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Do vegetative patients retain aspects of language comprehension? Evidence from fMRI

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A diagnosis of vegetative state is made if a patient demonstrates no evidence of awareness of self or environment, no evidence of sustained, reproducible, purposeful or voluntary behavioural response to sensory stimuli and critically no evidence of language comprehension. For those patients who retain peripheral motor function, rigorous behavioural assessment is usually able to determine retained function. However, some patients do not retain the ability to respond overtly to command and it is becoming increasingly accepted that assessment of these patients should include techniques, which do not rely on any 'motor action' on the part of the patient. Here, we apply a hierarchical functional magnetic resonance imaging (fMRI) auditory processing paradigm to determine the extent of retained language processing in a group of 14 aetiologically heterogeneous patients who met the diagnostic criteria for either the vegetative state ($n = 7$), the minimally conscious state ($n = 5$), or who were in a severely disabled condition having emerged from a minimally conscious state ($n = 2$). Three different levels of speech processing were assessed: (i) Low-level auditory responses were measured using a contrast between a set of auditory stimuli and a silence baseline; (ii) mid-level speech perception processing abilities were assessed by comparing intelligible speech to unintelligible noise stimuli and (iii) high-level semantic aspects of speech processing were assessed by comparing sentences that were made difficult to understand by the presence of words that were semantically ambiguous compared to matched low-ambiguity sentences. As expected the two severely disabled, but conscious patients showed preserved speech processing at all three levels. However, contrary to the diagnostic criteria defining the vegetative state, three patients (1 traumatic, 2 non-traumatic aetiology) demonstrated some evidence of preserved speech processing. The remaining four patients (1 traumatic, 3 non-traumatic aetiology) with a diagnosis of vegetative state showed no significant activation in response to sound compared with silence. These results provide further evidence that a subset of patients fulfilling the behavioural criteria for the vegetative state retain islands of preserved cognitive function.

Introduction

Detecting the residual cognitive function of patients with impaired consciousness following brain injury is notoriously difficult. At present a diagnosis of vegetative or minimally conscious state is made using prognostic markers from the patient's clinical history supported by detailed neurological and behavioural assessment by a multidisciplinary team over several weeks. However, the behavioural assessment of these patients predominately relies upon the subjective interpretation of observed spontaneous and

volitional behaviour. A diagnosis of vegetative state (VS) is supported if the patient demonstrates no evidence of awareness of self or environment, no evidence of sustained, reproducible, purposeful or voluntary behavioural response to visual, auditory, tactile or noxious stimuli and critically no evidence of language comprehension or expression (MSTF, 1994; Royal College of Physicians, 2003). In contrast the patient in a minimally conscious state (MCS) demonstrates partial preservation of awareness of self and environment, responding intermittently, but reproducibly, to verbal command and therefore demonstrating some degree of basic language comprehension (Giacino et al., 2002).

For those patients who retain peripheral motor function, rigorous behavioural assessment is usually able to establish a patient's level of wakefulness and awareness. However, it is becoming increasingly recognized that some brain-injured patients do not retain an intact peripheral motor system and are thus unable to respond overtly to command, even if they were to retain the cognitive ability to perceive and understand such commands. Consequently, there is a growing consensus that the assessment of these patients should include techniques that do not rely on overt motor responses. Particular progress towards addressing this objective has been made using brain imaging techniques such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI). This work has suggested that rather than a complete loss of cortical function some patients retain 'islands' of preserved cognitive function (Schiff et al., 2002). PET work has identified preserved responses to a variety of sensory stimuli, including photographs of familiar people (Menon et al., 1998), noxious, tactile (Laureys et al., 2002; Schiff et al., 2005) and auditory stimuli (Laureys et al., 2000; Owen et al., 2002, 2005; Boly et al., 2004; Schiff et al., 2005) in some vegetative and minimally conscious patients. More recent work by Owen et al. (2006) has also demonstrated preserved language comprehension and volitional responses in a patient who met international criteria defining the VS. Although behavioural observation failed to provide evidence of sustained, reproducible or purposeful response to stimulation including command, when this patient was asked to mentally imagine either playing tennis or moving around the rooms of her home, fMRI detected sustained activity in the supplementary motor area, parahippocampal gyrus, posterior parietal lobe and lateral premotor cortex indistinguishable from healthy volunteers asked to perform the same imagery tasks. These functional imaging results strengthen a growing consensus that some patients with impaired consciousness following brain injury may retain cognitive function, despite negative behavioural indicators.

