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The effect of left hemisphere brain tumours and their resection on speech production and visual processing

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Contributions

Patient selection	Alexandra Lloyd-Smith, Cathy Price
fMRI data analysis	Alexandra Lloyd-Smith, Cathy Price
Write-up	Alexandra Lloyd-Smith

The data analyzed and reported were originally collected by Alice Grogan, Goulven Josse, and Laura Mancini under the supervision of Cathy Price.

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Abbreviations

CAT Comprehensive Aphasia Test (Swinburn et al., 2004)

CNS Central Nervous System

CT Computed Tomography

fMRI functional Magnetic Resonance Imaging

LGG Low-grade Glioma

LH Left Hemisphere

LHR Left-handed Response

PET Positron Emission Tomography

RH Right Hemisphere

RHR Right-handed Response

rTMS repetitive Transcranial Magnetic Stimulation

WHO World Health Organization

Abstract

Functional reorganization may explain why, despite a large tumour in eloquent cortex, the patient has no neurological impairment. The aims of the present study were to 1. Investigate the effect of tumour growth on neural circuits for speech production and visual processing and 2. Determine the effect of tumour removal on speech production and visual processing. Three patients with large, left-hemisphere brain tumours had pre-surgery and post-surgery functional neuroimaging (fMRI) and language testing (CAT). In addition, these patients underwent surgery for tumour resection. Pre-operative fMRI demonstrated functional reorganization in the patients. All three patients showed regions of overactivation and underactivation in local and remote regions relative to tumour location. Of particular interest, two patients showed increased activity in the right hemisphere homologue of their left parietal tumour whereas one patient illustrated a decreased activation in the right hemisphere homologue region to her left postcentral tumour. A comparison of pre and post-surgery fMRI results demonstrated that functional reorganization primarily occurs prior to surgery although some changes in activation occur after surgery. This study provides evidence that the right hemisphere homologue region is differentially activated (over and under) across patients. Furthermore, our study suggests that the effect of brain tumour growth is more prominent than tumour resection.

Introduction

Large lesions in the dominant hemisphere are a challenge for the preservation of language function, especially when located within or near eloquent cortex (Duffau, 2005b). Due to the infiltrative nature of gliomas, it is common for some of the tumour to invade eloquent cortex. Despite a large tumour in an eloquent area, it is remarkable that there may be no neurological impairment. This project examines the effect of brain tumour progression and tumour removal on functional reorganization of speech production and visual processing and the ability of patients to perform a task despite their tumour. Three patients with large, left-hemisphere brain tumours were studied using a combination of neuropsychological testing and structural and functional imaging.

1. Background

Static vs Dynamic Nature of the Brain: Evidence for Brain Plasticity

The early view of the brain's structure-function relationship was based on the clinical anatomical method. Brain lesions described post mortem were correlated with cognitive deficits experienced in vivo. This led to the static lesion-related findings such as the involvement of Broca's area in speech production (Broca, 1861) and Wernicke's area in verbal comprehension (Wernicke, 1874). However, there are major limitations to this approach. First, language-related brain regions are involved in highly interconnected functional networks and thus language relies on the interplay of many different brain areas (Mesulam, 1990). Consequently, lesion-symptom relationships are likely to be influenced by a set of distributed regions rather than a single, distinct area. Second, the clinical anatomical approach for language is too static. Both language behavior and brain functions undergo significant changes following lesions. The neural reorganization

following damage is dependent on the nature and extent of the lesion and may be influenced by clinical factors such as surgery or therapy (Demonet et al., 2005).

During the 20th century, the view of static functional organization was dominant (Duffau, 2005b). Anatomical-functional associations as identified in lesion studies formed the basis of this theory and, as a result, the brain was segmented into 'eloquent' and 'silent' areas. This led to the ability to predict whether there would be neurological deficit (damage to 'eloquent' area) or no clinical effect (damage to 'silent' areas) following a brain lesion (Duffau, 2005b). However, functional improvement following damage to 'eloquent' areas has challenged this static view of the brain. The contemporary view of language suggests that language evolves throughout life and the ability exists for functional reorganization following brain injury. It is now established that the adult central nervous system (CNS) is capable of adaptive changes and cortical reorganization that may underlie functional recovery (Shih & Cohen, 2004). One leading hypothesis for functional reorganization is brain plasticity. Brain plasticity is "the process by which synaptic systems change via molecular and cellular transformations to increase communication efficiency in neural networks" (Demonet et al., 2005, p. 78). This plasticity plays a critical role during recovery from lesions in the CNS (Demonet et al., 2005; Duffau, 2005b).

The prediction of function through anatomical criteria alone is inaccurate due to the variability of cortical organization (Bookenheimer, 2007), distortion of cerebral topography as a result of the mass effect of the tumour, and functional reorganization due to plasticity (Ojemann et al., 1996; Bookenheimer, 2007). The brain is a complex

network of dynamic systems with numerous functional connections between local and remote brain areas (Varela et al., 2001).

Slow, progressive nature of brain tumour growth

Low-grade gliomas (LGG) are World Health Organization Grade II tumours and are slow-growing primary tumours of the CNS (Kleihues et al., 2002; Desmurget et al., 2007). LGG's are frequently situated in functional cortico-subcortical brain structures (Duffau et al., 2003). Preventative resection of LGG has become an increased therapeutic option following the discovery that removal of 'eloquent' regions did not lead to permanent deficits (Duffau, 2005b; Desmurget et al., 2007). These regions include Broca's area, the sensorimotor cortex, the supplementary motor area, the left angular gyrus, the left posterior parietal cortex and the left and right temporal lobes (as discussed in Desmurget et al., 2007).

In brain tumour patients, symptoms develop slowly and there is more potential for functional reorganization than for acute lesions (Petrovich et al., 2004; Desmurget et al., 2007). In acute lesions, post-lesional recovery primarily involves ipsilateral structures, especially those adjacent to the lesion. In progressive lesions, however, brain plasticity relies on both adjacent and distant areas within the same hemisphere and opposite hemisphere (Desmurget et al., 2007).

Brain re-organization: Effect of tumour growth (pre-operative plasticity) versus effect of tumour resection (post-operative plasticity)

Brain reorganization provides an explanation as to why tumours within 'eloquent' areas do not always lead to neurological deficits (Duffau, 2005b). There is evidence that the

brain compensates for the progressive, infiltrative invasion by slow-growing LGG's into eloquent areas (Duffau, 2005a; Desmurget et al., 2007). Furthermore, progression of LGG's may induce functional reorganization within the brain (Duffau, 2005b).The concept of brain plasticity supports the presence of functional reorganization and results in the absence of a deficit (Duffau, 2005b). This raises the question of the timing of functional reorganization. More specifically, does the reorganization occur due to the infiltrative, progressive nature of the tumour itself or as a consequence of surgery?

Pre-operative plasticity

Despite the large size of the tumour and the invasion of eloquent cortex, many LGG patients have no neurological deficit before surgery. One explanation is that the slowly progressing tumour has induced functional reorganization of brain networks (Duffau, 2005b).

In large lesions, other regions belonging to the same functional network may be recruited (Duffau, 2006). Four possible mechanisms of pre-operative functional reorganization may explain the absence of deficit in LGG patients (Duffau, 2005b). First, there may still be functional tissue within the tumour (Schiffbauer et al., 2001). In particular, there may be remaining functional astrocytes, intact neuron-glial interactions and eloquent neural networks within the tumour (Magistretti, 2000). These patients are especially challenging to the surgeon and post-operative deficit is likely. Second, reorganization of eloquent areas surrounding the tumour may occur (Wunderlich et al., 1998). In this case, post-operative deficit is likely but brief since recovery may occur within a few months (Duffau, 2005b). Third, compensation may exist by recruiting remote areas in the

ipsilateral hemisphere (Thiel et al., 2001). Fourth, due to the suppression of transcallosal inhibition, homologue regions of the contralateral hemisphere may be recruited (Fandino et al., 1999; Holodny et al., 2002; Meyer et al., 2003). In the third and fourth cases, post-operative deficits are likely to be more minor and transient (Duffau, 2005b).

In brief, Duffau (2005b) suggests that there are three levels of plasticity that are hierarchically arranged and successively recruited. First, there is an intrinsic reorganization within the lesion. Second, other remote areas in the functional network in the ipsilateral hemisphere are recruited. Third, homologue areas in the contralateral hemisphere are recruited.

Post-operative plasticity

The reorganization induced by surgical resection has been studied directly with post-operative neuroimaging after complete functional recovery to the pre-operative level. Possible mechanisms of post-operative plasticity include reliance on homologue areas of contralateral hemisphere (Krainik et al., 2004), reinforcement of compensation, and recruitment of remote areas.

Although transient immediate post-operative functional deterioration is common, most patients recover within three months. After this period, 95% of patients have a normal standard neurological examination (Berger & Rostomily, 1997; Fandino et al., 1999; Whittle et al., 2003; Duffau et al., 2005). In some patients, functional improvement over the pre-operative state is seen (Duffau et al., 2005).

Duffau et al (2003) showed that removal of eloquent areas may not induce a definite deficit. This post-surgical functional compensation may be due to brain plasticity similar to stroke and other brain injuries. In this study, the immediate post-operative deficits confirmed that some structures remain functional within the tumour mass or peri-tumoural brain. Immediately following surgery, the peri-tumoural reorganization is insufficient to maintain function. This is frequent if parts of the 're-organized' brain tissue around the tumour have been damaged by the surgical trauma. Subsequent reinforcement of this mechanism of reorganization and/or the recruitment of remote areas may explain the recovery (Rauchecker, 1997). The delay in recovery (1-3 months) may reflect the neurosynaptogenesis, a combination of sprouting axons and dendrites to local and remote regions, and may explain the main plasticity mechanism, as previously described in vitro and in animals (Bach-Y-Rita, 1990; Jacobs & Donoghue, 1991).

Compensatory Mechanisms: Right hemisphere versus perilesional compensation

Compensatory systems are likely to play a role in language reorganization following tumour invasion. There is a debate in the literature whether reorganization of language involves regions adjacent to lesion versus those involving homologue regions of the contralateral hemisphere and which mechanism is responsible for language recovery.

Evidence shows that although in children there is a shift of language to the right hemisphere following left hemisphere damage (Muller et al., 1999), after language acquisition has been completed (Maestu et al., 2004), peri-lesional reorganization (Stowe et al., 2000) or incompletely crossed lateralization (Muller et al., 1999) occurs. However, numerous studies have shown greater activity over the homologue areas to the dominant

but damaged hemisphere (Weiller et al., 1995; Billingsly et al., 2001; Hertz-Pannier et al., 2002) which suggests reorganization involving hemispheric dominance shift in adults (Maestu et al., 2004). Knopman et al (1983) suggest that right-hemisphere structures may be restricted to early stages of post-lesional recovery, whereas spared regions of the left hemisphere become critically important in late recovery. Previous studies of aphasic stroke patients have confirmed this finding, namely, that spared regions of the left hemisphere are the main substrate for recovery mechanisms (Price & Crinion, 2005). This is because, irrespective of the recovery stage, there was increased right hemisphere homologue activation whereas the left hemisphere activation correlated with language recovery. Thus, researchers have proposed that the homologue activation may be a result of transcallosal disinhibition (as discussed in Price & Crinion, 2005). Furthermore, Warburton et al (1999) suggest that activations in the right hemisphere might actually compromise the recovery of language function in the left hemisphere. Thiel et al (2005) used a combination of PET and repetitive TMS (rTMS); they separated the left-hemisphere brain tumour subjects into two groups: one with activation in the right inferior frontal gyrus (IFG) (homologue structure) and the other with activation restricted to the left IFG. They found that in both groups, but especially in patients with left IFG activation only, the residual language function of the left hemisphere is responsible for language recovery. In another study, Thiel et al (2006) found that patients with slowly progressing brain tumours recovered right hemispheric language function. On the contrary, patients with rapidly progressing brain lesions did not have right hemispheric language function and language performance was correlated with brain activation in the left hemisphere. Thus, they suggest that disease duration and rate of progression is

critical in determining whether right hemisphere homologue regions can be successfully integrated into the language network.

Holodny et al (2002) reported a case of a patient with a left inferior frontal glioma who had interhemispheric transfer of Broca's area as demonstrated by fMRI. By using language paradigms, they found Wernicke's area to be in the left hemisphere and Broca's area to be in the right hemisphere. The authors suggest that the growth of the tumour in the left inferior frontal lobe led to an inability of this area to function properly and led to the transfer of the functional Broca's area to the contralateral side. This translocation of a dominant language structure has been reported after strokes (Thulborn et al., 1999). The presence of some language function on the right side in the area corresponding to Broca's area may allow for limited reorganization of language function to the contralateral side (Lazar et al., 2000). Maestu et al (2004) report a case of partial reorganization of language involving a shift to the non-dominant hemisphere of only receptive language mechanisms.

