doi:10.1093/brain/awp183 Brain 2009: 132; 2541–2552 | 2541

BRAIN
A JOURNAL OF NEUROLOGY

Towards the routine use of brain imaging to aid the clinical diagnosis of disorders of consciousness

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Clinical audits have highlighted the many challenges and dilemmas faced by clinicians assessing persons with disorders of consciousness (vegetative state and minimally conscious state). The diagnostic decision-making process is highly subjective, dependent upon the skills of the examiner and invariably dictated by the patients' ability to move or speak. Whilst a considerable amount has been learnt since Jennett and Plum coined the term 'vegetative state', the assessment process remains largely unchanged; conducted at the bedside, using behavioural assessment tools, which are susceptible to environmental and physiological factors. This has created a situation where the rate of misdiagnosis is unacceptably high (up to 43%). In order to address these problems, various functional brain imaging paradigms, which do not rely upon the patient's ability to move or speak, have been proposed as a source of additional information to inform the diagnostic decision making process. Although accumulated evidence from brain imaging, particularly functional magnetic resonance imaging (fMRI), has been encouraging, the empirical evidence is still based on relatively small numbers of patients. It remains unclear whether brain imaging is capable of informing the diagnosis beyond the behavioural assessment and whether brain imaging has any prognostic utility. In this study, we describe the functional brain imaging findings from a group of 41 patients with disorders of consciousness, who undertook a hierarchical speech processing task. We found, contrary to the clinical impression of a specialist team using behavioural assessment tools, that two patients referred to the study with a diagnosis of vegetative state did in fact demonstrate neural correlates of speech comprehension when assessed using functional brain imaging. These fMRI findings were found to have no association with the patient's behavioural presentation at the time of investigation and thus provided additional diagnostic information beyond the traditional clinical assessment. Notably, the utility of brain imaging was further underlined by the finding that the level of auditory processing revealed by functional brain imaging, correlated strongly ($r_s = 0.81$, $P < 0.001$) with the patient's subsequent behavioural recovery, 6 months after the scan, suggesting that brain imaging may also provide valuable prognostic information. Although further evidence is required before consensus statements can be made regarding the use of brain imaging in clinical decision making for disorders of consciousness, the results from this study clearly highlight the potential of imaging to inform the diagnostic decision-making process for persons with disorders of consciousness.

Keywords: vegetative state; minimally conscious state; speech comprehension; brain imaging

Received April 2, 2009. Revised May 14, 2009. Accepted May 29, 2009

Abbreviations: CRS = Coma Recovery Scale; FDR = False discovery rate; fMRI = functional magnetic resonance imaging; SPM = statistical parametric mapping

Introduction

The accurate assessment of persons with impaired consciousness following brain injury is a considerable challenge for any clinician. At present a diagnosis is made largely on the basis of the patient's clinical history with further support gleaned from the observation of the patient's behaviour in response to stimulation. This procedure, applicable at the bedside, has remained largely unchanged since Jennett and Plum coined the term 'vegetative state' in 1972. At that time they needed a term to describe the growing number of patients, facilitated by improving critical care methods, who were neither comatose nor fully conscious. Early post-mortem work by Strich (1956) and French (1952) had failed to find a specific pathological abnormality and tests such as the electroencephalogram had demonstrated considerable variability amongst this patient population (Jennett, 2002). Thus, Jennett and Plum based their terminology on the patient's common behavioural features: namely a loss of any meaningful cognitive responsiveness, a presumed lack of awareness and therefore of consciousness, in the presence of spontaneous breathing and a range of reflex responses, as well as periods of wakefulness (eyes open). By choosing the term vegetative state, they neither assumed a particular pathological lesion or physio-anatomical abnormality and thus left the door open for others to clarify the underlying pathophysiological mechanisms and develop more appropriate assessment tools.

Although there has been a considerable amount of work to further understand these conditions, the clinical assessment of vegetative state patients remains highly subjective and dependent upon the patients exhibited behaviour despite extensive reviews and the attention of multi-society work groups (Multi-Society Task Force on PVS, 1994; Royal College of Physicians, 2003). This is largely due to the fact that sufficient evidence has not yet been obtained to advocate any particular objective test, despite a pressing need to address the unacceptably high rates of misdiagnosis highlighted by clinical audits, and the growing discussion of these conditions in relation to medical, ethical and legal issues. Clinical audits have discovered a misdiagnosis rate as high as 43% (Andrews *et al*., 1996) and attributed this rate of error, in part, to the reliance upon an intact motor ability to signal an awareness of self or environment. Indeed, the behavioural presentation of patients with disorders of consciousness is often ambiguous and frequently constrained by environmental and physiological factors. This has led to concerns that some people, who retain an awareness of self or environment, are being 'warehoused', without adequate access to appropriate assessment or rehabilitation (Fins *et al*., 2007).

At present, functional magnetic resonance imaging (fMRI) represents the most promising additional source of information to inform the clinical decision-making process. A number of studies have applied novel brain imaging paradigms to identify evidence of speech processing, face perception and even volition in patients behaviourally meeting the criteria defining vegetative state (Menon *et al*., 1998; Laureys *et al*., 2000; Schiff *et al*., 2002; Boly *et al*., 2004; Owen *et al*., 2005, 2006; Coleman *et al*., 2007). These studies have raised the possibility that fMRI could be used to inform the clinical decision-making process. However, these studies have only described data from a small number of patients, many of atypical aetiology and there has been no attempt to determine whether brain imaging offers any additional diagnostic or prognostic information beyond that provided by the patient's clinical history, behavioural presentation and natural recovery pattern. Hence, there is currently limited evidence to alter international practice guidelines, such as those of the Royal College of Physicians (2003) or the Multi-Society Task Force on PVS (1994), nor convene an expert panel to form consensus statements on the use of fMRI in clinical decision making for disorders of consciousness.

In this article, the speech processing abilities of 41 patients with impaired consciousness following brain injury are described. This cohort represents the largest population of vegetative (Multi-Society Task Force on PVS, 1994; Royal College of Physicians, 2003) and minimally conscious (Giacino *et al*., 2002) patients assessed to date with functional brain imaging. Consequently, these imaging data are used to assess whether the information generated by fMRI has any impact on the patient's diagnosis and secondly whether the fMRI findings have any prognostic utility. Our observations suggest that fMRI does offer valuable additional information to inform the diagnostic decision-making process and importantly provides accurate prognostic information.

Materials and Methods

Stimuli

A speech processing paradigm, which was first described in healthy volunteers by Rodd *et al*. (2005) and later by Coleman *et al*. (2007), in 14 patients with varying degrees of impaired consciousness was employed. The stimuli consisted of two speech conditions (high-ambiguity sentences and low-ambiguity sentences), an unintelligible noise and a silence condition. Using these stimuli it was possible to assess three levels of auditory processing: (i) a low-level contrast comparing hearing conditions (sentences and signal correlated noise) versus silence; (ii) a mid-level contrast comparing speech conditions versus signal correlated noise; and (iii) a high-level contrast comparing high-ambiguity sentences versus low-ambiguity sentences.