While the case reported by Owen et al. (2006) confirms that, at least in one case, successful language comprehension can be demonstrated without the need for an overt motor response, it is not clear that the technique used will be applicable to a broad range of patients. For example, 'performance' of the tasks used requires not only language comprehension, but also the translation of the instruction into a volitional act (e.g. to imagine playing tennis) and the initiation of that act. It is entirely possible that a given patient may retain aspects of language comprehension yet be unable to initiate the willed mental acts that are necessary to succeed in the task; in short, the patient may comprehend speech but be unable to act on it. This is a particularly important point because of the problem of false negatives in all functional neuroimaging studies and illustrates the need for a hierarchical approach to the assessment of preserved cognition in the VS (for discussion, see Owen et al., 2005). In the study by Owen et al. (2006), the patient also performed a speech-processing paradigm, during which the patient heard either high- or low-ambiguity sentences, unintelligible noise or silence. The comparison of high- and low-ambiguity sentences allowed the investigators to establish that the patient could process the content of speech prior to asking her to perform the more complex volition task. Thus, had she 'not' been able to activate the appropriate regions during the volition tasks, they would have been able to exclude the possibility that this was simply because her residual cognitive abilities did not even include those speech-specific processes necessary to comprehend the instructions.

In this study, we report the performance of a group of brain-injured patients on the same speech-processing paradigm, which comprises a critical component of our hierarchal approach to the fMRI assessment of patients with impaired consciousness. In doing so, we explore how prevalent such preserved aspects of speech processing are across a group of patients. This task was administered to a group of 14 heterogeneous patients, some with less common aetiologies (including the two case studies previously reported by Owen et al., 2005, 2006), who met the diagnostic criteria for either the VS (n = 7; Royal College of Physicians, 2003), the minimally conscious state (n = 5; Giacino et al., 2002), or who were in a severely disabled condition having emerged from a minimally conscious state following brain injury (n = 2, Jennett et al., 1981). Only one of these patients (described previously by Owen et al., 2006) has also performed the more complex mental imagery paradigm. The focus of this study was to identify preservation of specific components of language processing that are necessary for successful speech comprehension. Indeed, the extent to which patients can hear and understand speech is of critical importance for both relatives and carers, and in providing an optimal environment for rehabilitation.

The comprehension of spoken language is a complex, multi-stage process: listeners must analyse the acoustic properties of heard speech in order to identify individual linguistic units (e.g. phonetic features, syllables, words), stored representations of word meanings must be retrieved from memory and those representations appropriately combined so as to construct a representation of the whole sentence's meaning (McClelland and Elman, 1986; Gaskell and Marslen-Wilson, 1997). This sequence of

perceptual and cognitive functions is supported by a widely distributed network of (predominantly) left-lateralized cortical regions in the temporal and frontal lobe (Friederici, 2002; Hagoort, 2005). Evidence from functional neuroimaging studies in healthy volunteers supports the idea of multiple, hierarchically organized processing streams radiating outwards from primary auditory regions with low-level acoustic and phonetic processes located in and around auditory cortex in the superior temporal gyrus (Belin *et al.*, 2000; Binder *et al.*, 2000; Scott *et al.*, 2000; Davis and Johnsrude, 2003), with higher level linguistic processes involved in computing sentence meaning localised further away from primary auditory regions in anterior and inferior temporal and inferior frontal regions (Scott *et al.*, 2000; Davis and Johnsrude, 2003; Scott and Johnsrude, 2003; Rodd *et al.*, 2005).

In the present study, the language processing abilities of patients were assessed using a hierarchical subtraction approach (previously described in the single-case study by Owen *et al.*, 2005), in which fMRI responses are used to measure responses of three levels of processing (auditory, perceptual and semantic) that are critically involved in speech comprehension. Low-level auditory responses were measured using a contrast between a set of auditory stimuli (both intelligible speech and unintelligible noise) and a silent baseline. Such a contrast ordinarily highlights primary auditory regions which are engaged in processing all sounds, irrespective of whether they are speech or not. Speech-specific perceptual processes were assessed by comparing intelligible speech to unintelligible speech spectrum, amplitude-modulated noise stimuli (SCN) that is matched to speech for low-level acoustic properties. When assessed in healthy adults, this contrast controls for low-level, auditory processes that are engaged for all sounds, and highlights regions of the superior and middle temporal gyri, and left inferior frontal gyrus that are critically involved in perceiving spoken sentences (cf. Scott *et al.*, 2000; Davis and Johnsrude, 2003; Narain *et al.*, 2003). Finally, to assess neural responses to sentence meaning we can contrast responses to sentences that contain ambiguous words (such as 'bark', or 'rain/reign') with matched sentences that lack equivalent ambiguities. Ambiguous words are ubiquitous in spoken language (Rodd *et al.*, 2002), and an additional process of contextually constrained meaning selection is necessary for successful comprehension of sentences that contain an ambiguous word (Rayner and Duffy, 1986; Gernsbacher and Faust, 1991). Existing work has highlighted bilateral inferior frontal and left posterior inferior temporal regions which show an elevated response to sentences containing these transient ambiguities (Rodd *et al.*, 2005; Zempleni *et al.*, 2007). In this work, we use this additional response to high ambiguity sentences as one of several neural markers indicating that some aspects of language processing are intact in the VS. We accomplish this by comparing responses in patients to fMRI data from a previous study in which healthy volunteers listened passively to the same sentence stimuli (Rodd *et al.*, 2005, Expt 2).