Furthermore, studies of split-brain patients have shown that the right hemisphere has limited naming capacities but that this residual system could partially compensate for the effects of left-sided lesions at some stage of post-lesional recovery (Demonet et al., 2005).

Other evidence suggests the mechanism of cerebral reshaping could be the result of the recruitment of perilesional areas. This notion is supported by functional neuroimaging studies which shows activations around the glioma during sensorimotor and language tasks (Atlas et al., 1996; Thiel et al., 2001; Duffau & Cappelle, 2004).

2. Research Approaches

Single case studies

The neuroimaging approach to single case studies has been validated (Price et al., 1999). If a cognitive task is performed well above chance by a patient who suffers from a lesion located in a language-related region activated by normal subjects by the same task, then the damaged region is unlikely to be necessary for language. This raises the question of whether or not other neural structures would take over damaged regions or compensate for the defective mechanisms within the language-related network. An understanding of language recovery following brain injury requires knowledge of the structure-function relationships that are present in the neurologically normal brain before injury. This is because functional reorganization involves plasticity within pre-existing systems (Price & Crinion, 2005).

Interpreting abnormalities: Overactivation and Underactivation

Patient studies of the consequence of brain damage reveal activation patterns that show increasing or decreasing reliance on the remaining intact systems (Price & Crinion, 2005). Overactivation in regions reflects disinhibition or compensation in a system that is different from that to which the damaged area belongs. As such, damage to one normal system increases reliance on another normal system. Underactivation in the patient, however, indicates that a region is either damaged or disconnected following damage elsewhere and is no longer involved in interactions between brain areas. Areas in which

activation is reduced compared with normal individuals are likely to be part of the same system as the damaged area.

fMRI

fMRI is non-invasive and is readily available for pre-operative assessment.

The pre-operative use of fMRI to identify eloquent cortex near lesions is used increasingly for surgical planning. In language mapping, improvements in stimulation paradigms have led to the routine use of fMRI with high specificity and high sensitivity. fMRI enables identification of the language-dominant hemisphere and the distance between brain tumour and language areas before surgery (Stippich et al., 2007). Furthermore, fMRI can both depict the functioning cortex in anatomy distorted by the infiltrating tumour and demonstrate cortical reorganization (Holodny et al., 2002).

3. This study

Previous studies of post-lesion recovery and brain reorganization involved in functional compensation have used stroke patients (Duffau, 2005b). Due to the fact that brain plasticity and functional compensation are seen after stroke and following brain injury, it is likely that progressive brain infiltration by gliomas also leads to a reshaping or local reorganization of functional networks (Duffau et al., 2003). Furthermore, neural plasticity cannot be fully understood without considering the temporal pattern of the injury – both tumour growth and surgery - inflicted on the brain. The aims of the present study are to examine neuronal activation for a range of tasks in patients with brain tumours and to compare functional reorganization of language before and after surgery. In this study we are primarily interested in two research questions: 1.Does tumour growth interfere with neural circuits for speech production and visual processing? and 2.What is the effect of tumour removal on speech production and visual processing?

The first question involves a number of possibilities (see Figure 1). The first is that processing at a tumour is abnormal because tissue has been displaced. If this is the case, then we would expect to see underactivation in one part of the tumour and overactivation in another part or on the edge of the tumour. If the abnormality is simply spatial displacement, then we would not expect to see abnormalities distant to the site of the tumour. The second is that processing at the site of tumour is abnormal because neuronal responses have been disrupted. If so, then we would expect to see underactivation in tumour but no evidence for overactivation in other parts of tumour. However, we may see abnormalities distant to the site of the tumour. Within this explanation there are two

possibilities. The first is that abnormally low processing at the tumour site results in abnormally low activation in other brain regions that normally work in harmony with the damaged area (i.e., part of the same system). These brain regions may be in either the ipsilateral or contralateral hemisphere and, irrespective of their location, the underactive areas are likely to be part of the same system as the damaged area. The second is that abnormally low processing at the tumour site results in abnormally high activation in other brain regions that compensate for the loss of the damaged system. Again, these brain regions may be in either the ipsilateral or contralateral hemisphere. Areas where activation is increased are likely to be part of a different system than those where activation is reduced. Thus, we can infer that the set of overactivated areas was part of a different system than the damaged area.

The second question regarding the effect of tumour resection also involves several possibilities (see Figure 2). The first is that there are no activation changes pre and post-surgery. In this case, any functional reorganisation before surgery is able to support visual processing and speech production after surgery. The second is that there are different activations after surgery. If activation is more abnormal after surgery then surgery may have removed tissue that was previously functionally viable. If activation is less abnormal after surgery, however, then pre-surgery abnormalities may have been due to tissue compression or displacement. Furthermore, if there is evidence for both more and less abnormal activations after surgery, then a combination of the above may exist.

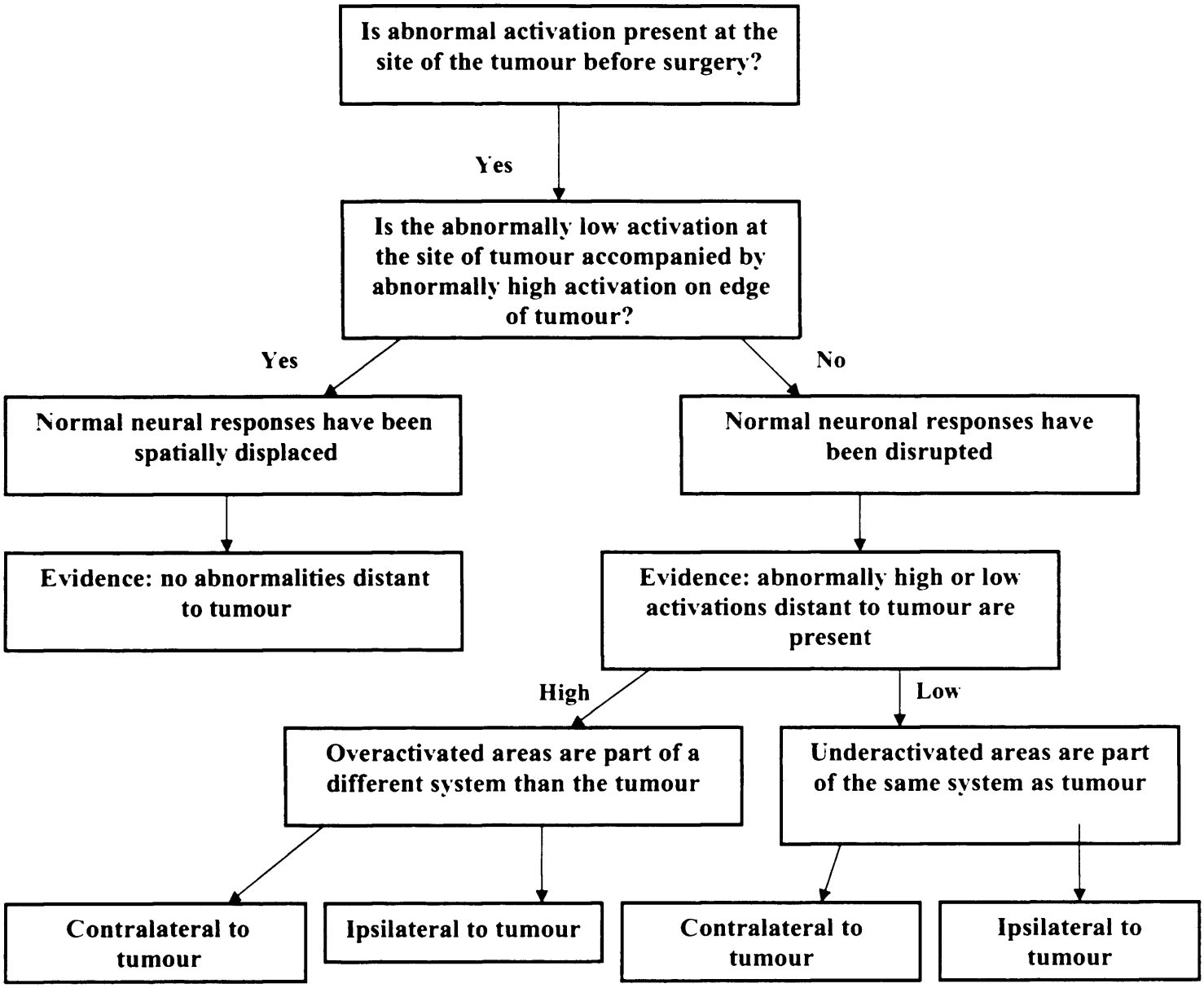

Figure 1: A systematic approach to interpreting the interference of tumour growth on neural circuits for speech production and visual processing.

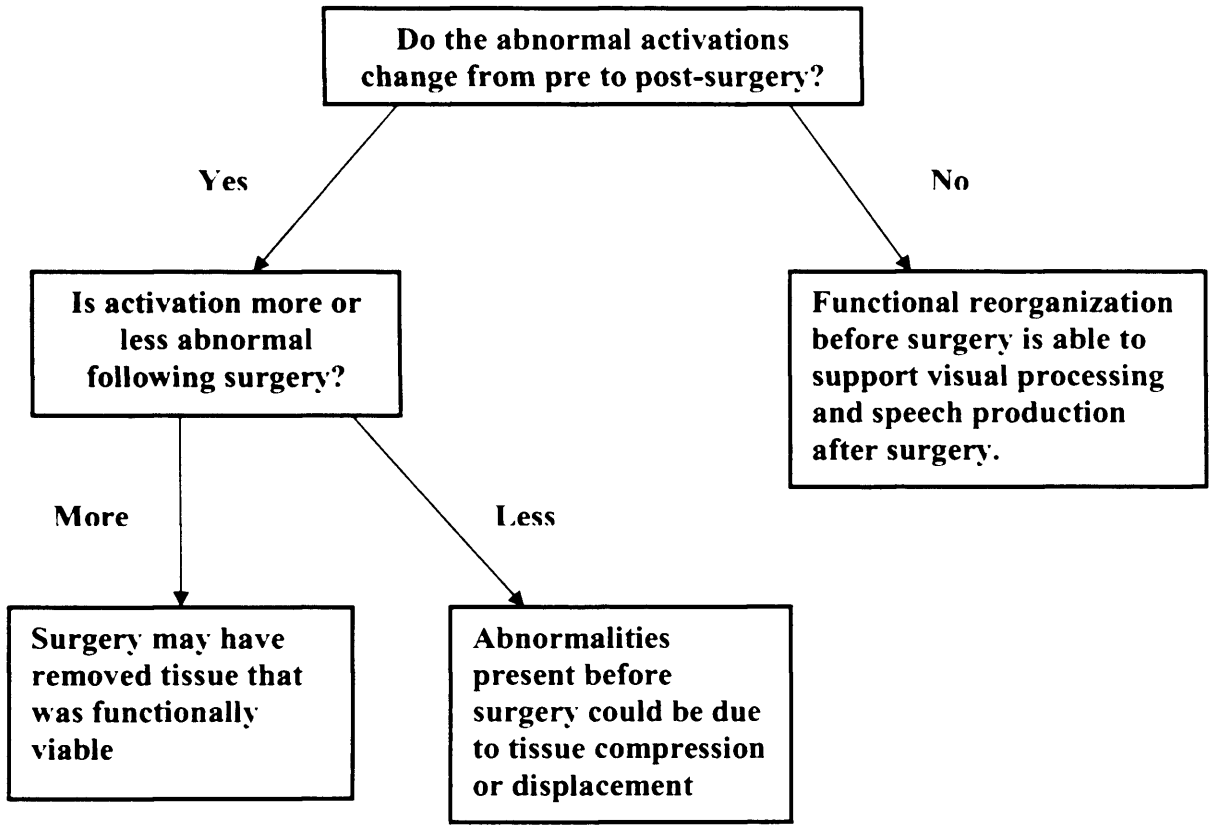

Figure 2. A systematic approach to investigate the effect of tumour removal on speech production and visual processing.

