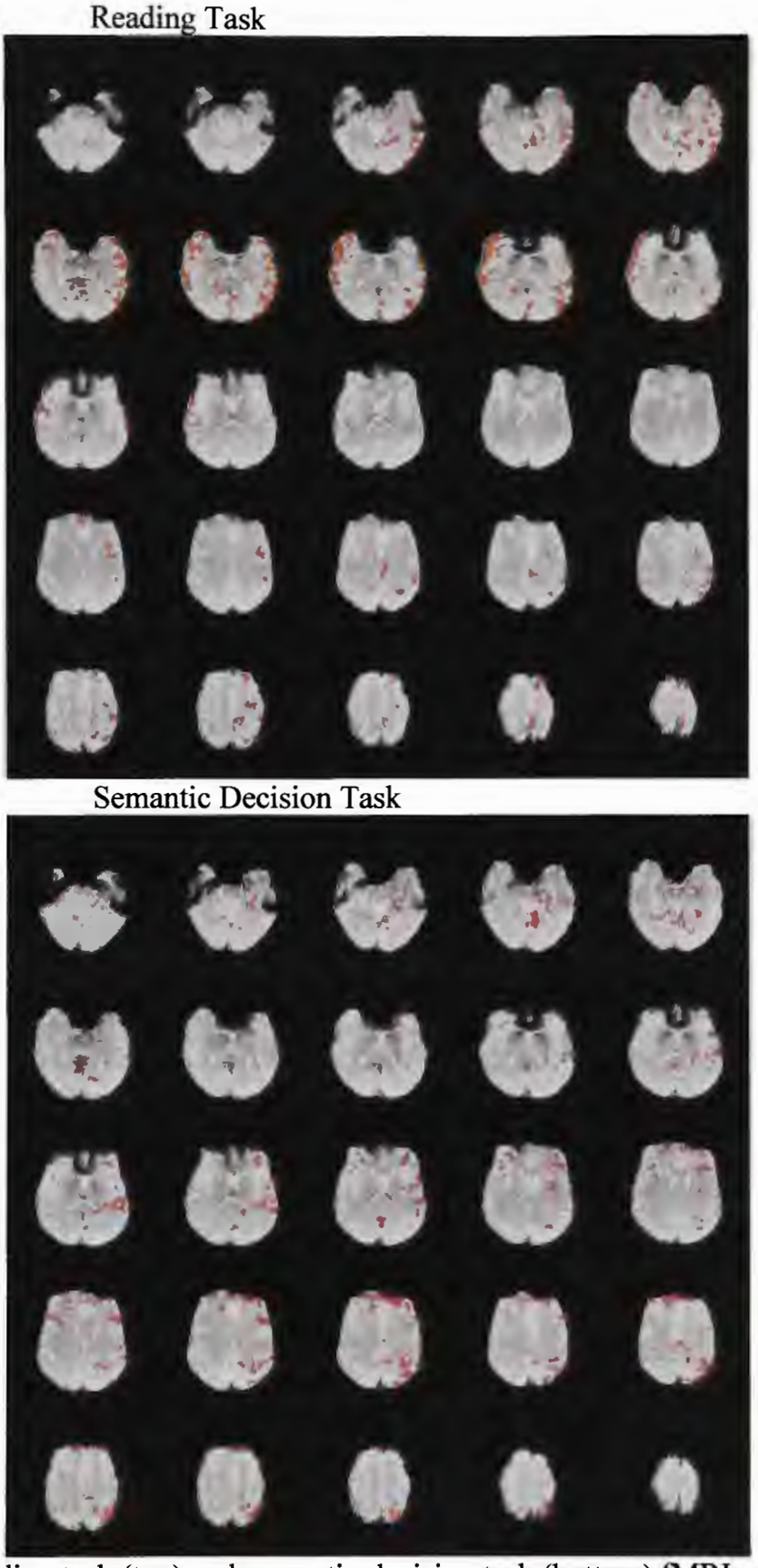


Figure 66. Reading task (top) and semantic-decision task (bottom) fMRI activation on axial slices for patient NP5. Images are shown in radiological convention: the left hemisphere is displayed on the right side of the image.

Table 67

Language task results for NP6.