Materials and method
Stimuli

The stimuli were taken from Rodd *et al.* (2005) and consisted of two speech conditions (high-ambiguity sentences and low-ambiguity sentences) and an unintelligible noise condition. There were 59 items in each of these three conditions. In addition, a baseline silence condition was included. For the first 5 patients (MCS1, VS7, MCS2, MCS3, MCS4) to be scanned there were 21 silent trials, for the remaining 9 patients, the number of silent baseline trials was increased to 60 so as to increase statistical power for the contrast between sound and silence. The addition of these extra baseline trials has no impact on the other speech and meaning contrasts in the study.

The high-ambiguity sentences all contained at least two semantically ambiguous words (e.g. 'There were ''dates'' and ''pears'' in the fruit bowl'). Each high-ambiguity sentence was matched to a low-ambiguity sentence that had the same number of words and the same syntactic structure but contained words with minimal ambiguity (e.g. 'There was ''beer'' and ''cider'' on the kitchen shelf'). The duration of the individual sentences ranged from 1.2 to 4.3 s. The two sets of sentences were matched for the number of syllables, physical duration, rated naturalness, rated imageability and word frequency (Rodd *et al.*, 2005). The unintelligible noise stimuli were created by converting a set of 59 sentences that were not used in the experiment (matched for number of syllables, number of words and physical duration to the experimental sentences) to signal-correlated noise (SCN, cf. Schroeder, 1968). The form of SCN employed in the current study has the same spectral profile and amplitude envelope as the original speech, but because all spectral detail is replaced with noise, they are entirely unintelligible. Although SCN stimuli do not control for other features of speech, such as pitch, this perceptual difference does not imply a lack of acoustic matching. Pitch is not an acoustic attribute of sound, but rather a perceptual correlate, computed at high levels of the auditory system (Patterson *et al.*, 2002). Furthermore, speech that is composed essentially of band-passed SCN does not evoke a pitch percept and is still intelligible (Shannon *et al.*, 1995). In previous work, we and others have used SCN as a control stimulus for speech studies (Mummery *et al.*, 1999; Rodd *et al.*, 2005) and shown that this comparison controls for activity in low-level auditory areas (Heschl's gyrus) in normal participants. Other potential control stimuli (such as rotated speech or reversed speech) have their own shortcomings. It is very difficult to create a control stimulus that matches the acoustic characteristics of speech in all respects, but is not treated as speech by the brain, and so a compromise is necessary. Our use of SCN as a control stimulus serves the purpose of revealing perceptual processes that are critical for successful speech comprehension and controlling for activation due to basic auditory processes that are shared for speech and non-speech stimuli (such as SCN).

Patients

Fourteen patients took part in the study; of these, seven patients met the diagnostic criteria defining the VS (Royal College of Physicians, 2003), five patients met the diagnostic criteria defining the minimally conscious state (Giacino *et al.*, 2002), and two patients met the diagnostic criteria defining a severely disabled condition having emerged from a minimally conscious state

Table I Summary of patients recruited to the study including aetiology and Glasgow Coma Score (GCS) during a five day admission period at the time of fMRI investigation