Methods

1. Participants

1.1 Patient Participants

All patients had left hemisphere brain tumours and underwent surgery at the National Hospital for Neurology and Neurosurgery (NHNN). In all patients, the histopathological diagnosis was determined according to the WHO Classification of Tumors affecting the CNS (Kleihues et al., 2002). The neurosurgeon referred candidates for surgery for an fMRI of language at the Functional Imaging Laboratory (FIL). The inclusion criteria consisted of the patient having a brain tumour in an area involved in word processing and being willing and able to perform a subset of our fMRI paradigm. After analyzing twenty three patients' pre-surgery results, we selected three patients with similar tumour locations and sizes who returned for a post-surgery scan (see Table 1).

KM

KM is a 26 year old right-handed female who was diagnosed with a left frontoparietal diffuse astrocytoma (WHO grade II) in January 2007. She presented with headaches and seizures and had a history of intermittent difficulty finding the correct word and spelling for six months. She was prescribed Dilantin for her seizures. On 22 January 2007, she had surgery with approximately 40% resection of her tumour. At the time of surgery, the main goals were to obtain a diagnosis, decompress the tumour, and leave minimal neurological dysfunction. Given the large size of her tumour and her reluctancy, an awake craniotomy was not carried out. The histopathology report demonstrated a grade II astrocytoma – a very slow-growing and non-

aggressive tumour. The patient was stable post-operatively with no speech deficits, no visual deficit, and no sensory or motor deficit. Of note she has had no seizure activity. She continued to take Phenytoin but was then switched to Tegretol due to its preferred side effect profile. On 01 August 2007, she had an awake craniotomy, which was well tolerated. The histopathological diagnosis on her second operation was that of a Grade II/III astrocytoma; this was primarily due to the high proliferation rate, however the majority of the tumour mass sent to the pathology department demonstrated Grade II astrocytoma. Approximately 80% of her tumour was resected. She has had no major seizures since the operation although she describes a few episodes of very short lived speech arrest associated with reading problems. She has had no other new problems.

JA

JA is a 33 year old right-handed female who was diagnosed in April 2007 with a left parietal anaplastic astrocytoma (WHO grade III). She presented with a two-month history of focal seizures characterized by twitching of the right side of her face and eye, feeling faint, and difficulty articulating words. Surgery was performed on 14 May 2007 with excision of the tumour and drainage of a cyst. Following surgery, her neurological symptoms stabilized however she had problems with her right hand function and had some speech difficulties. JA had a CT scan on 10 October 2007 which showed oedema likely related to post radiotherapy changes. She is taking Tegratol 400mg twice a day. Her seizures were less frequent post-operatively. These seizures are complex parietal seizures primarily involving her right face and occasionally her right arm. Furthermore, following surgery, she had reduced power - most notably distally in her right hand - with fine motor movements of the fingers.

JH

JH is a 20 year old right-handed male who was diagnosed with a parieto-occipital neurocytoma (WHO grade II). He was diagnosed in November 2006 after a 10 week history of grand mal seizures and right handed numbness. Of note, his vision became blurred before seizures started. Upon visual examination, an incongruous homonymous visual field defect was found which was predicted based on the location of his tumour. Previously, on 16 July 2004, he had a partial resection of the tumour due to the location within eloquent area. Following the resection he had adjuvant radiotherapy. On 11 November 2006, he had an MRI which revealed a heterogeneous tumour in the left parietal and temporal lobes which abutted the trigone of the left lateral ventricle. There was a large cystic component in the superior-medial aspect of the tumour. An MRI in June 2007 revealed progression of the cystic component of the tumour. There was a concern that it would cause raised intracranial pressure. The solid component of the tumour had remained unchanged. There was a moderate aspect of vasogenic oedema spreading into the temporal lobe. He was on sodium valproate at 300mg twice a day. An awake craniotomy and tumour resection was performed on 13 December 2007. He had regular speech therapy and at discharge was back to normal. Post-operative MRI images suggested total resection of the tumour. Following surgery he developed moderate expressive dysphasia affecting his speech and written output and comprehension difficulties affecting his reading. He had speech and language therapy and was almost back to normal. He continued to be on sodium valproate 300mg twice a day and remained fit free.

Table 1. Summary of the patients' characteristics

Patient	Age/gender	Histology	Tumour location	Pre-surgery scan date	Surgery Date	Post-surgery scan date
KM	26/F	Diffuse astrocytoma WHO II	Left frontoparietal	27 July 07	01 Aug 07	3 Oct 07
JA	33/F	Anaplastic astrocytoma WHO III	Left parietal	17 April 07	14 May 07	6 March 08
JH	20/M	Neurocytoma WHO II	Left parieto-occipital	17 Oct 07	13 Dec 07	9 April 08

F, Female; M, Male

1.2 Control Participants

Twenty-eight (9 males and 19 females, age range 18-73; mean 37) subjects participated in this experiment. All subjects were right-handed according to self-description with English as their native language and had no history of neurological or psychiatric disorders. The Edinburgh handedness questionnaire was missing for one subject but over all other subjects the range was from 50-100 with a mean of 90 (Oldfield, 1971). Subjects' consent was obtained according to the declaration of Helsinki.

2. Language Testing

2.1 The Comprehensive Aphasia Test (CAT) (Swinburn et al., 2004)

This set of tests was used to provide a comprehensive evaluation of the patients' cognitive and language abilities. The components are outlined in Table 2. The tests were administered in accordance with the CAT instruction manual and were tape recorded for increased scoring reliability.

Table 2: Components of the Comprehensive Aphasia Test (Swinburn et al., 2004).

Cognitive Screen
Line bisection
Semantic memory
Word fluency (category, letter)
Recognition memory
Gesture object use
Arithmetic
Language Comprehension
Comprehension of spoken language
Comprehension of spoken words
Comprehension of spoken sentences
Comprehension of spoken paragraphs
Comprehension of written language
Comprehension of written words
Comprehension of written sentences
Repetition
Repetition of words, complex words, and nonwords
Repetition of digit strings
Repetition of sentences
Spoken Language Production
Naming objects
Naming actions
Spoken picture description
Reading Aloud
Reading words, complex words, function words, and nonwords
Written Language Production
Copying
Writing picture names
Writing to dictation
Written picture description

3. Imaging

3.1 MRI data acquisition

A Siemens 1.5T scanner was used to acquire T2*-weighted echoplanar images with BOLD contrast. Each echoplanar image comprised 40 axial slices of 2 mm thickness with 1 mm slice interval and 3 × 3 mm in-plane resolution. A total of 412 volume images were acquired in four separate sessions with an effective repetition time (TR) of 3.6 s/volume. There were 103 volumes per session. To avoid Nyquist ghost artifacts, a generalized reconstruction algorithm was used for data processing. After reconstruction, the first four (dummy) volumes of each session were discarded to allow for T1 equilibration effects. In addition to the functional scans, a T1-weighted anatomical volume image was acquired from all subjects to ensure that there were no unknown neurological abnormalities and to obtain precise localization of the patients' tissue abnormalities.

3.2 fMRI stimuli and tasks

3.2.1 Tasks

The present study was longitudinal with both pre-surgery and post-surgery fMRI data. An identical paradigm was used during pre and post-surgery scans. In total, there were eight conditions: four involved the speech production and four involved a finger press response to indicate a categorical decision. In all eight conditions, three visual stimuli of the same type were presented, with one above fixation and two below fixation. Across conditions, half the stimuli were meaningful (pictures of objects or their written names) and half were meaningless (pictures of nonobjects and Greek letters) (see Figure 3). In the speech production conditions, the participants named the objects, read their names, and said "one, two, three" to the symbols

and nonobjects. In the finger press conditions, the participants chose either the lower left or lower right stimulus that matched the stimulus above either in its semantic association (e.g., anchor with ship rather than truck) or physical identity (see Figure 3). Half the controls responded with a key pad in their right hand (forefinger press for lower left/middle finger press for lower right) (RHR); the other half of controls responded with a key pad in their left hand (middle finger press for lower left/forefinger press for lower right) (LHR). All three patients responded with their right hand. Reaction times and accuracy were recorded.

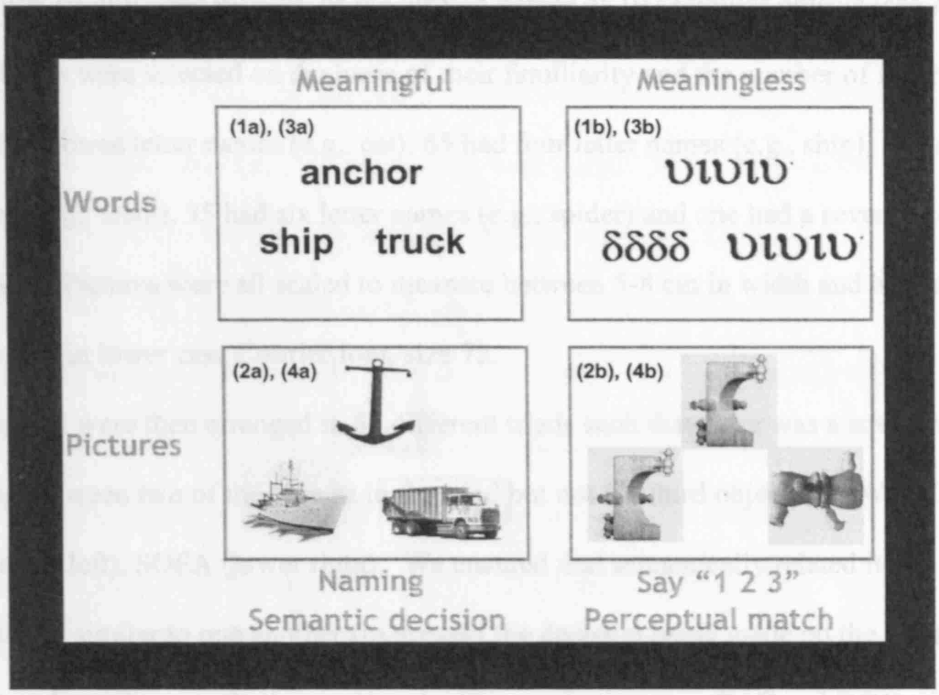

Figure 3: fMRI paradigm. 1a) semantic decisions on words, (2a) semantics decisions on pictures, (3a) reading aloud words, (4a) naming aloud pictures, (1b) perceptual decisions on triads of meaningless symbols, (2b) perceptual decisions on triads of meaningless nonobjects, (3b) saying "one, two, three" to triads of meaningless symbols, (4b) saying "one, two, three" to triads of meaningless nonobjects. For the sake of simplicity and to show that items were overall matched across tasks, the words match the pictures in this particular example. However, to avoid subjects from focusing on semantic relations during naming, triads were re-arranged for the naming condition.

3.2.2 Stimuli

The activation stimuli were pictures or the written names of 192 familiar objects (see Appendix A). The objects were selected on the basis of their familiarity and the number of letters in their names. 33 had three letter names (e.g., cat), 65 had four letter names (e.g., ship), 58 had five letter names (e.g., teeth), 35 had six letter names (e.g., spider) and one had a seven letter name (e.g., balloon). Pictures were all scaled to measure between 5-8 cm in width and height. Words were presented in lower case Courier font, size 72.

The 192 stimuli were then arranged in 64 different triads such that there was a strong semantic relationship between two of the objects in the triad but not the third object; e.g. WALL (above) FENCE (lower left), SOFA (lower right). We ensured that semantically related items were neither visually similar to one another (to prevent the decision being made on the basis of perceptual attributes) nor verbally associated with one another (e.g. CAT and DOG; KNIFE and FORK, SOCK and SHOE). In addition, a pilot study with 8 subjects ensured inter-subject agreement on all correct responses.

3.2.3 Presentation

All eight stimulus conditions and fixation were blocked. In the stimulus conditions, there were 4 triads per block. Each triad remained on the screen for 4.32 seconds followed by 180ms of fixation. The resulting block length was therefore 18 seconds for each condition [(4.32 + 0.18) x 4)]. Each block was preceded by 3.6 seconds of instructions (see below for details). Over the experiment, there were 8 blocks of each activation condition, 4 blocks of each baseline condition, and 20 blocks of fixation. Each block of fixation lasted 14.4 seconds.

Data for speech production and finger press conditions were acquired in different fMRI runs/sessions. For each subject, there were two sessions of speech production (S) and two

sessions of finger press response (F). The task order for half the subjects in each group was SFFS; for the other subjects, the task order was FSSF. Within each session, half the triads were presented as pictures of the objects and half the items were presented as the written names of objects. For the first two sessions, all 192 objects were presented as either words or pictures of objects. In the second two sessions, the same object was presented again but in a different stimulus modality. Thus, objects that were presented as pictures in the first two sessions were presented as written words in the second two sessions; objects that were presented as written words in the first two sessions were presented as pictures in the second two sessions. Consequently, no stimulus was repeated in any of the sessions. Within a session, there were four different types of stimuli: Pictures (P), Words (W) Symbols (S), Nonobjects (N) interspersed with fixation (F). The order of presentation was PWFSNFPWFWPFNSFWP for two sessions and WPFNSFWPFPWFSNFPW for two sessions.