Localisation	Cluster Size	Z	x	y	z
Reading Task					
R MTG BA21	6122	6.99	65.4	-5.33	-18.2
R PreCG BA6	393	5.95	56.7	2.35	38.3
L ParahipG BA34	316	5.58	-20.4	2.33	-23.1
L MFG BA6	314	6.46	-53.1	1.99	42.6
L Cuneus BA18	300	5.55	-0.641	-85	15.2
R Precuneus BA39	251	5.54	41	-66.9	33.3
R ParaCenLobBA4	209	5.04	6.67	-40.9	75.6
L STG BA38	206	5.12	-42.6	24.6	-25.5
L SFG BA10	199	4.32	-17.8	60.4	-6.23
R ParahipG BA30	178	4.83	31.9	-52	3.25
L Putamen	165	5.55	-23.4	-4.13	5.24
R Thalamus	142	4.54	5.49	-1.38	4.77
R Precuneus BA7	123	4.75	9.42	-81.7	42.1
R PostCing BA30	118	5.26	6.27	-50	19.7
R SFG BA10	116	4.23	25.1	46.7	24.8
L MTG BA21	11	4.35	-55.4	12.4	-36.7
R AngG BA39	97	5.66	49.8	-73.2	28.6
R MedFG BA11	96	5.53	0.556	32.7	-14.6
R Cuneus BA18	84	4.99	25.2	-70	15.6
L SFG BA9	81	3.89	-6.39	-72.4	44.4
Semantic Decision					
	Nil				

Note. Local maxima in MNI coordinates. Only the local maxima with highest Z score in each cluster are provided in the table. Cluster size is in voxels. When the cluster encompasses more than one anatomical location, the localization given corresponds to the local maxima with the highest Z score. L, left; R, right; MTG, middle temporal gyrus; PreCG, precentral gyrus; ParahipG, parahippocampal gyrus; MFG, middle frontal gyrus; ParCenLob, paracentral lobule; SFG, superior frontal gyrus; STG, superior temporal gyrus; PostCing, postcingulate gyrus; AngG, angular gyrus; MedFG, medial fronal gyrus.

Semantic Decision Task

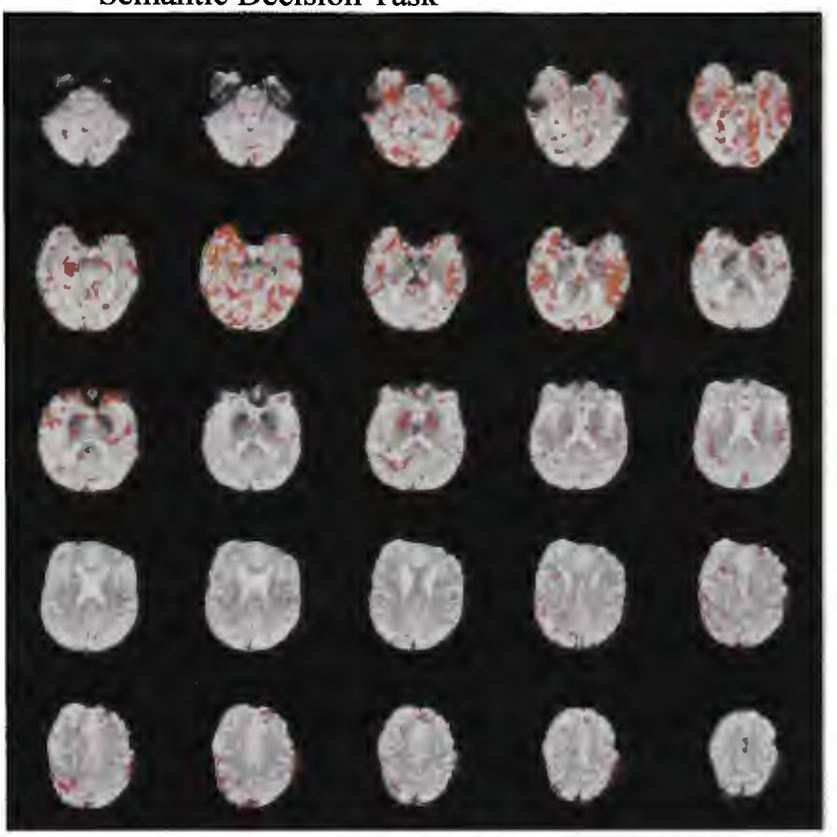


Figure 67. Reading task (top) and semantic-decision task (bottom) fMRI activation on axial slices for patient NP6. Images are shown in radiological convention: the left hemisphere is displayed on the right side of the image.