Patient	Diagnosis	Age	Sex	Aetiology	Time of scan post ictus	GCS
VSI	VS	58	M	Midbrain stroke	2 months	E4,VI,M2
VS2	VS	65	M	Anoxic brain injury post cardiac arrest	16 Months	E4,VI,M3
VS3	VS	36	F	Anoxic brain injury post cardiac arrest	108 Months	E4,V2,M4
VS4	VS	22	M	Diffuse axonal injury and frontal contusion following a fall	7 Months	E4,VI,M2
VS5	VS	56	F	Anoxic brain injury post cardiac arrest	9 Months	E4,VI,M2
VS6	VS	23	F	Diffuse axonal injury following road traffic accident	6 Months	E4,VI,M3
VS7	VS	4I	M	Brainstem stroke	4 Months	E4,VI,M3
MCSI	MCS	39	M	Diffuse axonal injury following a fall	122 Months	E4,V2,M4
MCS2	MCS	4I	M	Diffuse axonal injury and frontal contusion following a road traffic accident	49 Months	E4,VI,M3
MCS3	MCS	36	M	Diffuse axonal injury following a road traffic accident	7 Months	E4,V2,M4
MCS4	MCS	67	M	Brainstem stroke	8 Months	E4,VI,M3
MCS5	MCS	54	F	Brainstem stroke	5 Months	E4,VI,M4
SDI	SD	24	M	Diffuse axonal injury following a road traffic accident	22 Months	E4,VI,M6
SD2	SD	38	F	Diffuse axonal injury and frontal contusion following a fall	6 Months	E4,VI,M6

VSI–VS7 indicates vegetative patients recruited to study. MCSI–5 indicates minimally conscious patients recruited to the study. SDI–2 indicates severely disabled patients recruited to the study.
VS = vegetative state; MCS = minimally conscious; SD = severely disabled.

following brain injury (Jennett *et al.*, 1981) (Table 1). Although meeting the clinical criteria defining the VS, it should be emphasized that two VS patients had atypical aetiologies; impaired consciousness resulting from midbrain strokes, rather than traumatic cortical or non-traumatic anoxic brain injuries, which typically account for ~80% of vegetative patients. The VS cohort for this study contained three anoxic (cardiac arrest), two traumatic (fall and road traffic accident), in addition to the two patients with midbrain strokes. All patients recruited to the study had undergone a six-month assessment period during which International diagnostic guidelines and the multidisciplinary procedure described by Bates (2005) were followed. Extensive investigations by the referring centres had not supported a diagnosis of locked in state for the two patients with midbrain stroke. Both patients demonstrated vertical and horizontal eye movement and some spontaneous/non-purposeful upper limb movement. All participants were resident at two specialist rehabilitation centres in the United Kingdom. Each patient was transferred by ambulance to the research centre for a period of 5 days before return. Signed assent from the patient's next of kin and consultant in charge of care was obtained prior to participation in the study. This study was approved by the Cambridge Local Ethics Committee (UK). All relatives approached gave signed written assent for their relative to participate. No family withdrew assent. Patients VS6 and VS7 have previously been reported as case studies (Owen *et al.*, 2005, 2006).

Procedure

A sparse imaging technique was used (Hall *et al.*, 1999), to minimize interference from scanner noise. Each sentence (or noise-equivalent) was presented in a 7.4 s silent period before a single 1.6 s scan. The midpoint of each stimulus item (0.6–2.2 s after sentence onset) was temporally aligned with a point 5 s before the midpoint of the subsequent scan. This ensured that the predicted haemodynamic response to the stimuli would be approximately maximal at the time of the scan. The experiment was divided into three sessions with the items from each condition

equally divided between the three sessions and pseudorandomized such that items in each condition occurred equally often after each of the other conditions. Session order was varied across patients.

The stimuli were presented to both ears using a high-fidelity auditory stimulus-delivery system incorporating piezoelectric headphones inserted into sound-attenuating ear defenders (Resonance Technology, Commander XG system). To further attenuate scanner noise, participants wore insert earplugs. DMDX software running on a Windows 98 PC (Forster and Forster, 2003) was used to present the stimulus items.

The fMRI imaging data was acquired using a Bruker Medspec (Ettlingen, Germany) 3-Tesla MR system with a head gradient set. Each volume consisted of 21×4 mm thick slices with an interslice gap of 1 mm; FOV: 25×25 cm; matrix size, 128×128, TE = 27 ms; acquisition time 1.6 s; actual TR = 9 s. Acquisition was transverse-oblique, angled away from the eyes, and covered all of the brain. In addition to the functional data, a 3D T1-weighted SPGR image with 1 mm isotropic spatial resolution was acquired for each patient.

fMRI analysis method

The fMRI data were preprocessed 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 SCN, 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 preprocessing).