Patients

Forty-one patients [28 male, 13 female; mean 40 (range 17–68) years of age] took part in the study; of these, 22 patients met the diagnostic criteria defining the vegetative state (Royal College of Physicians, 2003) and 19 patients met the diagnostic criteria defining the minimally conscious state (Giacino *et al*., 2002). Twelve of the patients included in this cohort have previously been reported (VS1–7 and MCS1–5, Coleman *et al*., 2007). Overall, this extended cohort included 20 vegetative patients with common aetiologies for the

condition, including nine non-traumatic (cardiac arrest) and 11 traumatic brain injuries (assault, fall and road traffic accident). Two vegetative patients had atypical aetiologies having sustained midbrain strokes. The minimally conscious cohort for this study contained 17 patients with common aetiologies for the condition, including two who had sustained non-traumatic injuries (cardiac arrest) and 15 who had sustained traumatic brain injuries (fall and road traffic accident). The minimally conscious cohort also contained two patients who had atypical aetiologies (midbrain stroke). All the patients recruited to the study were admitted to a 1-week programme of assessment, which included repeated behavioural assessments employing the Coma Recovery Scale (CRS)-Revised (Giacino *et al*., 2004), a battery of electrophysiology, including brainstem auditory evoked potentials, axial T2, proton density, haemosiderin, inversion and diffusion sensitive structural imaging. All patients were admitted from one of two specialist rehabilitation units in the UK. Prior to admission, each patient had been assessed clinically by a specialist team employing the CRS or the Sensory Modality Assessment and Rehabilitation Technique (Gill-Thwaites and Munday, 1999). Referrals to the research unit (Addenbrookes Hospital, Cambridge, UK) were made during an active period of diagnostic assessment by the referring hospital. However, depending upon when the referring hospitals had initially admitted patients for assessment, some patients were assessed by the research team beyond 12 months *post ictus*. This was the case for 13 patients who had been admitted to the referring hospitals beyond normal prognostic thresholds (range 13–122 months) having been initially transferred to palliative care institutions without undergoing specialist assessment to establish diagnosis. Table 1 summarizes the clinical and demographic characteristics of the two patient groups.

Six months following the initial assessment at the research unit, the two referring hospitals undertook the CRS or Sensory Modality Assessment and Rehabilitation Technique to characterize the subsequent behavioural profile of each patient. These assessments were both undertaken by specialist teams repeating the observations across a minimum period of five sessions. In addition to the patient's behavioural profile, the referring hospitals also provided a summary of the natural recovery history of each patient.

This study was approved by the Cambridge Research Ethics Committee, and informed written assent was obtained from the patient's appointed 'consultee', as defined by the Mental Capacity Act (2005).

Procedure

A sparse imaging technique (Hall *et al*., 1999) previously described in Coleman *et al*. (2007) was employed. The stimuli were presented to both ears using a high-fidelity auditory stimulus delivery system incorporating piezo-electric headphones inserted into sound-attenuating ear defenders (Resonance Technology). To further attenuate scanner noise, participants wore insert earplugs. DMDX software running on a Windows PC (Forster and Forster, 2003) was used to present the stimulus items.

The fMRI imaging data were acquired using a Bruker Medspec (Ettlingen, Germany) 3-Tesla magnetic resonance system with a head gradient set (Coleman *et al*., 2007) or a 3-Tesla Magnetom Trio Tim Scanner (Siemens Medical Systems, Germany) at the Wolfson Brain Imaging Centre (Addenbrookes Hospital, Cambridge, UK). Each volume consisted of 21×4 mm thick slices with an interslice gap of 1 mm; field of view, 25×25 cm; matrix size, 128×128; time to echo, 27 ms; acquisition time, 1.6 s; and actual time to repetition, 9 s, setup identically on both scanners. Acquisition was transverse-oblique, angled away from the eyes and covered all of the brain. In addition to the functional data, a 3D T_1-weighted structural sequence, with 1 mm isotropic spatial resolution was acquired for each patient [Spoiled Gradient Recalled Acquisition (SPGR) Bruker MR System; or Magnetization Prepared Rapid Gradient Echo (MPRAGE) Siemens MR System].

fMRI analysis method

The fMRI data were pre-processed and analysed using Statistical Parametric Mapping software (SPM2, Wellcome Department of Cognitive Neurology, London, UK). Pre-processing steps included within-subject realignment, and spatial smoothing using a Gaussian kernel of 12 mm. Analysis was conducted using a single General Linear Model for each patient in which each scan within each session (after excluding two initial dummy volumes) was coded for whether it followed the presentation of signal correlated noise, a low-ambiguity or a high-ambiguity sentence. Scans following a silent period were modelled implicitly as null events. Each of the three scanning runs was modelled separately within the design matrix. Additional columns encoded subject movement (as calculated from the realignment stage of pre-processing).

Low-level auditory responses were assessed by comparing the haemodynamic responses to a set of auditory stimuli (both intelligible speech and unintelligible noise) to a silent, inter-scan baseline. This contrast identifies those brain regions that process the acoustic properties of both speech and non-speech stimuli. In healthy controls, this contrast produces activation in primary auditory regions on the superior temporal plane, centred on Heschl's Gyrus (Coleman *et al*., 2007; Fig. 1). The presence of appropriate activation for this contrast confirms that some aspects of cortical auditory processing are intact.

The second contrast that was employed assessed speech-specific perceptual processing by comparing fMRI responses to intelligible speech (both high- and low-ambiguity sentences) to unintelligible noise stimuli (signal-correlated noise). This contrast identifies those brain regions that process both acoustic–phonetic, and more abstract linguistic properties of spoken language (cf. Davis and Johnsrude, 2003), but critically controls for activation due to basic auditory processes that are shared for speech and non-speech stimuli such as signal correlated noise. In healthy controls, this contrast produces extensive bilateral activation that is centred on the superior temporal sulcus (Coleman *et al*., 2007; Fig. 1) as well as a left-lateralized response in the left inferior frontal gyrus. The presence of appropriate activation for this contrast suggests that some speech-specific perceptual processing remains intact.

The third and final contrast that was employed assessed high-level semantic aspects of speech processing using sentences that were made difficult to understand by the presence of semantically ambiguous words (such as 'bark', or 'rain'/'reign'). This contrast between high- and low-ambiguity sentences identifies those brain regions involved in processing the semantic aspects of speech. In healthy controls, this contrast produces activation in the posterior portion of the left posterior inferior temporal lobe as well as the left inferior frontal gyrus. The presence of appropriate activations in this contrast provides strong evidence that some high-level semantic aspects of speech comprehension are preserved.

The power of this contrast between high- and low-ambiguity sentences is considerably weaker than the two lower level contrasts. This is mainly due to the subtle nature of the linguistic distinction between the two types of sentences, but is also affected by the smaller number of scans that are included in the contrast. To increase the statistical power in this contrast, it was therefore necessary to construct individual regions of interest for each patient based on the results from the healthy controls on this contrast (Rodd *et al*., 2005; Experiment 2).