3.3 Analysis

3.3.1 fMRI image pre-processing.

Data were analyzed with statistical parametric mapping (SPM5: Wellcome Trust Centre for NeuroImaging, London, UK. http//www.fil.ion.ucl.ac.uk), running under Matlab 6.5.1 (Mathworks, Sherbon, MA, USA). All volumes from each subject were realigned and unwarped, adjusting for residual motion-related signal changes. The functional images were spatially normalized to a standard MNI-305 template using nonlinear basis functions (to allow intersubject averaging and comparisons) and spatially smoothed with a 6-mm full width half maximum isotropic Gaussian kernel to compensate for residual variability after spatial normalization and to permit application of Gaussian random-field theory for corrected statistical inference (Friston et al., 1995).

3.3.2 Statistical analysis of fMRI data

At the first level, the data were analyzed in a subject-specific fashion. Each of the eight conditions and the instructions were modeled separately, with event-related delta functions for each trial, convolved with a canonical hemodynamic response function (HRF). The nine regressors were then entered into the design matrix and condition effects were estimated according to the general linear model. To exclude low frequency confounds, the data were high-pass filtered using a set of discrete cosine basis functions with a cutoff period of 128 seconds. The contrasts of interest at the first level were each of the 8 experimental conditions relative to fixation.

1) Naming pictures > Fixation
2) Reading aloud > Fixation
3) Saying 1, 2, 3 to Symbols > Fixation
4) Saying 1, 2, 3 to Nonobjects > Fixation
5) Semantic decisions on Words > Fixation
6) Semantic decisions on Pictures > Fixation
7) Perceptual decisions on Symbols > Fixation
8) Perceptual decisions on Nonobjects > Fixation

For each patient, a single second level analysis modeled the effects of each of the eight contrast images from the first level analyses a) pre-surgery, b) post-surgery, and c) for all controls. The effects of interest were the differences in activation for:

1) Pre-surgery and post-surgery relative to the controls
2) Pre-surgery, but not post-surgery, relative to the controls
3) Post-surgery, but not pre-surgery, relative to the controls

We focused on activation differences that were common to speech production and finger press decisions or specific to speech production (i.e., not for finger press decision). The results correspond to the effects of the tumour/surgery on visual processing or speech production. In addition, the effects of meaningful relative to meaningless stimuli were analyzed, but these effects were weak and inconsistent and did not contribute to a better understanding of the main conclusions (see Appendix B for list of precautions we took against artifacts).

The contrasts at the second level modeled the following effects:

i. Pre-surgery speech production

ii. Pre-surgery finger press

iii. Post-surgery speech production

iv. Post-surgery finger press

v. Controls speech production

vi. Controls finger press

Overactivation

vii. Pre-surgery speech production > Controls speech production

viii. Pre-surgery finger press > Controls finger press

ix. Post-surgery speech production > Controls speech production

x. Post-surgery finger press > Controls finger press

xi. [Pre-surgery speech production + Pre-surgery finger press + Post-surgery speech production + Post-surgery finger press] > [Controls speech production + Controls finger press]

Underactivation

xii. Controls speech production > Pre-surgery speech production

xiii. Controls finger press > Pre-surgery finger press

xiv. Controls speech production > Post-surgery speech production

xv. Controls finger press > Post-surgery finger press

xvi. [Controls speech production + Controls finger press] > [Pre-surgery speech production + Pre-surgery finger press + Post-surgery speech production + Post-surgery finger press]

Pre-surgery versus Post-surgery

xvii. Pre-surgery speech production > Post-surgery speech production

xviii. Post-surgery speech production > Pre-surgery speech production

xix. Pre-surgery finger press > Post-surgery finger press

xx. Post-surgery finger press > Pre-surgery finger press

xxi. [Pre-surgery speech production + Pre-surgery finger press] > [Post-surgery speech production + Post-surgery finger press]

Significant effects were those that were different in the patients in comparison to both groups of controls. The threshold for significance was set at $p < 0.05$ corrected for multiple comparisons across the whole brain. Where masking was used, the mask threshold was set at $p < 0.001$.

Results

1. Language testing results

The patients' scores on the CAT subtests are presented in Table 3. Each patient's pre and post-surgery results are explained below.

1.1 KM

1.1.1 Pre-Surgery CAT results

KM had a low score for both letter (8) and category (10) fluency. In terms of comprehension of spoken words she was below the 5th percentile of non-aphasic performance and so considered impaired (28/30). For comprehension of written words, she was below the 5th percentile of non-aphasic performance (28/30). Furthermore, for naming, she scored (just) below the 5th percentile. For reading and writing KM only had problems reading pseudo-words (6/10).

1.1.2 Post-Surgery CAT results

KM made improvements, with only her comprehension of written words (27/30) and her naming of actions (8/10) being impaired. She still scored at ceiling on tests of repetition, cognition and memory. Her letter fluency was 10 and category fluency was stable at 12. For comprehension of spoken words she scored 26/30 and thus is not considered impaired. For comprehension of written words she scored 27/30 which is still considered impaired. She scored 47/48 in naming objects (within the normal range) and 8/10 in naming actions (impaired). For reading and writing KM had problems reading pseudo-words (8/10). On the previous testing occasion, she was impaired in her writing, this time she almost scored at ceiling (73/76).

1.2 JA

1.2.1 Pre-Surgery CAT results

JA scored very well on all tasks except in arithmetic and in recognition memory where she scored below the 5th percentile. However, as both these scores were normal post-surgery, they might be explained by her emotional state and her inability to concentrate.

1.2.2 Post-Surgery CAT results

JA scored below the 5th percentile of non-aphasic performance on most sub-tests including the following: Comprehension of both spoken (27/32) and written (18/32) sentences, Word (24/32) and sentence (10/12) repetition, Object (28/48) and action (8/10) naming, and Reading (35/70). She had a digit span of 4/7 and named 14 items in the category fluency task and 5 items in the letter fluency task. Some additional features of note were that she wrote with her right hand which was very weak, she did not do written picture description, and she took a long time with arithmetic.

1.3 JH

1.3.1 Pre-Surgery CAT results

JH scored at ceiling on all subtests of the CAT, but self-reported that he sometimes found it difficult to remember things and also experienced some problems finding words – he knew what he wanted to say but "the words wouldn't come."

1.3.2 Post-Surgery CAT results

JH scored below the 5th percentile of non-aphasic performance, and is thus considered impaired, on reading of complex words (4/6 - previously unimpaired at 6/6), and recognition memory

(8/10 - previously unimpaired at 9/10). He did score at ceiling on action word naming, which was impaired in his pre-surgery test.

Table 3: Patient scores on CAT subtests. Asterisks (*) indicate scores below the normal cut-off. Non-aphasic performance data from the CAT manual (Swinburn et al., 2004).

	Subtest	JA		JH		KM		Max. possible score	Normal cut-off	Non-aphasic performance		
		Pre	Post	Pre	Post	Pre	Post			n	mean	SD
COGNITIVE SCREEN	Semantic memory	10	10	10	10	10	10	10	8	27	9.81	0.4
	Word fluency	25	19	37	39	18	22	no max	13	27	32	10.1
	Category (animals)	16	14	19	19	10	12	n/a	n/a	n/a	n/a	n/a
	Letter (s)	9	5	18	18	8	10	n/a	n/a	n/a	n/a	n/a
	Recognition memory	8*	9	9	8*	9	10	10	8	27	9.70	0.54
	Gesture object use	12	12	11	11	11	11	12	9	26	11.15	0.78
	Arithmetic	1*	4	6	6	5	5	6	1	24	4.58	1.69
LANGUAGE COMPRE-HENSION	Spoken words	30	27	27	27	28	26	30	25	27	29.15	1.35
	Spoken sentences	30	15	32	32	28	30	32	27	23	30.17	1.85
	Spoken paragraphs	4	4	4	4	4	4	4	2	23	3.87	0.34
	Written words	30	28	28	28	28	27	30	27	27	29.63	0.79
	Written sentences	28	18	27	27	28	27	32	23	23	29.78	2.5
REPETITION	Words	32	24*	32	32	32	32	32	29	26	31.73	0.67
	Complex words	3	0*	6	6	6	6	6	5	26	6.00	0
	Nonwords	10	8	10	10	10	10	10	5	26	9.23	1.48
	Digit strings	14	8*	14	14	12	10	14	8	27	6.44	0.8
	Sentences	12	10*	12	12	12	12	12	10	27	6.00	0
SPEAKING	Naming objects	24	28*	46	46	44	47	48	43	27	46.37	1.6
	Naming actions	10	8*	10	10	6*	8*	10	8	26	9.88	0.43
	Picture description	44	30*	46	46	68*	77	no max	33	21	52.19	18.25
READING ALOUD	Words	48	28*	47	47	46	48	48	45	26	47.42	1.06
	Complex words	6	1*	4*	4*	6	6	6	4	26	5.85	0.37
	Function words	6	6	6	6	6	6	6	3	21	5.81	0.6
	Nonwords	10	0*	10	10	6*	8	10	6	26	9.38	1.13
WRITING	Copying	27	17*	27	27	27	27	27	25	25	26.84	0.62
	Writing picture names	21	0*	20	20	12*	21	21	15	26	20.15	1.8
	Writing to dictation	28	0*	27	27	23*	25	28	24	26	27.00	1.5
	Picture description	23	17*	31	31	27	32	no max	19	21	32.19	11.72

2. Structural MRI results

Each patient's structural MRI results are shown in Figure 4 to illustrate the location of the lesions and the similarities across patients.

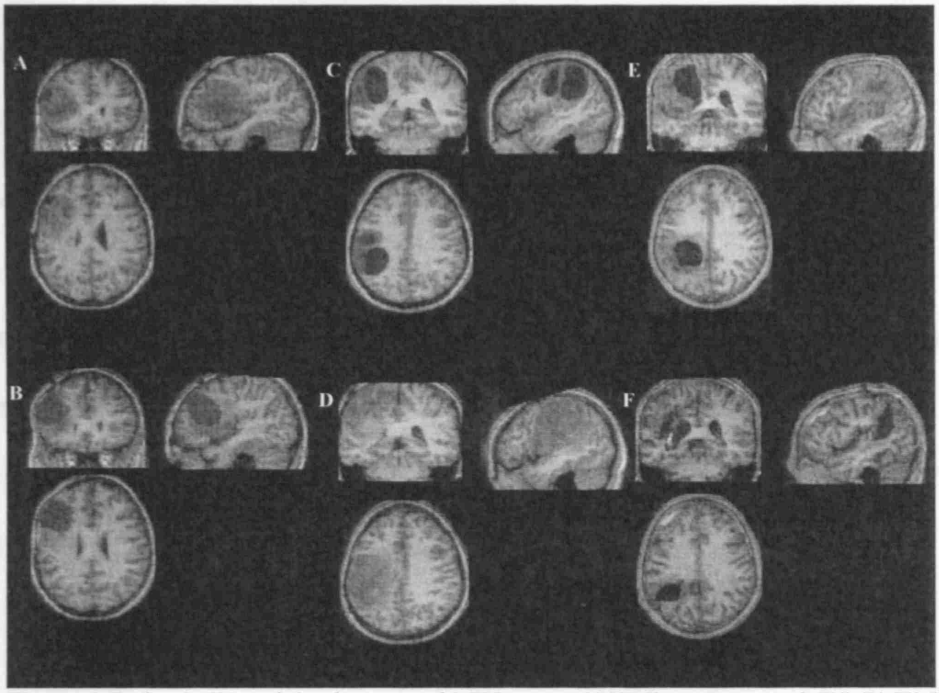

Figure 4. Patient's T1-weighted structural MRI scans. A) KM's pre-surgery MRI, B) KM's post-surgery MRI, C) JA's pre-surgery MRI, D) JA's post-surgery MRI, E) JH's pre-surgery MRI, F) JH's post-surgery MRI.

3. fMRI results

3.1 Task performance

Control and patient participants were able to perform the task. The mean number of correct responses for both tasks and the response times for the control groups and each patient for the semantic task is given in Table 4 and Table 5.

3.2 KM

For a summary of KM's regions of significant underactivation and overactivation see Tables 6 and 7 and Figures 5 and 6, respectively. Abnormally low activation was observed in midline visual areas and the left cerebellum for all tasks and in bilateral postcentral motor regions in the speech production tasks (i.e., the region of the left tumour and its homologue). Abnormally high speech-related activation was found in right cerebellum, left cerebellum, and right brainstem regions.