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,
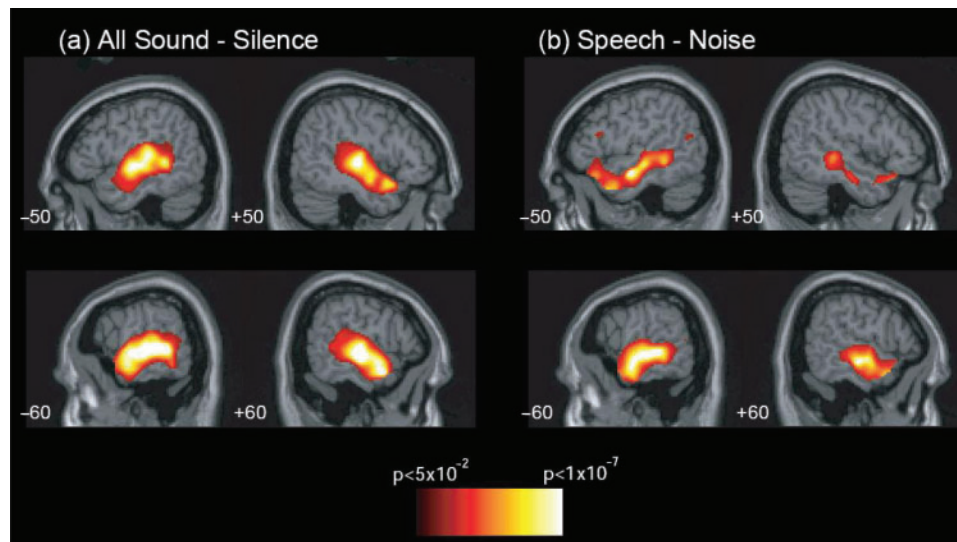
Fig. I Results from random effects group analyses of healthy volunteers (Data from Rodd *et al.*, 2005, Expt 2) for all sound versus silence (**A**) and intelligible speech versus unintelligible noise (**B**). Activations are thresholded at $P < 0.05$ FDR corrected for multiple comparisons.

interscan baseline. This contrast identifies those brain regions that process the acoustic properties of both speech and non-speech stimuli. In healthy controls, this contrast produced activation in primary auditory regions on the superior temporal plane, centred on Heschl's Gyrus (Fig. 1A). The presence of appropriate activation for this contrast confirms that some aspects of basic 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 (SCN). This contrast identifies those brain regions that process both acoustic–phonetic, and more abstract linguistic properties of spoken language (cf. Davis and Johnsrude, 2005), but critically will control for activation due to basic auditory processes that are shared for speech and non-speech stimuli such as SCN. In healthy controls, this contrast produces extensive bilateral activation that is centred on the superior temporal sulcus (Fig. 1B) as well as a left-lateralized response in the left inferior frontal gyrus (LIFG). The presence of appropriate activation for this contrast would suggest that some speech-specific perceptual processing remains intact, though it is unclear whether such a response necessarily implies that comprehension is intact. Based on existing data (Scott *et al.*, 2004; Davis *et al.*, 2006) and theoretical arguments (Friederici, 2002; Hagoort, 2005), we might consider LIFG activity in response to spoken sentences to be of greater significance than temporal lobe activity, which can in some circumstances be elicited by speech stimuli that fail to reach conscious awareness.