Table 1 Summary of patients recruited to the study including aetiology and Glasgow Coma Score (GCS, Teasdale and Jennett, 1974) during a 5-day admission period at the time of fMRI investigation

Patient	Diagnosis	Age (years)	Sex	Aetiology	Time of scan *post ictus* (months)	GCS
VS1	VS	58	M	Midbrain stroke	2	E4,V1,M2
VS2	VS	65	M	Anoxic brain injury post-cardiac arrest	16	E4,V1,M3
VS3	VS	36	F	Anoxic brain injury post-cardiac arrest	108	E4,V2,M4
VS4	VS	22	M	Diffuse axonal injury and frontal contusion following a fall	7	E4,V1,M2
VS5	VS	56	F	Anoxic brain injury post-cardiac arrest	9	E4,V1,M2
VS6	VS	23	F	Diffuse axonal injury following road traffic accident	6	E4,V1,M3
VS7	VS	41	M	Brainstem stroke	4	E4,V1,M3
VS8	VS	46	M	Right subarachnoid and petechial midbrain haemorrhages following assault	2	E4,V1,M3
VS9	VS	48	F	Anoxic brain injury post-cardiac arrest	18	E4,V1,M4
VS10	VS	30	M	Right subdural haematoma and diffuse axonal injury following a fall	11	E4,V1,M4
VS11	VS	58	M	Left subdural haematoma following assault	6	E2,V1,M3
VS12	VS	50	F	Hypoxic brain injury due to aspiration following encephalitis	8	E2,V1,M3
VS13	VS	39	F	Right subdural haemorrhage following a fall	10	E2,V1,M3
VS14	VS	21	M	Left extradural haematoma and diffuse axonal injury following road traffic accident	19	E4,V1,M4
VS15	VS	41	F	Anoxic brain injury post-cardiac arrest	11	E4,V1,M4
VS16	VS	34	M	Anoxic brain injury post-cardiac arrest	10	E2,V1,M3
VS17	VS	42	F	Anoxic brain injury post-cardiac arrest	50	E2,V1,M4
VS18	VS	68	M	Diffuse axonal injury following road traffic accident	14	E2,V1,M3
VS19	VS	21	M	Left subdural haemorrhage following assault	6	E2,V1,M3
VS20	VS	45	M	Left intracerebral haemorrhage and midbrain contusions following road traffic accident	3	E2,V1,M2
VS21	VS	42	M	Anoxic brain injury post-cardiac arrest	8	E4,V1,M4
VS22	VS	49	M	Bifrontal haemorrhagic and midbrain contusions following road traffic accident	3	E2,V1,M3
MCS1	MCS	39	M	Diffuse axonal injury following a fall	122	E4,V2,M4
MCS2	MCS	41	M	Diffuse axonal injury and frontal contusion following road traffic accident	49	E4,V1,M3
MCS3	MCS	36	M	Diffuse axonal injury following a road traffic accident	7	E4,V2,M4
MCS4	MCS	67	M	Brainstem stroke	8	E4,V1,M3
MCS5	MCS	54	F	Brainstem stroke	5	E4,V1,M4
MCS6	MCS	21	M	Right subarachnoid haemorrhage and diffuse axonal injury following road traffic accident	51	E4,V1,M5
MCS7	MCS	17	M	Left frontal lobe contusion and diffuse axonal injury following road traffic accident	7	E4,V2,M4
MCS8	MCS	26	M	Diffuse axonal injury following road traffic accident	11	E4,V1,M5
MCS9	MCS	65	M	Left subarachnoid bleed following a fall	6	E4,V1,M4
MCS10	MCS	54	F	Anoxic brain injury post-cardiac arrest	13	E4,V1,M4
MCS11	MCS	29	F	Diffuse axonal injury following road traffic accident	2	E4,V1,M4
MCS12	MCS	32	M	Bifrontal and midbrain contusions following road traffic accident	52	E4,V1,M5
MCS13	MCS	36	F	Left frontal and bilateral haemorrhagic contusions following road traffic accident	3	E4,V1,M4
MCS14	MCS	19	F	Diffuse axonal injury following road traffic accident	2	E4,V1,M4
MCS15	MCS	19	M	Bifrontal and midbrain contusions following road traffic accident	8	E4,V1,M5
MCS16	MCS	57	M	Anoxic brain injury post-cardiac arrest	6	E4,V2,M4
MCS17	MCS	26	M	Right subarachnoid haemorrhage and midbrain contusions following road traffic accident	8	E4,V1,M5
MCS18	MCS	24	M	Diffuse axonal injury following road traffic accident	11	E4,V2,M4
MCS19	MCS	37	M	Left parietal subdural haematoma and diffuse haemorrhages following road traffic accident	30	E4,V1,M4

VS1–22 indicates vegetative patients recruited to study. MCS1–19 indicates minimally conscious patients recruited to the study.
VS = vegetative state; MCS = minimally conscious state.

This was achieved by thresholding the results of the random effects group analysis of the control data (Rodd *et al*., 2005) at a threshold of $P<0.01$ (uncorrected) and creating mask images of the two large clusters of activation in the left frontal lobe and the left posterior temporal lobe (Coleman *et al*., 2007; Fig. 2). The structural scan of each patient was then co-registered to the patient's functional images, and then normalized to a standard T_1-weighted template using the segmentation procedure implemented in SPM 5 (Wellcome Department of Cognitive Neurology, London, UK). The inverse of these normalization parameters was then used to warp the region of interest masks onto the unnormalized structural image for that patient. For each patient, the activation for the semantic ambiguity contrast

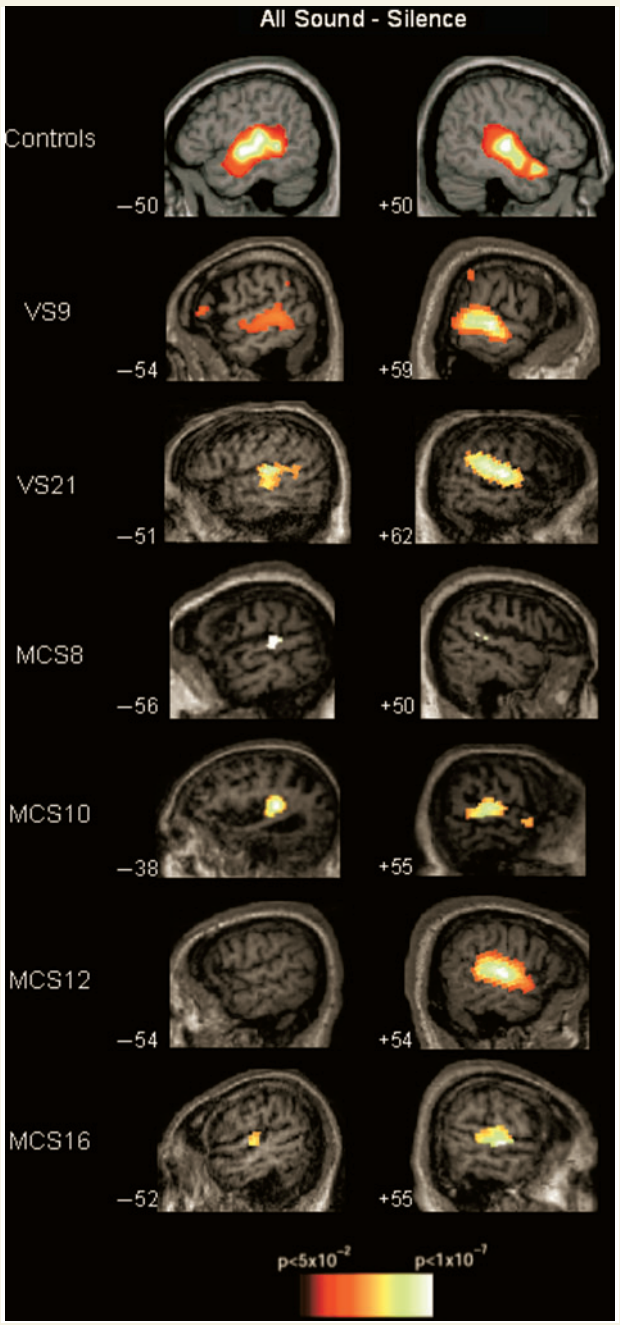

Figure 1 Low-level auditory contrast results for six patients diagnosed as either vegetative state (VS) or minimally conscious state (MCS). Activations are thresholded at $P<0.05$ false discovery rate corrected for multiple comparisons and shown on slices where the peak activation was observed.

within each region of interest was then averaged for each scan and the significance of this difference was assessed using the MarsBar software (Brett *et al*., 2002).