3.3 JA

For a summary of JA's regions of significant underactivation and overactivation see Tables 8 and 9 and Figures 7 and 8, respectively.

3.3.1 Visual processing areas (common to speech production and fingers)

Abnormally low activation was observed in the left parietal part of her tumour (as expected) and distant to the tumour in the left lingual gyrus and the left cerebellum.

Abnormally high activation was observed in the right parietal lobe, contralateral to her tumour, as well as in her left parietal areas surrounding her tumour. These effects were consistent pre and post-surgery.

3.3.2 Speech production areas

Abnormally low activation was observed in the left postcentral motor part of the tumour. Following surgery that removed the left pre and postcentral cortex, activation was also abnormally low in left precentral and left superior temporal regions.

Abnormally high speech-related activation was remarkably extensive both pre and post-surgery. Overactivation in areas activated by controls included the right superior parietal, right superior temporal, left cerebellum, and right motor and premotor regions. Overactivation in areas that were not activated by the control subjects included bilateral temporal poles, bilateral dorsolateral prefrontal regions, and left posterior cingulate. In addition, prior to surgery, activation was abnormally high in bilateral pre and postcentral cortices, the left superior temporal cortex and right cerebellum.

3.4 JH

For a summary of JH's regions of significant underactivation and overactivation see Tables 10 and 11 and Figures 9 and 10, respectively.

3.4.1 Visual processing areas (common to speech production and fingers)

Abnormally low activation was not consistent across sessions and tasks due to noisy signal surrounding the left parietal tumour.

Abnormally high activation was observed in right superior parietal cortex (homologue to tumour), left parietal (peri-tumour) and in bilateral ventral and dorsal occipital regions and the left occipitotemporal cortex. Prior to surgery, overactivation was also observed in

right temporal and left inferior frontal regions that were not activated in controls. Post-surgery, overactivation was observed in the right cerebellum.

3.4.2 Speech production areas

Abnormally low activation was observed in the left postcentral part of the tumour and the left cerebellum. Following surgery activation in the right cerebellum was also reduced.

Abnormally high speech-related activation was found in right parietal (contralateral to tumour), bilateral occipital (ventral and dorsal) regions, frontal midline, and right temporal regions. Prior to surgery, these effects were more extensive in bilateral superior temporal, right middle temporal, right cerebellum, and right superior parietal (contralateral to tumour) regions. Following surgery, activation was abnormally high in the left dorsal occipital and left anterior temporal pole (not activated by controls).

Table 4. Mean accuracy on the speech production and finger press fMRI tasks for controls and patient participants.

Condition	RHR Controls	LHR Controls	KM		JA		JH	
			Pre	Post	Pre	Post	Pre	Post
Naming	0.954	0.9375	0.625	0.938	0.875	0.375	0.938	0.719
Reading	0.958	0.955	0.969	0.875	1.000	0.782	1.000	0.969
Saying "1,2,3" to words	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
Saying "1,2,3" to objects	1.000	1.000	1.000	1.000	1.000	0.250	1.000	1.000
Word match	0.911	0.933	0.907	0.907	0.844	0.751	0.876	0.875
Picture match	0.907	0.933	0.813	0.813	0.875	0.719	0.876	0.876
Nonobject match	0.980	0.995	1.000	1.000	1.000	1.000	1.000	0.875
Symbol match	0.964	0.976	1.000	1.000	0.875	0.875	1.000	1.000

Table 5. Mean response time (ms) for correct responses of finger press tasks for control and patient participants.

Condition	RHR Controls	LHR Controls	KM		JA		JH	
			Pre	Post	Pre	Post	Pre	Post
Word match	1770	1545	2362	2128	2464	2640	2079	1844
Picture match	1822	1616	1868	1879	2523	2792	1989	1959
Nonobject match	1134	1066	1177	1219	1824	1972	1092	1214
Symbol match	1126	1023	1359	1444	1941	2129	1028	1095

Table 6. KM's underactivation. All regions reach a corrected level of significance of $p < 0.05$.

Session	Visual processing areas						Speech production areas					
	Location	Hemisphere	Coordinates	Z score		Voxels	Location	Hemisphere	Coordinates	Z score		Voxels	
				Diff	Int					Diff	Int	Diff	Int
Both sessions	Visual	Midline	-2 -78 4	Inf		13	Postcentral (motor)	Left	-48 -12 36	Inf	7.0	252	72
								Right	50 -10 42	5.9	4.4	6	
	Cerebellum	Left	-24 -70 -14	6.2		14							
Pre-surgery Only	ns	ns	ns	ns		ns	ns	ns	ns	ns	ns	ns	
Post-surgery Only	ns	ns	ns	ns		ns	ns	ns	ns	ns	ns	ns	

Table 7. KM's overactivation. All regions reach a corrected level of significance of $p < 0.05$.

Session	Visual processing areas						Speech production areas					
	Location	Hemisphere	Coordinates	Z score Diff	Z score Int	Voxels	Location	Hemisphere	Coordinates	Z score Diff	Z score Int	Voxels Diff	Voxels Int
Both sessions	ns	ns	ns	ns	ns	ns	Cerebellum / Brain stem	Left	-10 -38 -46	7.3	7.1	17	15
								Right	12 -40 -46	5.9	5.7	4	3
							Cerebellum		16 -72 -18	7.6	5.4	13	5
Pre-surgery Only	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	
Post-surgery Only	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	

Table 8. JA's underactivation. All regions reach a corrected level of significance of $p < 0.05$.

Session	Visual processing areas						Speech production areas					
	Location	Hemisphere	Coordinates	Z score		Voxels	Location	Hemisphere	Coordinates	Z score		Voxels
				Diff	Int					Diff	Int	Diff Int
Both sessions	Dorsal Parietal	Left	-30 -50 50	Inf		101	Postcentral (motor)	Left	-46 -14 36	Inf	7.2	278 289
									-50 -12 38	Inf	7.2	"" ""
	Lingual	Left	-22 -66 -8	5.8		20						
	Cerebellum	Left	-26 -78 -18	6.7		3						
Pre-surgery Only	ns	ns	ns	ns		ns	ns	ns	ns	ns	ns	ns ns
Post-surgery Only	ns	ns	ns	ns		ns	Superior temporal	Left	-44 -24 8	6.6	4.9	29 38
									-54 -26 10	5.9	3.2	"" ""
									-42 -30 16	5.8	ns	10 0
							Precentral	Left	-62 -6 26	5.9	5.0	5 3

Table 9. JA's overactivation. All regions reach a corrected level of significance of $p < 0.05$. * indicates an area not activated by controls. + indicates a region within tumour.

Session	Visual processing areas						Speech production areas					
	Location	Hemisphere	Coordinates	Z score Diff	Int	Voxels	Location	Hemisphere	Coordinates	Z score Dif	Int	Voxels Diff	Int
Both sessions	Parietal	Right	32 -60 52	Inf		12	Superior parietal	Right	18 -58 64	7.1	5.3	11	2
			30 -54 46	7.3		"							
			16 -62 46	Inf		9							
			36 -74 26	7.8		12	Superior temp	Right	52 -14 6	7.6	5.6	20	8
			26 -58 30	7.8		18	Cerebellum	Left	-2 -68 -42	Inf	P<0.001	42	0
									20 -42 -46	6.8	"	15	0
	Parietal	Left	-28 -30 16 +	Inf		10	Motor	Right	44 -6 58	Inf	P<0.001	15	7
			-30 -28 28 +	6.9		1			36 -6 62	6.8	6.5	"	"
			-32 -20 18 +	6.5		2							
	Motor	Right	44 -6 50	Inf		9	Premotor	Right	62 -4 34	Inf	Inf	16	16
									60 0 14	7.8	6.3	38	21
							Temporal pole	Left	-32 -8 -32 *	Inf	Inf	67	61
									-34 6 -32 *	7.3	6.6	"	"
									-46 8 -24 *	7.4	7.0	21	18
							Temporal pole	Right	32 -6 -36 *	Inf	Inf	92	70
								Right	40 -2 -36 *	7.6	7.6	"	"
									30 6 -34 *	6.8	5.6	"	"
									34 12 -32 *	6.7	5.8	21	12
							Dorsolateral prefrontal	Right	22 54 32 *	Inf	Inf	45	42
								Right	14 48 44 *	Inf	6.1	7	6
								Left	-10 50 42 *	7.6	6.0	24	8
								Left	-24 50 34 *	5.1	p<0.001	"	0
								Left	-34 50 26 *	Inf	"	13	0

							Post cingulate	Left	-4 -48 18 *	Inf	P<0.001	20	0
Pre-surgery Only	ns	ns	ns	ns		ns	Precentral	Right	60 -6 34	Inf	6.7	98	37
							Postcentral		58 -12 44	7.3	5.8	"	7
									40 -16 38	6.0	4.6	18	0
							Precentral	Left	-62 -6 26	5.9	5.1	11	1
							Postcentral		-40 -28 16	5.7	ns	7	0
									-38 -12 24 *	6.5	3.2	58	0
							Superior Temporal	Left	-46 -26 8	6.5	4.9	34	1
							Cerebellum	Right	38 -66 -44 *	6.2	5.5	14	4
							Tumour +	Left	-32 -40 18 *	Inf	Inf	129	50
Post-surgery Only	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	

Table 10. JH's underactivation. The effects are only significant at $p < 0.001$ but did not survive a correction for multiple comparisons.

Session	Visual processing areas						Speech production areas					
	Location	Hemisphere	Coordinates	Z score		Voxels	Location	Hemisphere	Coordinates	Z score		Voxels
				Diff	Int					Diff	Int	Diff Int
Both sessions	Dorsal Parietal	Left	-26 -52 46	6.7		1	Postcentral	Left	-44 -12 30	6.2	4.8	24 0
	Lingual	Left	-2 -86 6	Inf		2	Cerebellum	Left	-18 -70 -18	5.9	4.4	37 0
			-2 -60 2	7.3		4						
	Cerebellum	Left	-20 -66 -18	6.0		2						
Pre-surgery Only	ns	ns	ns	ns		ns	ns	ns	ns	ns	ns	ns ns
Post-surgery Only	ns	ns	ns	ns		ns	Cerebellum	Right	18 -82 -22	Inf	7.2	13 9

Table 11. JH's overactivation. All regions reach a corrected level of significance of $p < 0.05$. * indicates region is not activated by controls. + indicates region is within/surrounding tumour. WM = White Matter

Session	Visual processing areas						Speech production areas					
	Location	Hemisphere	Coordinates	Z score Diff	Z score Int	Voxels	Location	Hemisphere	Coordinates	Z score Diff	Z score Int	Voxels Diff / Int
Both sessions	Visual Ventral	Left	-30 -84 -16	Inf	Inf	74	Temporal	Right	56 -18 -10	Inf	Inf	65 / 64
		Right	14 -76 -12	Inf	Inf	6			66 -40 10	Inf	Inf	235 / 81
									48 -38 0	7.5	7.5	" / 38
									50 -18 2	Inf	6.5	26 / 10
									46 -34 16	7.5	6.3	61 / 30
	Dorsal	Left	-4 -86 32	Inf	Inf	16	Visual ventral	Right	28 -74 -12	Inf	Inf	519 / 216
			-10 -90 28	Inf	"				16 -86 -14	Inf	7.6	" / "
			-26 -90 14	Inf		69			20 -86 -16	7.7	5.2	" / "
		Right	22 -88 18	Inf		24			10 -80 2	Inf	6.8	" / 26
			18 -98 14	Inf		13	Visual ventral	Left	-30 -84 -18	Inf	Inf	361 / 147
									-10 -92 -14	Inf	7.7	" / 28
	Occipito-temp	Left	-40 -60 -12	Inf		10	Visual dorsal	Left	-26 -90 14	Inf	5.7	608 / 12
									-10 -90 28	Inf	Inf	" / 255
									0 -80 30	Inf	Inf	" / "
								Right	10 -82 30	Inf	6.8	" / "
	Superior parietal	Right	14 -60 64	Inf		23	Parietal	Right	32 -66 52	7.2	7.2	59 / 19
			20 -58 58	Inf		"			20 -78 46	6.8	7.2	22 / 9
							Frontal	Midline	12 66 8	6.0	6.4	10 / 6
Pre-surgery Only	Temporal cortex	Right	54 4 0 *	Inf		17	Middle temporal	Right	62 -42 -6 *	5.9	5.4	25 / 6
								Right	62 -18 6	6.3	4.5	14 / 0
	Inferior frontal	Left	-54 18 28 *	Inf		26	Superior temporal	Left	-58 2 -10	7.4	5.3	17 / 2
			-60 10 18 *	6.6		10						
	Parietal	Right	42 -62 52 *	7.7		23	Cerebellum	Right	18 -82 -22	Inf	7.2	19 / 12
	Tumour+	Left	-22 -34 22 *	6.7		12	Superior parietal	Right	40 -62 54	7.5	5.5	15 / 2