This suggestion that frontal responses to speech are of greater significance in using neural responses as evidence for comprehension is supported by our final contrast, which 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 (LIFG). 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, Expt 2). This was done by thresholding the results of the random effects group analysis of the control data at a threshold of $P < 0.05$ (uncorrected) and creating mask images of the two large clusters of activation in the left frontal lobe and the left posterior temporal lobe (Fig. 2). The structural scan (SPGR) of each patient was then coregistered to the patients' functional EPI images and then normalized to a standard T1-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 (ROI) masks onto the unnormalized structural image for that patient. The resulting regions of interest are shown in Fig. 2. For each patient, the activation for the semantic ambiguity contrast within each ROI 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 (Table 1) recruited to the study underwent a five day behavioural assessment in addition to completing the fMRI paradigm. During the behavioural assessment period, all patients were assessed using the JFK Coma Recovery Scale (CRS, Giacino *et al.*, 2004). Tables 2–4 summarizes their responses on this scale.
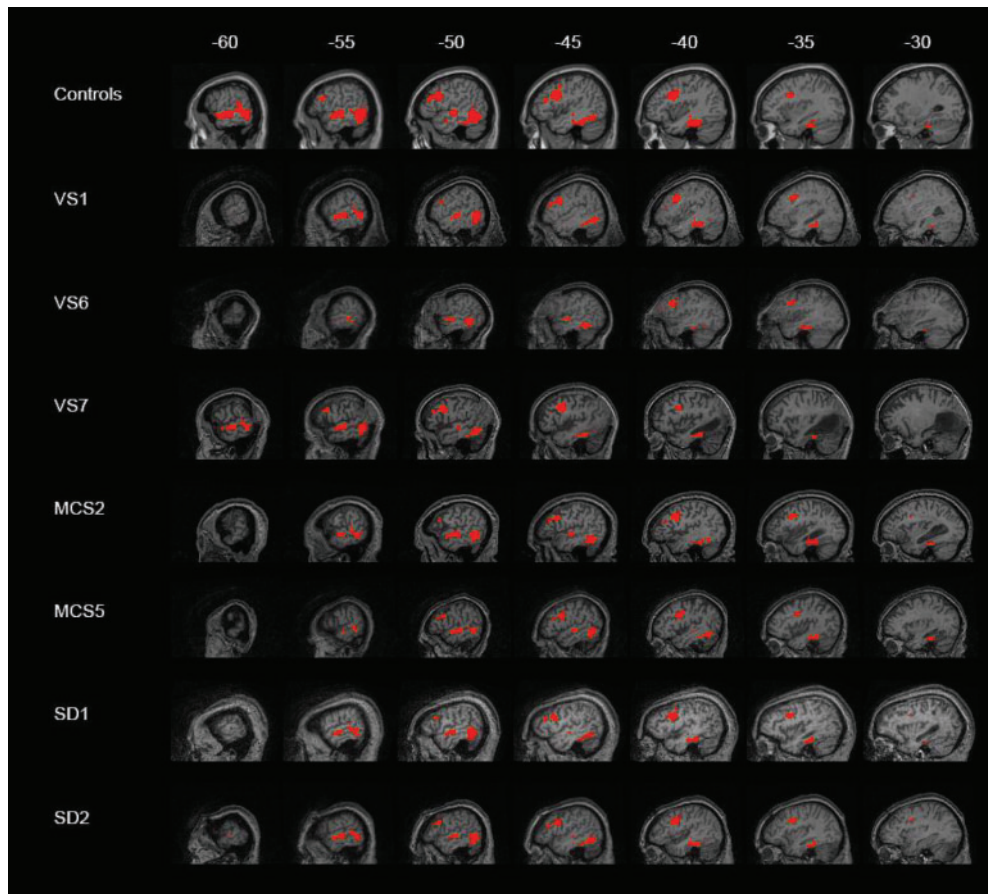
Fig. 2 Regions of interest for contrast between high- and low-ambiguity sentences based on results from random effects group analyses for healthy volunteers (Data from Rodd *et al.*, 2005, Expt 2) and then inverse-normalized onto the structural images for the individual patients (see Imaging Methods section).

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 (FDR) procedure (Genovese *et al.*, 2002). This is an adaptive procedure that provides an appropriate combination of sensitivity to detecting 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 14 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 I: severely disabled patients

Two of the patients were classified as severely disabled at the time of assessment having emerged from a minimally conscious state (SD1, SD2). Both these patients demonstrated accurate and consistent responses to spoken command, moving their hand or upper limb to complete a battery of neuropsychological tasks. It was therefore expected that these patients would respond to sound and speech in a similar way to control subjects and they are therefore reported separately to the more severely impaired patients. Consistent with their diagnosis, both these patients showed significant anatomically appropriate responses in both the low-level auditory contrast (Fig. 3A) and the mid-level speech perception contrast (meaningful speech versus SCN; Fig. 3B). For both patients, these responses extended along the entire length of the superior temporal lobe (bilaterally), as well as a portion of the left inferior frontal gyrus.

The results of the high-level semantic ambiguity analyses were more variable. Although no results reached significance when corrected for multiple corrections at the whole-brain level ($P > 0.5$ FDR), the ROI procedure did reveal significant increases in activity for the semantically ambiguous sentences. SD2 showed a significant ambiguity effect in the temporal lobe ($P < 0.05$). Activation in the frontal lobe approached statistical

Table 2 Highest JFK Coma Recovery Scale (CRS) scores for the vegetative patient group during a five day assessment period at the time of fMRI investigation