Behavioural assessment of patients

All patients recruited to the study underwent a 5-day behavioural assessment employing the CRS at the time of brain imaging. The referring unit then repeated the behavioural assessment 6 months later over a minimum of five sessions. Table 2 summarizes their average responses on this scale at both time points (follow-up CRS denoted in brackets).

Pre-fMRI auditory screening

All patients recruited to the study underwent electrophysiological assessment of the auditory pathway prior to fMRI. All patients demonstrated preserved responses from the eighth cranial nerve, pons and midbrain on a standard short-latency auditory evoked potential paradigm (American Neurophysiology Society, 2006). Onset latencies were within the normal range.

fMRI results

In all cases (except where stated), we applied a statistical threshold of $P<0.05$ corrected for multiple comparisons using the false discovery rate procedure (Genovese *et al*., 2002). This is an adaptive procedure that provides an appropriate combination of sensitivity to detect what we anticipate to be extensive patterns of activation for patients with intact auditory and speech processing, while also providing stringent control of false positives where fMRI responses are absent. For each of the 41 patients, three contrasts were analysed: all sound versus silence, speech versus unintelligible noise and high-ambiguity speech versus low-ambiguity speech. On the basis of the results of these contrasts, the patients were divided into three groups.

Group 1: patients who showed significant responses to sound only

Six of the patients who had been diagnosed as either vegetative or minimally conscious showed significant temporal lobe responses in the low-level auditory contrast (VS9, VS21, MCS8, MCS10, MCS12 and MCS16; FDR <0.05; Fig. 1), but did not show significant responses in the mid-level speech perception contrast (meaningful speech versus signal correlated noise) at a corrected false discovery rate $P<0.05$ threshold. However, five of these patients (VS9, VS21, MCS 8, MCS12 and MCS16) did show some anatomically appropriate clusters of activation for this speech–noise contrast in the left and/or right superior temporal lobe at an uncorrected $P<0.01$ threshold. Interestingly, all of these patients produced substantial movement of their head during the scanning runs (displacements of up to 14 mm). Although correction for head motion is a routine part of fMRI pre-processing, such head movement is well-known to introduce substantial task-irrelevant noise into fMRI time series, reducing the power of statistical analyses.

Group 2: patients who showed significant responses to both sound and speech

Nineteen of the patients (VS1, VS6, VS7, VS8, VS11, VS19, VS20, MCS2, MCS5, MCS6, MCS7, MCS9, MCS11, MCS13, MCS14, MCS15, MCS17, MCS18 and MCS19) who had been diagnosed as either vegetative or minimally conscious showed significant temporal lobe responses in the low-level auditory contrast and in the mid-level speech perception contrast (meaningful speech versus signal correlated noise, Fig. 2).

Within this set of patients there was some variation in the extent of these neural responses to speech stimuli. Some patients showed

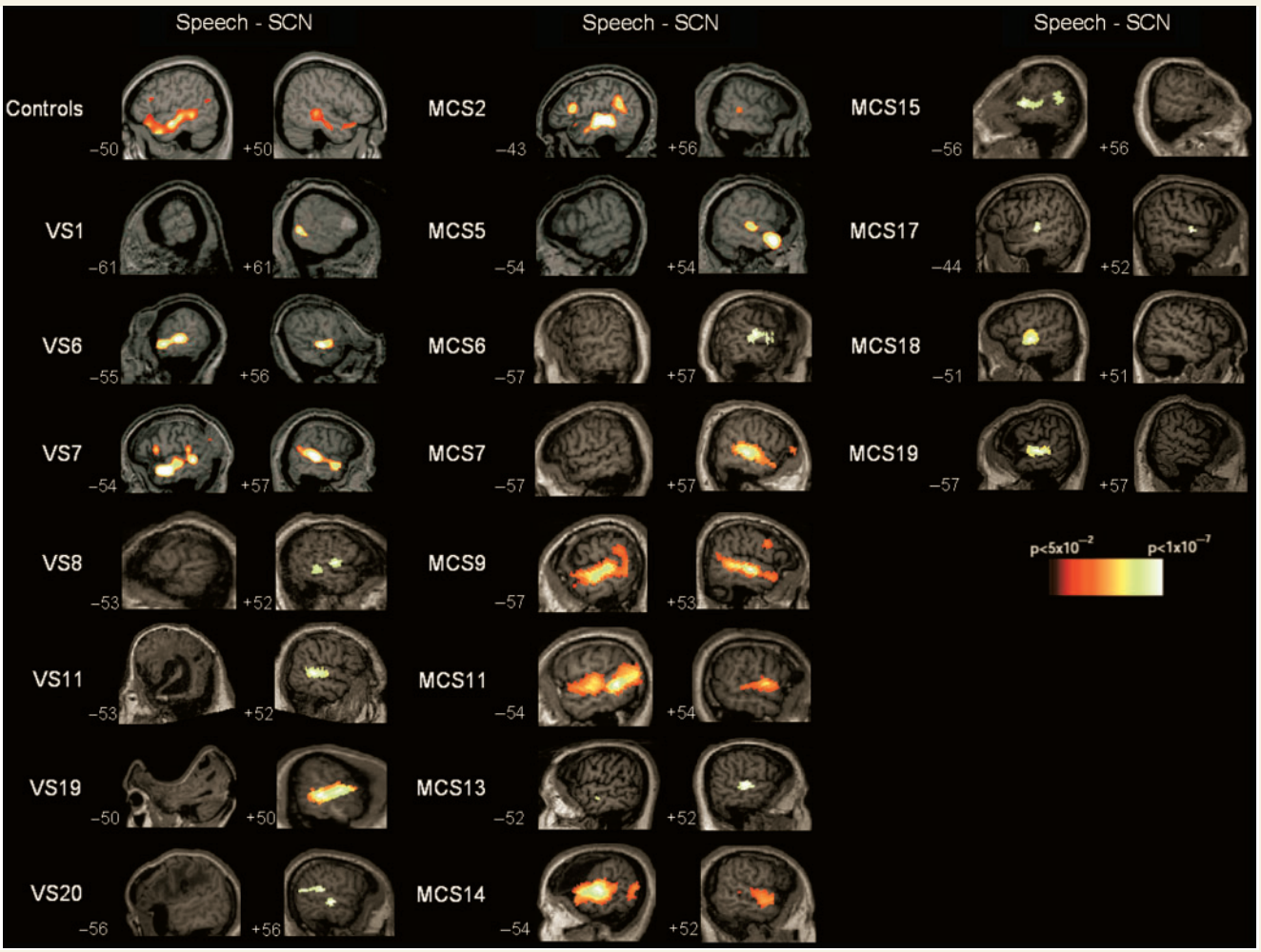

Figure 2 Mid-level speech contrast results for 19 patients diagnosed as either vegetative state (VS) or minimally conscious (MCS). Activations are thresholded at $P<0.05$ false discovery rate corrected for multiple comparisons and shown on slices where the peak activation was observed.

temporal lobe responses that were very similar to the control subjects with extensive, bilateral superior temporal activation (VS6, VS7, VS20, MCS9, MCS11 and MCS14), whereas for other patients the activation was extensive only in one hemisphere (MCS2, MCS13, MCS15, MCS17, MCS18 and MCS19 left hemisphere; VS8, VS11, VS19, MCS5, MCS6 and MCS7 right hemisphere), or was restricted to the posterior portions of the temporal lobes (VS1).