Post-surgery Only	Cerebellum	Right	46 -58 -40 *	Inf	47	Anterior temporal pole	Left	-56 6 -20 *	Inf	Inf	72	47
	Occipital	Left	-26 -88 16	6.2	10	Dorsal Occipital	Left	-8 -86 30	6.3	4.8	24	00
								-20 -82 32	6.6		16	01
	Parietal +	Left	-48 -50 34	6.1	11	Ventricle	Right	28 -42 20	5.8	5.0	10	
	Peri-tumour		-46 -64 22	5.5	5							
	WM	Left	-32 0 24	6.6	15							
	Tumour/ ventricle +		-18 -36 14	7.7	29							

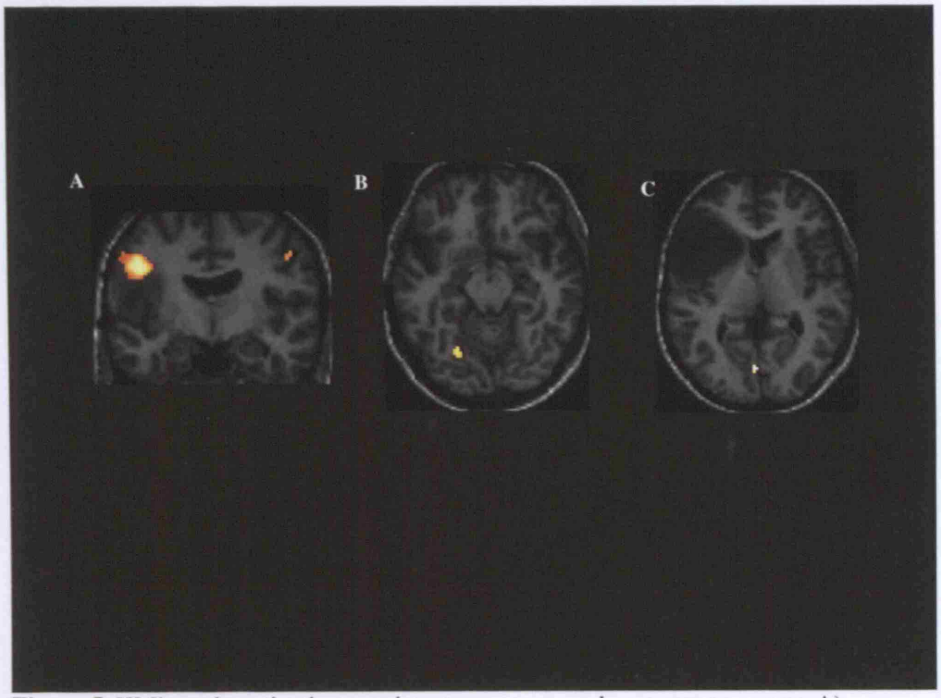

Figure 5. KM's underactivation consistent across pre and post-surgery scans. A) Bilateral postcentral for speech production task only, B) Left cerebellum for both tasks, C) Visual midline for both tasks.

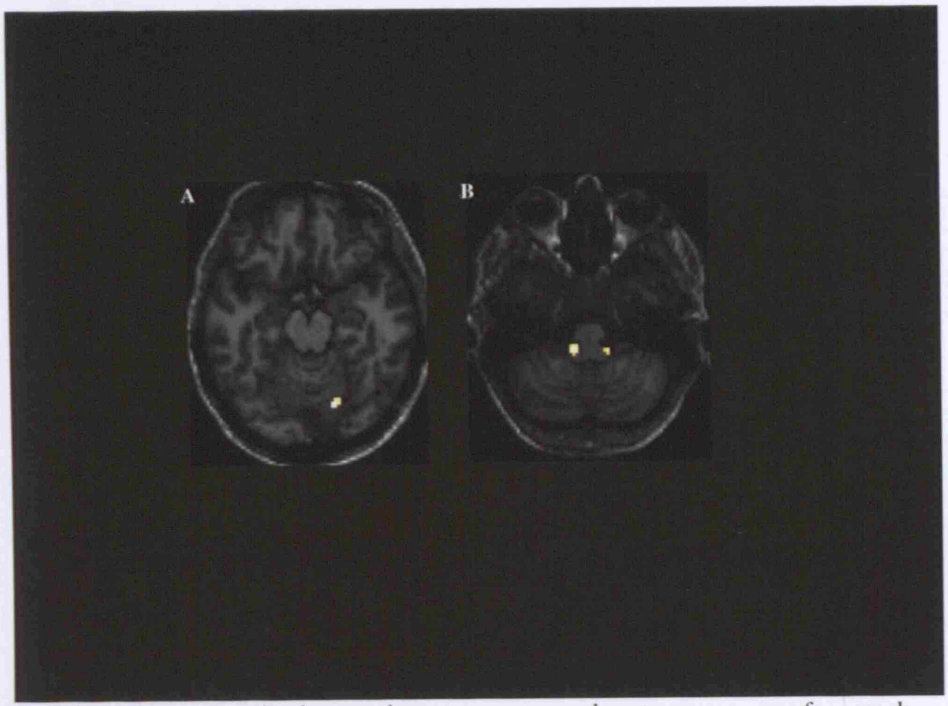

Figure 6. KM's overactivation consistent across pre and post-surgery scans for speech production task only. A) Right cerebellum, B) Left cerebellum and right brainstem

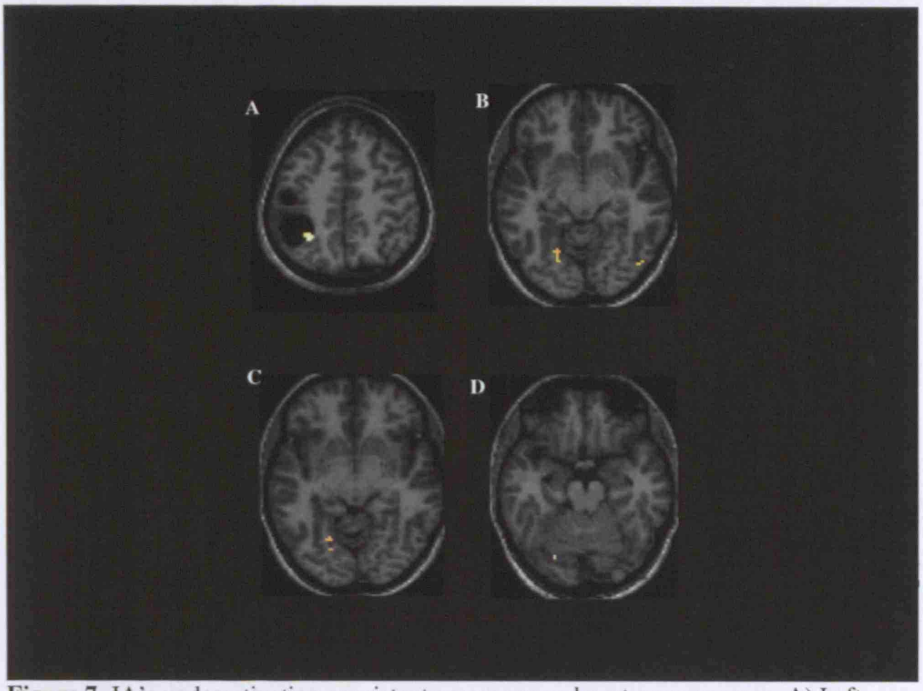

Figure 7. JA's underactivation consistent across pre and post-surgery scans. A) Left parietal for both tasks, B) Right occipto-temporal for speech production task only, C) Left lingual for both tasks, D) Left cerebellum for both tasks.

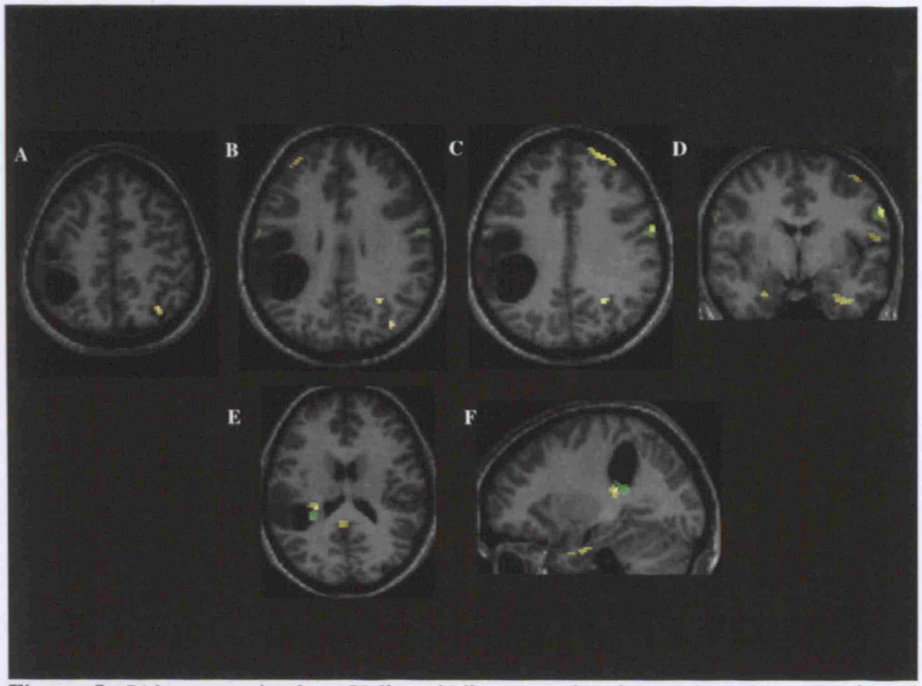

Figure 8. JA's overactivation. Yellow indicates region is consistently overactivated across pre and post-surgery scans. Green indicates region is overactivated during pre-surgery scan only. A) Right parietal (contralateral to tumour) for both tasks, B) Left superior frontal for speech production task only, C) Right superior frontal for speech production task only, D) Bilateral premotor for speech production task only, E) & F) Peri-tumoural activation and artifacts in white matter for both tasks .

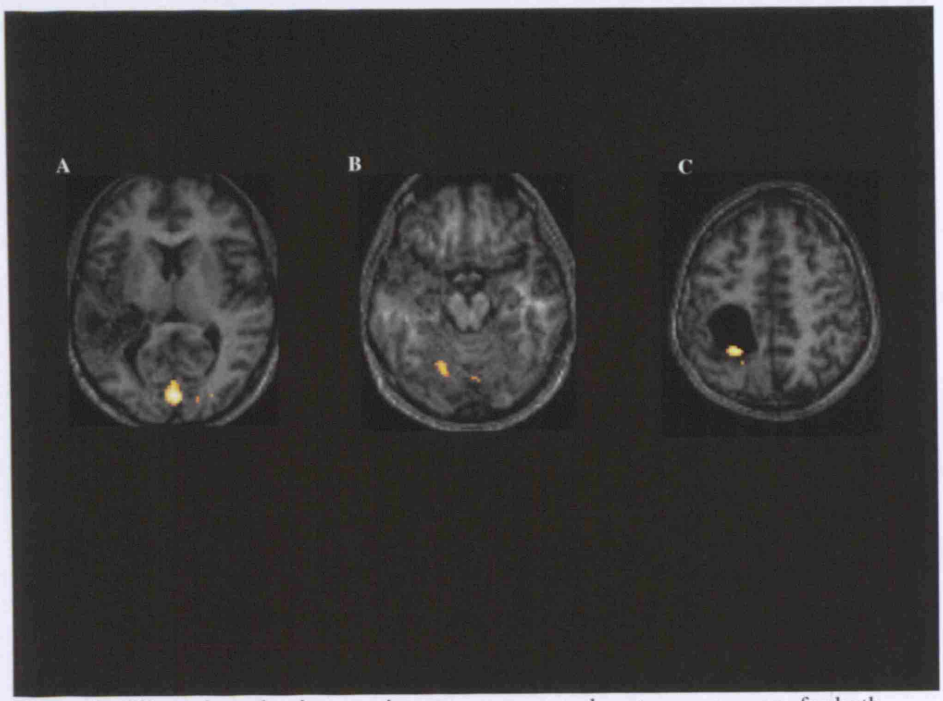

Figure 9. JH's underactivation consistent across pre and post-surgery scans for both tasks. A) Left lingual, B) Left cerebellum, C) Left parietal.