CRS/patient	VSI	VS2	VS3	VS4	VS5	VS6	VS7
Auditory function scale	1—Auditory startle	1—Auditory startle	1—Auditory startle	1—Auditory startle	1—Auditory startle	1—Auditory startle	1- Auditory startle
Visual function scale	1—Visual startle	1—Visual startle	1—Visual startle	0—None	0—None	1—Visual startle	1—Visual startle
Motor function scale	1- Abnormal posturing	2—Flexion withdrawal	2—Flexion withdrawal	2—Flexion withdrawal	2—Flexion withdrawal	2—Flexion withdrawal	2—Flexion withdrawal
Oromotor/verbal function scale	1—Oral reflex movement	1—Oral reflex movement	1—Oral reflex movement	1—Oral reflex movement	1—Oral reflex movement	1—Oral reflex movement	1—Oral reflex movement
Communication scale	0—None	0—None	0—None	0—None	0—None	0—None	0—None
Arousal scale	2—Eye opening w/o stimulation	2—Eye opening w/o stimulation	2—Eye opening w/o stimulation	2—Eye opening w/o stimulation	2—Eye opening w/o stimulation	2—Eye opening w/o stimulation	2—Eye opening w/o stimulation
Total score	6	7	7	6	6	7	7

All behaviours observed were consistent with the individual patient's original rehabilitation hospital diagnosis of vegetative state. VSI–VS7 indicates individual vegetative patients recruited to study.

Table 3 Highest JFK Coma Recovery Scale (CRS) scores for the minimally conscious patient group during a five day assessment period at the time of fMRI investigation

CRS/Patient	MCSI	MCS2	MCS3	MCS4	MCS5
Auditory function scale	3—Reproducible movement to command[a]	3—Reproducible movement to command[a]	2—Localization to sound	2—Localization to sound	3—Reproducible movement to command[a]
Visual function scale	3—Pursuit eye movements[a]	3—Pursuit eye movements[a]	3—Pursuit eye movements[a]	2—Fixation[a]	3—Pursuit eye movements[a]
Motor function scale	2—Flexion withdrawal	2—Flexion withdrawal	2—Flexion withdrawal	2—Flexion withdrawal	2—Flexion withdrawal
Oromotor/verbal function scale	2—Vocalization/Oral movement	2—Vocalization/Oral movement	1—Oral reflexive movement	1—Oral reflexive movement	1—Oral reflexive movement
Communication scale	0—None	0—None	0—None	0—None	0—None
Arousal scale	2—Eye opening w/o stimulation	2—Eye opening w/o stimulation	2—Eye opening w/o stimulation	2—Eye opening w/o stimulation	2—Eye opening w/o stimulation
Total score	12	12	10	9	11

All behaviours observed were consistent with the individual patient's original rehabilitation hospital diagnosis of minimally conscious state.
[a]Indicates behaviours on the CRS consistent with the criteria defining the minimally conscious state (Giacino *et al.*, 2002). MCSI-5 indicates individual minimally conscious patients.

significance ($P = 0.07$). For SD1, activations in the frontal lobe ($P < 0.06$) and the temporal lobe ($P = 0.14$) did not reach significance.

Group 2: VS and MCS patients who show significant responses to both sound and speech

Five of the patients who had been diagnosed as either vegetative or minimally conscious showed significant temporal lobe responses in the low-level auditory contrast (VS1, VS6, VS7, MCS2, MCS5) (Fig. 4). Interestingly, all these patients also showed significant temporal lobe responses in the mid-level speech perception contrast (meaningful speech versus SCN). These five patients had a range of clinical diagnoses: three were classified as vegetative (VS1, VS6, VS7) and two were classified as minimally conscious (MCS2, MCS5) according

to international criteria and recognized clinical assessment procedure.

Within this set of patients, there was some variation in the extent of these neural responses to speech stimuli. Some patients showed temporal lobe activations that were very similar to the control subjects with extensive, bilateral superior temporal activation (VS6, VS7) whereas for other patients the activation was extensive only in one hemisphere (MCS2 Left Hemisphere; MCS5 Right Hemisphere), or was restricted to the posterior portions of the temporal lobes (VS1). For the high-level semantic ambiguity contrast, three patients provided some evidence of intact semantic processing. The whole-brain analysis for VS6 showed an ambiguity effect that just failed to reach statistical significance ($P < 0.1$ FDR) within the LIFG, while the more sensitive ROI procedure revealed significant increases in activity for the semantically ambiguous sentences for VS7 and MCS2

Table 4 Highest JFK Coma Recovery Scale (CRS) scores for the severely disabled patient group during a five day assessment period at the time of fMRI investigation

CRS/Patient	SD1	SD2
Auditory function scale	4—Consistent movement to command[a]	4—Consistent movement to command[a]
Visual function scale	5—Object recognition[a]	5—Object recognition[a]
Motor function scale	4—Object manipulation[a]	3—Localization to noxious stimulation[a]
Oromotor/verbal function scale	0—None	1—Oral reflexive movement
Communication scale	0—None	0—None
Arousal scale	3—Attention	2—Eyes open w/o stimulation
Total score	16	15