For the high-level semantic ambiguity contrast, four patients provided some evidence of intact semantic processing. The whole-brain analysis for VS6, VS7, MCS2 and MCS9 showed an ambiguity effect that just failed to reach statistical significance ($P<0.1$ FDR) within the left inferior frontal gyrus, while the more sensitive region of interest procedure revealed significant increases in activity for the semantically ambiguous sentences in VS7 and MCS2. VS7 showed a significant effect in the temporal lobe region of interest ($P<0.01$) but not in the frontal lobe ($P>0.5$), while MCS2 showed a significant effect in the left inferior frontal gyrus region of interest ($P<0.05$), but not in the temporal lobe ($P<0.1$). Although VS6 and MCS9 showed activation for high-ambiguity sentences at the whole brain level, their patterns of activation overlapped only partially with the regions of interest and did not produce a significant effect ($P>0.5$). In both cases, we suggest that the method used to create the region of interest has been affected by the distortion of the brain in comparison to the control brain.

Group 3: no significant auditory responses

Sixteen of the patients showed no significant activation in the low-level auditory contrast (sound versus silence; all false discovery rate corrected $P>0.6$). Thirteen of these patients had a diagnosis of vegetative state (VS2, VS3, VS4, VS5, VS10, VS12, VS13, VS14, VS15, VS16, VS17, VS18 and VS22), while three had a diagnosis of minimally conscious (MCS1, MCS3 and MCS4). In six cases (VS2, VS3, VS5, VS10, VS13 and MCS4) when the statistical threshold was substantially reduced to $P<0.01$ uncorrected, there was still no evidence of appropriate auditory activations. In 10 cases (VS4, VS12, VS14, VS15, VS16, VS17, VS18, VS22, MCS1 and MCS3), although no activation approached the corrected significance level, anatomically appropriate clusters of activation were observed below threshold. In five of these patients (VS4, VS15, VS16, MCS1 and MCS3), some activity confined to the left superior temporal lobe at the reduced

Table 2 Highest CRS scores for VS and MCS patient groups during the initial 5-day assessment period at the time of fMRI investigation

Patient	Auditory function	Visual function	Motor function	Oromotor/verbal function	Communication	Arousal	Total score
VS1	1-Auditory startle (2)	1-Visual startle (3)	1-Abnormal posturing (2)	1-Oral reflex movement (2)	0-None (0)	2-Eye opening w/o stimulation (2)	6 (11)
VS2	1-Auditory startle (1)	1-Visual startle (1)	2-Flexion withdrawal (2)	1-Oral reflex movement (1)	0-None (0)	2-Eye opening w/o stimulation (2)	7 (7)
VS3	1-Auditory startle (1)	1-Visual startle (1)	2-Flexion withdrawal (2)	1-Oral reflex movement (1)	0-None (0)	2-Eye opening w/o stimulation (2)	7 (7)
VS4	1-Auditory startle (1)	0-None (0)	2-Flexion withdrawal (2)	1-Oral reflex movement (1)	0-None (0)	2-Eye opening w/o stimulation (2)	6 (6)
VS5	1-Auditory startle (1)	0-None (0)	2-Flexion withdrawal (2)	1-Oral reflex movement (1)	0-None (0)	2-Eye opening w/o stimulation (2)	6 (6)
VS6	1-Auditory startle (3)	1-Visual startle (5)	2-Flexion withdrawal (5)	1-Oral reflex movement (1)	0-None (0)	2-Eye opening w/o stimulation (3)	7 (17)
VS7	1-Auditory startle (3)	1-Visual startle (3)	2-Flexion withdrawal (3)	1-Oral reflex movement (1)	0-None (0)	2-Eye opening w/o stimulation (3)	7 (13)
VS8	1-Auditory startle (3)	1-Visual startle (4)	1-Abnormal posturing (3)	1-Oral reflex movement (1)	0-None (0)	2-Eye opening w/o stimulation (2)	6 (13)
VS9	1-Auditory startle (1)	1-Visual startle (1)	2-Flexion withdrawal (2)	1-Oral reflex movement (1)	0-None (1)	2-Eye opening w/o stimulation (2)	7 (7)
VS10	2-Localization to sound (2)	1-Visual startle (3)	2-Flexion withdrawal (3)	1-Oral reflex movement (1)	0-None (0)	2-Eye opening w/o stimulation (2)	8 (11)
VS11	2-Localization to sound (2)	1-Visual startle (4)	2-Flexion withdrawal (4)	1-Oral reflex movement (2)	0-None (0)	1-Eye opening with stimulation (2)	7 (14)
VS12	1-Auditory startle (1)	1-Visual startle (1)	2-Flexion withdrawal (2)	1-Oral reflex movement (1)	0-None (0)	2-Eye opening w/o stimulation (2)	7 (7)
VS13	1-Auditory startle (1)	0-None (0)	2-Flexion withdrawal (2)	1-Oral reflex movement (1)	0-None (0)	1-Eye opening with stimulation (1)	5 (5)
VS14	2-Localization to sound (1)	1-Visual startle (3)	2-Flexion withdrawal (2)	1-Oral reflex movement (1)	0-None (0)	2-Eye opening w/o stimulation (2)	8 (9)
VS15	1-Auditory startle (2)	1-Visual startle (1)	2-Flexion withdrawal (2)	2-Vocalization/oral movement (1)	0-None (0)	2-Eye opening w/o stimulation (2)	8 (8)
VS16	1-Auditory startle (2)	1-Visual startle (0)	2-Flexion withdrawal (2)	1-Oral reflex movement (1)	0-None (0)	1-Eye opening with stimulation (1)	6 (6)
VS17	1-Auditory startle (1)	1-Visual startle (1)	2-Flexion withdrawal (2)	1-Oral reflex movement (1)	0-None (0)	2-Eye opening w/o stimulation (2)	7 (7)
VS18	0-None (1)	1-Visual startle (1)	2-Flexion withdrawal (2)	1-Oral reflex movement (1)	0-None (0)	1-Eye opening with stimulation (1)	5 (6)
VS19	1-Auditory startle (3)	1-Visual startle (3)	2-Flexion withdrawal (3)	1-Oral reflex movement (1)	0-None (1)	1-Eye opening with stimulation (2)	6 (13)
VS20	1-Auditory startle (2)	0-None (3)	1-Abnormal posturing (2)	0-None (2)	0-None (0)	1-Eye opening with stimulation (2)	3 (11)
VS21	1-Auditory startle (1)	1-Visual startle (1)	2-Flexion withdrawal (2)	2-Vocalization/oral movement (2)	0-None (0)	2-Eye opening w/o stimulation (2)	8 (8)
VS22	1-Auditory startle (1)	1-Visual startle (1)	2-Flexion withdrawal (2)	1-Oral reflex movement (1)	0-None (0)	1-Eye opening with stimulation (1)	6 (6)
MCS1	3-Reproducible movement to command (2)	3-Pursuit eye movements (3)	2-Flexion withdrawal (2)	2-Vocalization/oral movement (2)	0-None (0)	2-Eye opening w/o stimulation (2)	12 (11)
MCS2	3-Reproducible movement to command (3)	3-Pursuit eye movements (5)	2-Flexion withdrawal (2)	2-Vocalization/oral movement (1)	0-None (0)	2-Eye opening w/o stimulation (2)	12 (13)
MCS3	2-Localization to sound	3-Pursuit eye movements	2-Flexion withdrawal	1-Oral reflex movement	0-None	2-Eye opening w/o stimulation	10 (D)
MCS4	2-Localization to sound (2)	2-Fixation (3)	2-Flexion withdrawal (2)	1-Oral reflex movement (1)	0-None (0)	2-Eye opening w/o stimulation (2)	9 (10)
MCS5	3-Reproducible movement to command (3)	3-Pursuit eye movements (4)	2-Flexion withdrawal (2)	1-Oral reflex movement (1)	0-None (0)	2-Eye opening w/o stimulation (2)	11 (12)
MCS6	2-Localization to sound	3-Pursuit eye movements	3-Localization to noxious stimulation	2-Vocalization/oral movement	0-None	2-Eye opening w/o stimulation	12 (D)
MCS7	3-Reproducible movement to command (3)	3-Pursuit eye movements (4)	2-Flexion withdrawal (3)	2-Vocalization/oral movement (2)	0-None (0)	2-Eye opening w/o stimulation (2)	12 (14)
MCS8	2-Localization to sound	3-Pursuit eye movements	3-Localization to noxious stimulation	1-Oral reflex movement	0-None	2-Eye opening w/o stimulation	11 (D)
MCS9	1-Auditory startle (3)	3-Pursuit eye movements (3)	2-Flexion withdrawal (3)	1-Oral reflex movement (1)	0-None (0)	2-Eye opening w/o stimulation (2)	9 (12)
MCS10	3-Reproducible movement to command (3)	2-Fixation (2)	2-Flexion withdrawal (2)	2-Vocalization/oral movement (2)	0-None (0)	2-Eye opening w/o stimulation (2)	11 (11)
MCS11	1-Auditory startle (2)	3-Pursuit eye movements (4)	2-Flexion withdrawal (4)	0-None (1)	0-None (0)	2-Eye opening w/o stimulation (2)	8 (13)