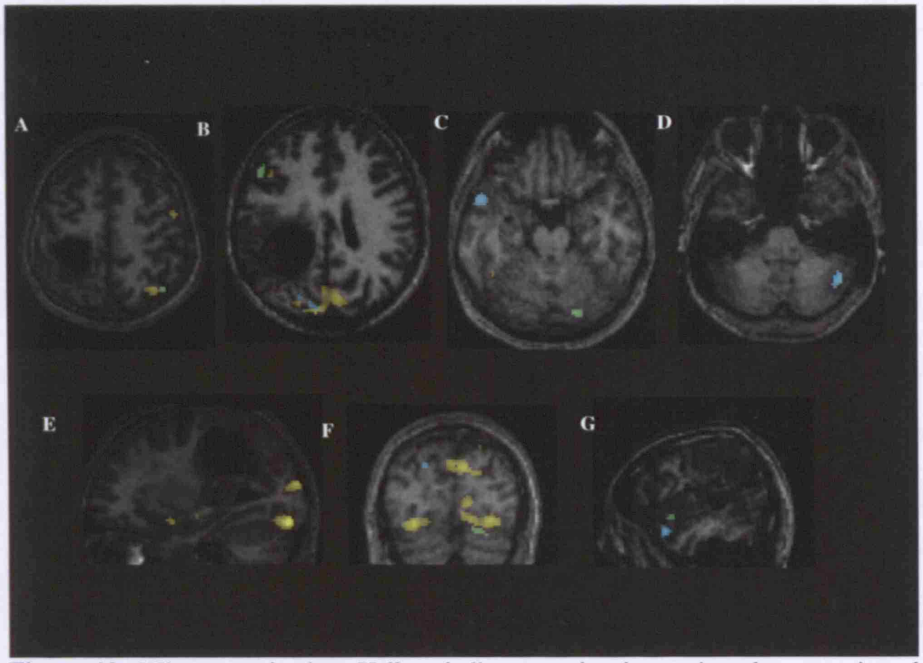

Figure 10. JH's overactivation. Yellow indicates region is consistently overactivated across pre and post-surgery scans. Green indicates region is overactivated during pre-surgery scan only. Blue indicates region is overactivated during post-surgery scan only. A) Right parietal (contralateral to tumour) for both tasks, B) Left inferior frontal during pre-surgery scan only for both tasks, C) Left anterior temporal during post-surgery scan only for speech production task, D) Right cerebellum during post-surgery scan only for both tasks, E) and F) Inferior and superior bilateral occipital for both tasks, G) Left inferior frontal gyrus during pre-surgery scan only for both tasks and left anterior frontal pole during post-surgery scan only for speech production task.

Discussion

The longitudinal experimental design of this study allows the assessment of brain reorganization in patients with brain tumours. More specifically, it allows the examination of whether regional activation was abnormally high or low before surgery and/or following surgery and whether these abnormal activations were consistent or changed over time. This enables us to investigate our two research questions: namely, how does tumour growth interfere with neural circuits for speech production and visual processing? and, what is the effect of tumour removal on speech production and visual processing?

These effects were assessed by looking for abnormal activation relative to neurologically intact control subjects using fMRI. To answer the first question, we began by focusing on abnormal activations surrounding the tumour site. Abnormal activation is expected at the site of the tumour because the neural responses have been either disrupted or spatially displaced. Evidence to distinguish these alternatives rests on whether abnormally low activation at the site of the tumour is accompanied by abnormally high activation on the edge of the tumour. In the case of disrupted neural responses, interpretation of the abnormality depends on whether the abnormally low processing at the tumour site resulted in abnormally low or high activations in distant brain regions. This allows the determination of whether the activated region is part of the same system as the tumour (abnormally low activation) or a separate system (abnormally high activation). Of particular interest is the effect of the tumour in the hemisphere that is not affected by

tumour. Abnormal activations contralateral to the tumour cannot be interpreted in terms of tissue displacement but suggest real evidence for functional reorganization.

To answer the second question, the presence of abnormal activation changes pre and post-surgery was investigated. If no changes in activation were present, then this suggests that functional reorganization before surgery is able to support visual processing and speech production after surgery. On the contrary, if there were activation changes present, then an assessment of whether the activations were more or less abnormal following surgery would determine the effect of surgery. If activation was more abnormal following surgery then surgery may have removed tissue that was previously functionally viable. However, if activation was less abnormal following surgery then abnormalities present before surgery may have been due to tissue compression or displacement. Evidence from our patients' results can be interpreted systematically according to this framework.

1. Effect of tumour growth on neural circuits for visual processing and speech production

The combination of underactivation and overactivation in the left parietal tumours of patients JA and JH is consistent with the possibility that abnormal activation within the tumour may partly be due to tissue displacement. However, in all three patients, there was also evidence of functional reorganization distant to tumour (see below) which suggests that the tumour had disrupted normal function. For example, all three patients had abnormally low activation in the left cerebellum, ipsilateral to but distant from their tumours. In addition, KM and JA had abnormally low activation in midline visual

association cortex and KM had abnormally low activation in the right postcentral area that was the homologue to the left hemisphere area affected by the tumour.

The results from all three patients also provided evidence for abnormally high activations in regions distant from the brain tumour. Of particular interest was the observation that two patients (JA and JH) showed evidence that activation was abnormally high in right hemisphere regions contralateral to their tumour. In addition, JA and KM had over activation in the left cerebellum, KM had overactivation in the right cerebellum and right brainstem, and JH showed overactivation in the left occipitotemporal cortex and bilateral ventral and dorsal occipital regions.

These results suggest that functional reorganization involves both local (perilesional) regions and distant ipsilateral and contralateral areas. This is in accordance with previous research that has shown a combination of peri-tumoural and contralateral homologue activations in patients with tumours within sensorimotor (Fandido et al., 1999) and language systems (Heiss et al., 2003; Meyer et al., 2003) that underlie recovery. For example, Thiel et al (2001) used PET to study the reorganization of language networks in 61 patients with left hemisphere tumours. A combination of inter and intrahemispheric compensation was found in more than 60% of patients. Interestingly, while some patients had pure intra-hemispheric compensations, there were no patients with unmixed contralateral recruitment. Bartolomei et al (2006) used MEG and showed that patients with brain tumours have a loss of functional connectivity as compared to controls; this loss of connectivity was observed in remote areas in both ipsilateral and contralateral

hemispheres and thus is not restricted to regions close to tumour. Evidence from our study and others suggest that plasticity implies changes in the whole functional network.

The role of the right hemisphere

When combined, right hemisphere activations we observe provide evidence that some contralateral regions are part of the same system as the damaged region (i.e the post central gyri in patient KM) and other contralateral regions are part of a different compensatory system than the damaged region (e.g. the parietal lobe in patients JA and JH). Previous studies have also provided evidence for recruitment of right hemisphere homologue structures in functional reorganization but have not provided evidence that the right hemisphere homologues work in harmony with the damaged area. For example, in a preoperative study Borbely et al (2005) investigated areas activated during speech production in both controls and patients. In controls, speech activation resulted in significant activation in Brodmann's area 44 and 45, contralateral cerebellum, superior middle and posterior temporal gyrus. In the patients, additional regions of activation were seen in contralateral frontal and temporal regions and in ipsilateral temporal region suggesting increased reliance on the contralateral hemisphere following damage to the dominant hemisphere. Furthermore, for language function, translocations of Broca's area to the right hemisphere were observed following a LGG within the left inferior frontal cortex (Holodny et al, 2002). Similarily, translocations of Wernicke's area to the contralateral hemisphere were reported in patients with left temporo-parietal tumours (Petrovich et al, 2004). In addition, Peru et al (2006) showed left visual field and thus a right hemisphere advantage during a simple naming and reading task in a patient with a left hemisphere brain tumour. Together, these studies suggest that recruitment of the right

hemisphere into the functional networks occurs in response to left hemisphere brain tumours.

The results of the present study offer a novel perspective, highlighting the observation that the right homologue does not always compensate for left fronto-parietal tumours. This result was illustrated by patient KM who showed abnormally low activation in bilateral postcentral regions as would be expected if the homologues in this region were part of the same, damaged, network.

Previous studies have shown that there is increased right homologue activation in left frontal tumour patients (Duffau, 2006; Meyer et al, 2003). In cases of left precentral glioma, homologous areas in right precentral gyrus generating the same motor response were identified by stimulation in some patients (Duffau, 2006). Meyer et al (2003) showed that one patient with a glioma in Broca's area and four patients with other left frontal lesions activated the right-hemisphere homologoue of Broca's area. One possible interpretation of the results is that in functionally compromised patients, increasing effort and time on task is paralleled by an increasing amount of right-sided activation (Just, Carpenter, Keller et al, 1996).

Guye et al (2003) studied a patient with a left medial precentral tumour and found that, relative to controls, the patient had increased contralateral connections passing through the posterior half of the corpus collosum to the precentral area. The authors suggest that modified M1 connectivity in the right hemisphere could be due to functional reorganization as a consequence of damage to dominant hemisphere. Our results do not

support this as KM appears to have disrupted connections to the contralateral postcentral region.

Guggisberg et al (2008) found greatest connectivity estimates in functionally critical brain areas such as visual, sensorimotor and language regions. Specifically, they found significantly lower connectivity values in brain areas that were damaged by a lesion than in the intact contralateral tissue thus confirming that dysfunctional tissue is disconnected from the interactions among healthy tissue. Importantly, they only found lower connectivity in ipsilateral hemisphere whereas our study found disrupted connectivity in the contralateral homologue region in KM. Thus, brain tumours cause a loss of functional connectivity that affects multiple brain regions not only in ipsilateral hemisphere (Bartolomei et al., 2006; Guggisberg et al., 2008) but contralateral as well.

An interesting study by Thiel et al (2006) found that patients with slow growing brain tumours recovered right-sided language functions whereas patients with rapidly progressing tumours did not. The authors concluded that time is the factor which determines successful integration of the right hemisphere into the language network following left hemisphere damage. In support of this, JH had a Grade II tumour and demonstrated right hemisphere homologue activation. However, KM had a slow-growing Grade II/III tumour and did not show recruitment of right hemisphere homologue region whereas JA had a Grade III tumour and demonstrated right hemisphere recruitment.

2. Effect of tumour removal on visual and speech production processing

All three patients provide strong evidence that the functional reorganization before surgery also supports visual processing and speech production function after surgery. The patterns of underactivation and overactivation are remarkably consistent longitudinally thus supporting the concept that, in this sample of patients, preoperative functional reorganization is more prevalent than postoperative functional reorganization. Furthermore, this suggests that the effect of tumour growth is more prominent than the effect of surgery.

This is in accordance with previous findings. Numerous studies have shown that brain tumour growth triggers neuronal reorganization (Desmurget et al., 2007). In progressive lesions, brain plasticity relies on both adjacent and distant areas within the same hemisphere and opposite hemisphere (Desmurget et al., 2007) and differs from patient to patient (Carpentier et al., 2001). Desmurget et al (2007) suggest compensatory mechanisms are recruited in a hierarchal manner. First, intrinsic reorganization occurring within the injured or perilesional structures occurs (Thiel et al., 2001; Heiss et al., 2003). Second, remote recruitments in the ipsi- and contralateral hemispheres occur when local reorganizations become insufficient. Our results suggest that both of these phases have occurred before surgery due to the infilatrative nature of LGGs.

A previous study by Shinoura et al (2006) assessed the difference in activation of right homologue region by comparing pre and post-surgery scans in two patients with left frontal tumours. Both patients had increased reliance on the right hemisphere following

surgery. However, our results show that right homologue activations (over or under) are present before surgery and remain consistent over time.

There were nevertheless some significant effects of surgery. For example, JA showed reduced activation in left precentral and left superior temporal regions that may have been surgically excised. In addition, JH showed abnormally high activation in the left and right cerebellum, left dorsal occipital and left anterior temporal pole. In contrast, JH showed reduced activation in a different region of the right cerebellum. Furthermore, the overactivation in the right cerebellum that both JA and JH showed before surgery normalized following surgery. Other regions that were less abnormally activated following surgery include bilateral superior temporal, left inferior frontal, right middle temporal and right superior parietal regions in JH and bilateral pre and post-central cortices and left superior temporal regions in JA.