(continued)

Table 2. Continued

Patient	Auditory function	Visual function	Motor function	Oromotor/verbal function	Communication	Arousal	Total score
MCS12	2-Localization to sound (1)	3-Pursuit eye movements (1)	3-Localization to noxious stimulation (2)	1-Oral reflex movement (1)	0-None (0)	2-Eye opening w/o stimulation (2)	11 (7)
MCS13	1-Auditory startle (3)	3-Pursuit eye movements (4)	2-Flexion withdrawal (4)	1-Oral reflex movement (2)	0-None (0)	2-Eye opening w/o stimulation (2)	9 (15)
MCS14	2-Localization to sound (3)	3-Pursuit eye movements (4)	2-Flexion withdrawal (4)	1-Oral reflex movement (1)	0-None (0)	2-Eye opening w/o stimulation (2)	10 (14)
MCS15	1-Auditory startle (1)	3-Pursuit eye movements (3)	4-Object manipulation (4)	1-Oral reflex movement (1)	0-None (0)	2-Eye opening w/o stimulation (2)	11 (11)
MCS16	3-Reproducible movement to command (3)	3-Pursuit eye movements (3)	2-Flexion withdrawal (2)	2-Vocalization/oral movement (2)	1-Non functional: intentional (1)	2-Eye opening w/o stimulation (2)	13 (13)
MCS17	2-Localization to sound (3)	3-Pursuit eye movements (4)	3-Localization to noxious stimulation (3)	1-Oral reflex movement (1)	0-None (0)	2-Eye opening w/o stimulation (2)	11 (13)
MCS18	3-Reproducible movement to command (4)	3-Pursuit eye movements (4)	2-Flexion withdrawal (4)	1-Oral reflex movement (1)	1-Non-functional: intentional (1)	2-Eye opening w/o stimulation (2)	12 (16)
MCS19	2-Localization to sound (2)	3-Pursuit eye movements (3)	2-Flexion withdrawal (2)	2-Vocalization/oral movement (2)	0-None (0)	2-Eye opening w/o stimulation (2)	11 (11)

CRS scores in brackets indicate those obtained 6 months later during follow-up assessment, which took place over a minimum of five sessions.
VS = vegetative state; MCS = minimally conscious state.

threshold of $P<0.01$ (uncorrected) was detected. In four of these patients (VS12, VS14, VS17 and VS18), an anatomically appropriate cluster of activation was detected confined to the right superior temporal lobe at the reduced threshold of $P<0.01$ (uncorrected). Finally, in one patient (VS22), anatomically appropriate activation in the left and right superior temporal lobe was observed at a $P<0.01$ (uncorrected) threshold. This suggests that although these patients may be able to perform some low-level auditory processing, neural responses are either too weak or too variable to be statistically reliable. All of these patients failed to show significant activation in the speech–noise contrast (all $P>0.15$ false discovery rate corrected).

Correspondence between brain imaging results and clinical diagnosis

At the time of investigation, the referring hospitals felt that 22 of the referred patients met the criteria defining vegetative state, having already undertaken extensive clinical examinations of these patients in accordance with the Royal College of Physician Guidelines (2003). The referring hospitals felt that a further 19 patients met the criteria defining the minimally conscious state, having also undergone extensive clinical examination to reveal behaviours consistent with the Aspen workgroup definition (Giacino *et al*., 2002). In the clinically diagnosed vegetative state group, two patients (VS6 and VS7) demonstrated high-level semantic ambiguity contrast activations, which by definition were inconsistent with the definition of vegetative state, and their behavioural presentation as indicated by the CRS score. The presence of appropriate activations in this contrast provides strong evidence that some aspects of speech comprehension, and thus, higher order function, are preserved despite absent behavioural markers.

Correspondence between level of auditory processing on fMRI and behavioural score at 6 months

The Spearman rank correlation coefficient was used to examine the extent to which the level of auditory processing exhibited on fMRI by each patient was associated with the behavioural presentation of the patient at (i) the time of investigation and (ii) 6 months following investigation. Each patient's level of auditory processing was ranked as a numeric score (1 = no response to sound; 2 = low-level response to sound only; 3 = mid-level response to speech stimuli; and 4 = high-level response to semantic aspects of speech). This was compared with the CRS score acquired at the time of investigation and at 6 months post-investigation. Prior to follow-up assessment at 6 months post-fMRI, three patients had died due to chest infections (MCS3, MCS6 and MCS8), and these patients were subsequently removed from the analysis. In the remaining patient group ($n=38$), the analysis revealed a strong association between the level of auditory processing demonstrated on fMRI and the patient's 6-month CRS score (Fig. 3; $r_s=0.81$, $P<0.001$). Indeed, of the eight vegetative patients who showed behavioural CRS scores consistent with emergence to a minimally conscious state at 6 months post-scan, all but one (VS10) had, 6 months earlier, shown a high level of auditory processing during fMRI (mid-level response to speech stimuli or high-level response to semantic aspects of speech). Interestingly, at the time of scanning the association between each patient's fMRI performance and CRS score just failed to reach the significance ($r_s=0.3$, $P=0.06$).

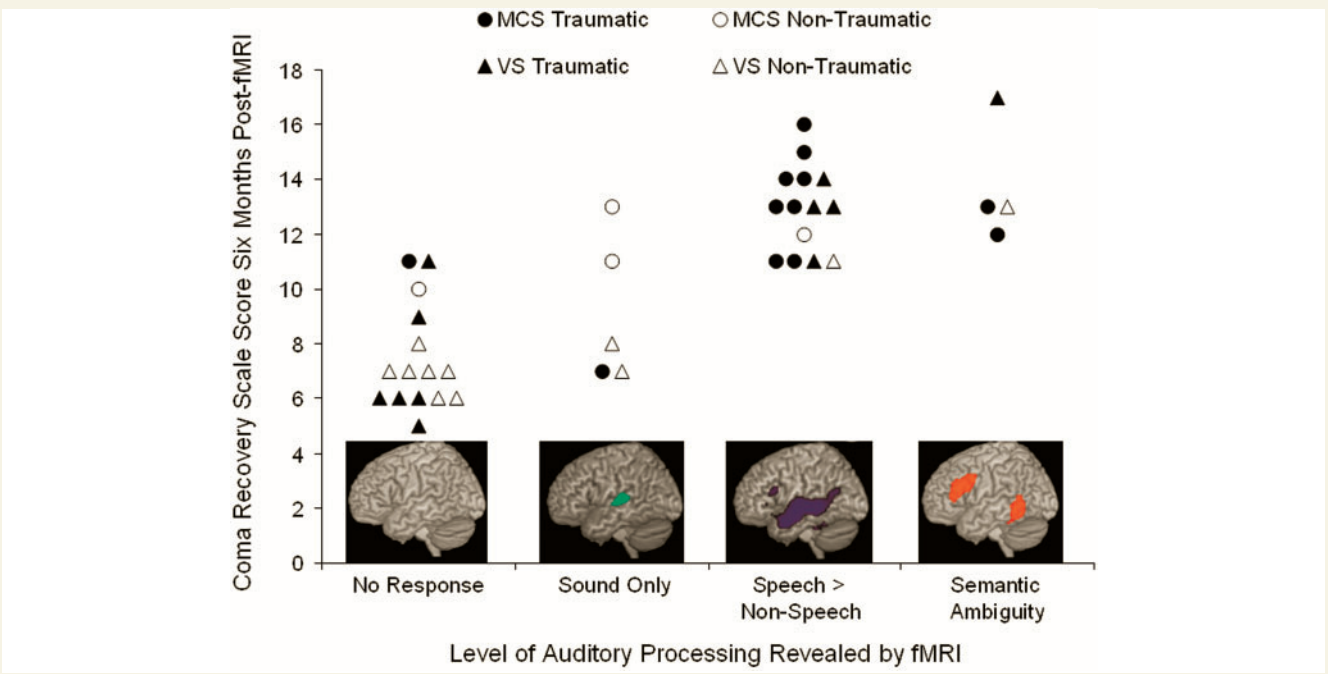

Figure 3 Level of auditory processing achieved by each patient grouped by diagnosis and aetiology during fMRI, plotted against their 6-month highest CRS score. Images at the bottom show left hemisphere activation for each level of auditory processing from groups of healthy participants in previous control studies. Responses to sound only depict the contrast of non-speech noise compared with silence from Davis and Johnsrude (2003). Responses to speech versus non-speech and high versus low ambiguity are reported from Rodd *et al*. (2005).

Within each diagnostic group, the association between the level of auditory processing demonstrated on fMRI and 6-month CRS score was maintained: vegetative group, $n = 22$; $r_s = 0.8$; $P < 0.001$; minimally conscious group, $n = 16$; $r_s = 0.5$; $P = 0.02$. Comparison between the level of auditory processing demonstrated on fMRI and CRS score at the time of investigation showed no association in either groups (vegetative state $r_s = -0.07$, $P = 0.38$; minimally conscious state $r_s = -0.15$, $P = 0.29$).

When patients were grouped according to aetiology, regardless of clinical diagnosis, the association between the level of auditory processing achieved on fMRI and 6-month CRS score was $r_s = 0.76$, $P < 0.001$ for non-traumatic injuries and $r_s = 0.74$, $P < 0.001$ for traumatic injuries. In both the groups, the association between fMRI activation and CRS score at the time of scan was not statistically significant (non-traumatic $r_s = 0.24$, $P = 0.2$; traumatic $r_s = 0.3$, $P = 0.08$).

Discussion

In this study, the level of auditory processing, revealed by fMRI, in 22 vegetative state and 19 minimally conscious state patients was compared with their bedside clinical diagnosis and 6-month outcome. A range of activation patterns were seen: while some patients did not show any significant responses to the auditory stimuli, others, including patients clinically diagnosed as being in a vegetative state, showed significant auditory, speech perception and semantic responses that were anatomically appropriate and comparable with the results observed in healthy volunteers (Rodd *et al*., 2005). The level of auditory processing revealed by fMRI was not statistically associated with each patient's clinical diagnosis at the time of scan, with two vegetative patients showing aspects of speech comprehension, despite absent behavioural markers. However, this study notably found that the level of auditory processing revealed by fMRI was strongly correlated with each patient's 6-month outcome, confirming Di *et al*. (2008) earlier prediction that fMRI might offer important prognostic information. Indeed, it was found that of eight vegetative state patients who demonstrated behaviours consistent with emergence to the minimally conscious state 6 months post-scan, seven of these patients had shown high-level responses to speech during fMRI. Furthermore, no false positives were acquired—all vegetative patients who demonstrated high-level speech responses had subsequently progressed to a minimally conscious state 6-month's post-investigation.

Diagnosis

Although only two patients referred to this study with a clinical diagnosis of vegetative state were found to harbour covert aspects of higher order function when assessed by fMRI, this number is not insignificant, especially when one considers that all the patients referred to this study were already undergoing assessments at specialist rehabilitation centres. In contrast to patients referred from non-specialist centres, where you might expect to find a number of cases of misdiagnosis (even via behavioural assessment), the patients entered into this study had been assessed over a prolonged period of time using appropriate tools

such as the Sensory Modality Assessment and Rehabilitation Technique (Gill-Thwaites and Munday, 1999) and the CRS-Revised (Giacino *et al*., 2004), suggesting that even specialist teams employing appropriate behavioural tools can sometimes fail to detect evidence of higher order function. Hence, this study reiterates the conclusions of many fMRI studies—namely, appropriately designed fMRI paradigms may provide additional information to inform the clinical diagnostic decision-making process that is not available from standard bedside behavioural assessments (Owen *et al*., 2005, 2006).