The post-operative literature supports the pre-surgical observations by suggesting functional recovery involves an interaction of complementary mechanisms (Desmurget et al., 2007). Combinations of local and remote reorganizations have been found in the language domain after resection of Broca's area involving reorganizations within premotor cortex, inferior frontal gyrus and insula (Duffau et al., 2003). These results are compatible with others which showed language networks changing from surgery to surgery (Duffau et al., 2002). Evidence comes from removal of supplementary motor area (SMA) proper which leads to functional compensation involving contralateral SMA, contralateral premotor cortex (Krainik et al., 2004) and ipsilateral primary motor cortex (Desmurget et al., 2007).

There are few previous studies that directly investigate the effect of surgery. Douw et al (2008) used magnetoencephalography (MEG) to investigate the effect of surgery on functional connectivity. They found a significant decrease of interhemispheric functional connectivity after tumour resection and suggested this reflected normalization of functional connectivity. Our results support this as both JA and JH had overactivation before surgery that normalized following surgery. Furthermore, Shinoura et al (2006) showed that tumour resection restores functioning in pre-operatively damaged motor areas resulting in improved motor function. Krainik et al (2004) showed that, during resection, acute remapping can be stabilized leading to long-term reorganization of the functional network both in ipsilateral and contralateral hemisphere, as shown by comparing both pre and post-operative fMRI. Thus, the authors imply that brain surgery leads to functional reorganization. However, our results suggest that there is a limited effect of surgery and most reorganization occurs before surgery and remains consistent over time. In our study we showed that patients were cognitively intact before and following surgery. In accordance with previous findings, our results suggest that remote activation in the intact or lesioned hemisphere is not a marker of poor recovery (Desmurget et al., 2007).

3. Limitations and Future Research

Anatomical shift

Evidence for pre and post surgery differences in activation are confounded by structural changes over time. This is especially the case when interpreting activations in the perilesional regions and in the damaged hemisphere. However, the non-damaged hemisphere can also change structurally due to relief of intracranial pressure or mass effect. When interpreting regions of abnormal activation, the proximity to the tumour must be taken into consideration. Abnormal activation in a homologue region is likely to support reorganization because there are tight connections between hemispheres via the corpus callosum. Perilesional activation, however, is more susceptible to artefacts.

Variability within the normal controls

Another potential confound is that the differences observed between patients and controls may be due to normal variance only. That is, the patient may have had abnormal language-related activation prior to the tumour.

fMRI and brain tumours

Distinguishing between recruitment or compensatory mechanisms and genuine cortical reorganization with fMRI is complex (Ulmer et al., 2004). There are a number of limitations and cautions to the use of fMRI in brain tumour patients.

First, sensitivity of fMRI ranges from 66% to 100% for identification of language areas (Roux et al., 2003; Petrovich et al., 2005) and the specificity is around 61% (Rutten et al., 2002). This is in part due to the BOLD signal around the tumour is not as accurate as in healthy brain tissue (Holodny et al., 2000). The BOLD signal can be reduced in patients

with tumours both at the edge of the tumour and in normal vascular areas distant from the tumour (Scheiber et al., 2000). This is thought to be due to changes in neurovascular and metabolic coupling (Scheiber et al., 2000). In addition, the potential for mass effect restricting blood flow and reducing or eliminating activation in language areas can create false negatives in the pre-operative assessments of brain tumour patients (Bookheimer, 2007).

Second, a major limitation with fMRI use in pre-operative mapping is that it cannot differentiate the structures essential for a function (which should be surgically preserved) from the 'modulatory' areas, which can be functionally compensated (and hence resected without permanent deficit) (Duffau et al., 2003).

Third, pre-operative images do not accurately reflect intra-operative conditions due to the loss of cerebrospinal fluid and tissue removal that cause anatomical brain shift (Roberts et al., 1998).

Timing of surgery

Future research should control for the time interval between the fMRI scans and the surgery. This is because time is an important factor in reorganization of brain structure and function (Thiel et al., 2001).

Therapeutic interventions

Various therapeutic interventions during the course of brain tumour patient management could confound our results. For example, medication could influence the extent of reorganization. Furthermore, it is not possible to disentangle whether the reorganization

is caused by the tumour itself or by its various treatments. Exploring the influence of therapy on brain functions is a new topic and warrants further research.

Neurosurgeon

In an attempt to control for differing levels of performance, strategy and skill, the same neurosurgeon should be used in all patients. This may potentially account for some of the differences found in the results. In our study, two patients (JA and JH) were operated by the same neurosurgery, while KM had a different neurosurgeon.

Intra-operative testing

Assessing the presence of intra-operative compensation with the use of intra-operative electrical stimulation (IES) could elucidate the difference between intra-operative reorganization and post-operative reorganization. This study did not include IES results or perform CAT scores immediately following surgery and therefore cannot directly address this phase of functional reorganization. This can be pursued in future studies that incorporate both these measures to investigate the presence of intra-operative plasticity. Indirectly, this phase can be assessed with only pre-operative and post-operative imaging if the results are similar. This scenario suggests that there is not significant intra-operative or postoperative compensation occurring.

TMS

Future experiments should include TMS in an attempt to determine the role of the right hemisphere in functional reorganization. Of particular interest is whether increased activation in the right hemisphere homologue region is a result of transcollosal disinhibition (not correlated to functional recovery) or compensatory strategies

(correlated to functional recovery). Interestingly, a study by Thiel et al (2005) found that TMS induces speech disruption when applied to the contralateral homologue structures activated during the task.

Connectivity Neuroimaging

Lastly, future studies should incorporate DTI or DCM in order to investigate anatomical and functional connectivity in the brain. This would enable the elucidation of functional connections and disconnections between brain regions of interest. Furthermore, there is a need to elucidate the functional role of specific activated regions, their contribution to task performance or functional recovery, and their functional connectivity.

Conclusion

This study has demonstrated that brain tumour progression induced local and distant functional reorganization, involving both the hemispheres ipsilateral and contralateral to the tumour. The right hemisphere homologue was recruited into a compensatory network in two patients, however, was disconnected in the third. Furthermore, this study illustrated that the effects of the slow, infiltrative nature of brain tumour was responsible for the majority of functional reorganization, whereas surgery had a minimal effect. In conclusion, treatment of brain tumours will benefit from an understanding of the dynamic biological nature of the tumour, the dynamic organization of the brain, and the dynamic interaction between tumour and the functional reorganization of the nervous system as a result of the tumour invasion and surgery (Duffau, 2005b).

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Appendix A: Activation stimuli

Target	Lower left	Lower right
Anchor	ship	truck
Axe	plant	log
Baby	bib	shirt
Bacon	peach	egg
Bag	basket	door
Ball	dice	bell
Balloon	razor	kite
Belt	medal	tie
Bench	stool	chain
Bomb	bottle	gun
Bone	dog	badger
Boot	hand	foot
Bowl	bin	plate
Brain	skull	shell
Bread	drum	cheese
Broom	flag	mop
Cake	leaf	cookie
Car	boat	shoe
Carrot	donkey	fox
Cat	camel	rat
Chips	potato	apple
Clock	wheel	watch
Coat	web	hat
Coffin	church	window
Cot	bed	table
Drill	grater	pliers
Flower	bee	crab
Fork	sword	knife
Glove	sock	rope
Goat	tiger	cow
Hammer	screw	nail
Hanger	dress	guitar
Key	house	tent
Lamp	saw	torch
Lion	zebra	horse
Mole	wasp	worm
Money	barrel	purse
Mug	cup	jug
Nest	book	bird
Nose	ear	vase
Onion	leek	lemon
Parrot	swan	frog
Piano	oven	harp
Pig	bear	lamb
Pipe	match	bulb
Plug	basin	chair

Target	Lower left	Lower right
Rake	biro	spade
Ruler	pencil	dagger
Seal	fish	budgie
Shark	snail	whale
Shower	fridge	bath
Snake	lizard	mouse
Spider	ant	fly
Spoon	whisk	hook
Swing	gate	slide
Tap	bucket	camera
Teapot	lock	kettle
Teeth	mouth	eyes
Tree	owl	duck
Wall	fence	sofa
Wool	wolf	sheep
Zip	candle	button

Appendix B: Interpretation of abnormal patient activation

Prior to reaching any interpretations, several factors that may cause abnormal activation were excluded. Below are the precautions to ensure that the abnormal activations were not due to artifact.

Check 1: ***Spatial normalisation error***
This involved assessing the mean EPI images for the patient and controls and each area of abnormal activation. Do the structures with abnormal activation look out of alignment in the patient and controls? If so, then there was an increase of spatial normalization and spatial smoothing.

Check 2: ***Movement artifacts***
This was investigated by:

(a) Checking whether abnormal activation is on the edge of an anatomical landmark with sharp signal changes (e.g., lesion or ventricles). If so, then this might reflect stimulus-correlated movement that is not present in controls that have no moving anatomical boundary at this position (because no lesion and smaller ventricles).

(b) Assessing if the realignment parameters showed more movement during activation trials than baseline trials (or other activation trials) which may either increase signal to noise (overactivation) or increase noise to signal (under-activation).

(c) Including the realignment parameters at the first level and assessing if the abnormality was still significant

(d) Limiting the second level analysis to sessions or trials where there was minimal movement.

(e) Examining if the time course of the abnormal signal matched the movement parameters or was delayed by 4-6 seconds. If the signal was caused by motion of anatomical boundaries, then it should have a different time course to the hemodynamic signal associated with neuronal activation. The former (motion artifact) occurred immediately but the latter (hemodynamic signal) is delayed by 4-6 seconds. Furthermore, our first level analyses were biased against motion artifacts because we did not include temporal and spatial derivatives that may have incorporated more of the early signals generated by motion. Nevertheless, our first level analyses are still susceptible to motion artifact if (i) the signal associated with movement is enormous relative to the activation of interest and (ii) not fully correlated with the realignment parameters which only measure between scan movement, not within scan movement.

Check 3: ***Abnormal neuronal response or abnormal perfusion***
This was checked by using perfusion imaging and examining session or condition specific abnormalities, if the area activates normally in other sessions or tasks, then the abnormal response was less likely to be a perfusion abnormality.

Check 4: ***Overactivation contributing to task performance***

The following was considered:

(a) ***Disinhibition*** In this case, the overactive area(s) may be inhibited/ deactivated in controls (see Price & Crinion, 2005).

(b) ***Correct responses*** In this case, activation would be greater for correct responses than incorrect responses; and

(c) ***Activation in the abnormal region is correlated/functionally connected with activation in areas that (i) are associated with output (e.g. articulation) and (ii) respond normally*** Any observed correlation/functional connectivity would be more useful if it can be shown that the over-activated region is more correlated/functionally connected to an output region than to another region (e.g., that associated with error responses).

Check 5: ***Analysis artifact***

(a) Overactivation at the second level may result from a combination of (i) very low between subject variance in the control group (which dominates a patient vs controls analysis) coupled with (ii) noise in the patient contrast image in an area high inter-trial variability in the patient's first level analysis. This was checked by assessing if the over-activated regions at the second level were also activated at the first level. If they were not activated at the first level, then the with-in patient error variance was checked and compared to the control group. Interpretation of a noisy signal at the first level patient analysis is difficult because it may be driven by a few trials where the patient moved or was distracted for some reason.

(b) Underactivation at the second level also was checked at the first level. Under-activation was expected in a damaged region if this area was normally activated by the controls during the task. However, under-activation can either be driven by activation in the controls or de-activation in the patient and significant de-activation in the lesion would not expected. Therefore, under-activations were categorized in terms of (i) activation in controls vs. de-activation in patient and (ii) deactivation of lesion in patient at the second level. In this case, the patient's deactivation of the region at the first level was checked. In an undamaged region, deactivation could be due to abnormal inhibition. In a damaged region, however, further consideration as to whether it could be an analysis artifact was required (e.g., a global normalisation error).

Check 6: ***Other unknown condition-specific artifacts***

(a) ***Abnormal patient activation replicates across sessions.*** If it was an artifact, then it would come from part of one session only. Therefore, two contrast images for each condition (one for each session) were created and abnormalities were considered if consistent over both sessions. At the same time the presence of a sufficient number of correct trials in each session was checked. If all the correct trials were coming from one session, then the analysis would be limited to this session only.

(b) ***Abnormal patient activation replicates in another patient with a similar lesion.*** If so, then it is unlikely to be a patient artifact because there is no reason to believe that movement artifacts are group specific (i.e., patients are unlikely to move in a different way to controls).

(c) ***Abnormal patient activation is more "abnormal" than expected*** An outlier analysis script was utilized that identifies the degree to which each subject (patient and control) is unique at the global level summed over all voxels.