The fMRI paradigm employed here clearly provides a source of additional information to the clinical team. We now ask whether this information would be sufficient to change the patient's diagnosis. In this study, two vegetative state patients demonstrated a distributed pattern of cortical activation consistent with healthy volunteers processing semantic aspects of speech. This level of activation implies a degree of speech comprehension and is theoretically inconsistent with the criteria defining the vegetative state (Royal College of Physicians, 2003). Two lines of argument would suggest that this is insufficient evidence to change the patient's diagnosis: (i) the pattern of activation could be automatic, requiring no conscious input from the patient and (ii) the two vegetative state patients who demonstrated this activity did so within prognostic thresholds (i.e. before the 12 months post-traumatic brain injury threshold for prognostic decisions), subsequently demonstrating behaviours consistent with the minimally conscious state within 6 months of scan. In relation to the first argument, it is true that such patterns of activation could be automatic and hence not imply consciousness. In relation to the fMRI speech processing paradigm described in this study, the work of Davis *et al*. (2007) provides encouraging evidence, that in healthy participants sedated with Propofol, activation patterns do show systematic changes associated with different levels of awareness. Davis and colleagues used the fMRI paradigm described in this study to measure the speech processing abilities of 12 healthy volunteers in three conditions: awake, lightly sedated (a slowed response to conversation) and deeply sedated (no conversational response, rousable by loud command). Whilst temporal lobe activation to sound and speech were maintained across all three states, the response to high-level semantic aspects of speech was only observed in the awake condition. This might imply that those patients showing a high-level response to speech are also likely to show evidence of awareness. However, further investigation using paradigms that require the patient to actively respond (see Owen *et al*., 2006) would provide stronger evidence from which to reject a diagnosis of vegetative state. Indeed, we have recently proposed a hierarchical protocol of fMRI investigation whereby successful activation to semantic aspects of speech creates the impetus for further investigation requiring the patient to demonstrate evidence of volition (Owen and Coleman, 2008).

In relation to whether the fMRI evidence obtained for the two vegetative state patients in this study changed their diagnosis, the answer depends upon when one considers the diagnosis to have been made. In routine practice, patients undergo formal assessment once they have fulfilled a number of criteria (Royal College of Physician Guidelines, 2003), which includes ensuring that they are medically stable. This assessment process may start at slightly different times, but typically occurs within the first 12 months following the injury. When this assessment is undertaken using the Sensory Modality Assessment and Rehabilitation Technique (Gill-Thwaites and Munday, 1999), it typically lasts a minimum of 10 weeks. Over this period, the clinical team accumulate a detailed impression of the patient, which usually results in formulating a diagnosis. Although this may alter depending on the natural recovery pattern of the patient, the clinical team meet the patient's family at the end of this period of assessment to convey their findings. Hence, one could argue that where fMRI findings demonstrating retained aspects of speech comprehension have been acquired during this formal process, the clinical team would take this into consideration and possibly change their diagnosis. This would clearly depend on the strength of information and clearly benefit from additional evidence from higher level paradigms such as the volition task described by Owen *et al*. (2006).

Prognosis

The most important finding from this study, however, is that the higher the level of speech processing demonstrated by a patient during fMRI investigation, the more likely they are to demonstrate an improvement in their behavioural profile 6 months post-investigation. Whilst this prognostic utility is maintained in both vegetative and minimally conscious state groups, particular attention should be drawn to the finding that of the eight vegetative state patients in this study who subsequently progressed to a minimally conscious state, seven of these had shown a speech-specific or semantic response to sentence stimuli 6 months earlier during fMRI. Although these findings indicate that fMRI may fail to identify all the patients who might subsequently show signs of recovery, notably in this study, there were no false positives—none of the vegetative state patients who demonstrated a response to aspects of speech during fMRI failed to demonstrate a behavioural profile consistent with the minimally conscious state 6 months post-investigation. Therefore, this finding suggests that the fMRI paradigm employed here may provide beneficial prognostic information to the clinical team. In this study, all the recruited patients underwent specific programmes of sensory stimulation at their respective rehabilitation centres. However, each programme of intervention was dictated by the results of the patient's behavioural assessment and it is unclear what effect the patient's fMRI results might have had on their treatment—for instance, treatment blocks attempting to establish a motor output to verbal command. Whilst there is evidence that commencing therapeutic interventions early can promote recovery (Mackay *et al*., 1992), further investigation is clearly warranted to determine whether treatment blocks initiated by fMRI findings have any additional effect on recovery patterns. Further investigation is also required to determine what effect (if any) the presence of aspects of speech processing might have on the attitudes and motivations of families and carers. In this study, there would appear to be strong support for the care team indicating that some degree of recovery could be expected in the following 6-month period, but this information needs to be put in context and expressed carefully.

Limitations and a word of caution

Despite these positive findings, the use of fMRI has many limitations and one needs to be careful when presenting this information to families and carers. In particular, we advise that clinicians stress the limitations of how much can be inferred from fMRI results. As we have argued previously (Coleman *et al*., 2007; Owen and Coleman, 2007), only positive findings can be interpreted and an absent response does not suggest that the same patient, at another time, might not respond to the same task. Indeed, as highlighted in the results of those patients classified in Group 1 (significant response to sound only), patients producing substantial head motion raise significant methodological challenges and further work is required to control for motion before these techniques can be used outside of specialist centres. In this study, five patients showed some anatomically appropriate clusters of activation for the speech–noise contrast (Level 2 auditory processing) at an uncorrected $P<0.01$ threshold. Whilst these could be false positives created by head motion, clinically one would have to look to additional sources of information to resolve the possibility that these could be genuine clusters of activity. To address this issue, all patients recruited to this study were investigated clinically using a multimodal approach, which combined behavioural assessments with those of electrophysiology and brain imaging. In each modality, a series of hierarchical paradigms are employed, which enable the clinical team to substantiate their clinical impression from multiple sources. Although fMRI represents a powerful technique for assessing brain function, cognitive event-related potentials have also been shown to offer valuable information, detecting evidence of residual cognitive function, which should be utilized to resolve such dilemmas where they occur (Kotchoubey *et al*., 2005; Machado *et al*., 2007; Schnakers *et al*., 2008). It is also important to stress that unless a patient has reproducibly responded to command through mental imagery or another form of mental activity indicating volition, we cannot say unequivocally that they retain an awareness of self or environment. Accumulating fMRI and electrophysiological evidence clearly suggests that some patients with behavioural patterns consistent with vegetative state retain aspects of cognitive function (Schiff *et al*., 2002; Boly *et al*., 2004; Kotchoubey *et al*., 2005; Owen *et al*., 2005, 2006; Coleman *et al*., 2007; Di *et al*., 2007; Machado *et al*., 2007; Schnakers *et al*., 2008), but in many cases the responses observed could be automatic, not requiring the patient to be consciously aware of themselves or the stimuli.

Towards the routine use of fMRI in the diagnostic decision-making process

In this study, we have presented encouraging evidence, from a large group of patients, that fMRI can inform the diagnostic decision making process and most notably offer valuable prognostic information. This new information marks a substantial addition to a growing body of literature documenting the utility of brain imaging with this patient group (see Owen and Coleman, 2007 for a review). However, before consensus statements can be made regarding the use of fMRI in clinical decision making for disorders of consciousness, there needs to be a coordinated effort to validate a series of standardized paradigms that can be used outside of the research unit. Indeed, many of the paradigms employed to date, including the one described in this study, do not provide all the information and reassurance required by the clinical team. Work is required to develop a standardized hierarchal series of paradigms that help the clinical team to resolve the many dilemmas they face when assessing patients with disorders of consciousness. When this is achieved it is likely that we will see a considerable fall in the level of misdiagnosis.

Acknowledgements

The authors are grateful to the staff of the Wolfson Brain Imaging Centre and Wellcome Trust Clinical Research Facility at Addenbrookes Hospital, Cambridge. We also thank Sue Joyce (RGN), Joanne Outtrim (RGN), Dot Chatfield (RGN) and Prof. David Menon for their assistance.

Funding

This work was supported by the National Institute for Health Research Biomedical Research Centre at Cambridge, the UK Department of Health Technology Platform, in addition to project grants from the Medical Research Council and the McDonnell Foundation.

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