Note although both patients showed consistent and accurate responses to command on every trial, because they were unable to use an object (i.e. comb or tooth brush) or speak, they are actually considered to be minimally conscious on the CRS. This is in contrast to their care home diagnosis as severely disabled. You can see they get higher CRS scores than the MCS group and demonstrate MCS behaviours in more than one functional modality, indicating a more complex high functioning behavioural profile. SD1–2 indicates individual severely disabled patients.
[a]Indicates behaviours on the CRS consistent with the criteria defining the minimally conscious state (Giacino *et al.*, 2002).
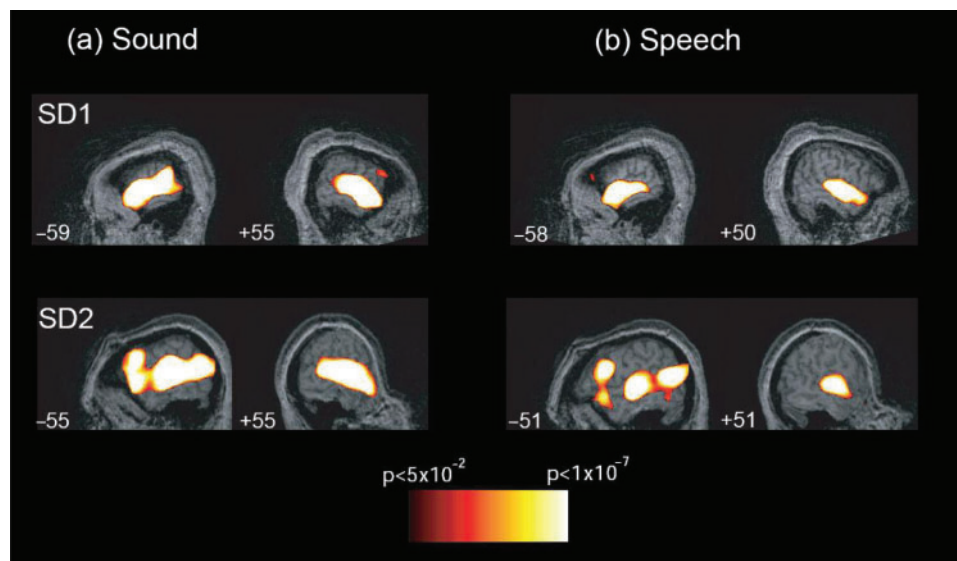

Fig. 3 Results for patients diagnosed as being severely disabled for contrasts all sound versus silence (**A**) and intelligible speech versus unintelligible noise (**B**). Activations are thresholded at $P < 0.05$ FDR corrected for multiple comparisons and shown on slices where the peak activation was observed.

[VS6 has previously been reported to show anatomically appropriate semantic ambiguity effects in the LIFG (Owen *et al.*, 2006). Although this additional activation for high-ambiguity sentences is marginally significant when corrected for multiple corrections at the whole-brain level ($P < 0.1$ FDR), it only overlaps partially with the ROI and therefore does not produce a significant effect. We suggest that for this patient, the method used to create the ROI has been affected by the severe distortion of this brain region compared with the control brain (Fig. 2)]. VS7 showed a significant effect in the temporal lobe ($P < 0.01$) but not in the frontal lobe ($P > 0.5$), while MCS2 showed a significant effect in the frontal lobe ($P < 0.05$), but not in the temporal lobe ($P < 0.1$). Interestingly, two of these patients also produced significant frontal activations in the mid-level perception contrast between speech and SCN providing convergent evidence of intact higher level language function. VS1 and MCS5 showed no significant semantic effects in either of the left hemisphere ROIs

(all $P > 0.15$). VS6 was the only patient to show LIFG activation at a significance level that approached the whole-brain corrected statistical threshold.

Group 3: no significant auditory responses

Seven of the patients showed no significant activation in the low-level auditory contrast (sound versus silence; all FDR $P > 0.6$). Four of these patients had a diagnosis of VS (VS2, VS3, VS4, VS5) while three had a diagnosis of MCS (MCS1, MCS3, MCS4). In four cases (VS2, VS3, VS5, MCS4) when the statistical threshold was substantially reduced to $P < 0.01$ uncorrected, there was still no evidence of appropriate auditory activations. In two cases (VS4, MCS1), although no activation approached the corrected significance level, there were anatomically appropriate clusters of activation within the left superior temporal lobe at the reduced threshold of $P < 0.01$ uncorrected (Fig. 5). This suggests that although these patients may be able to perform some low-level
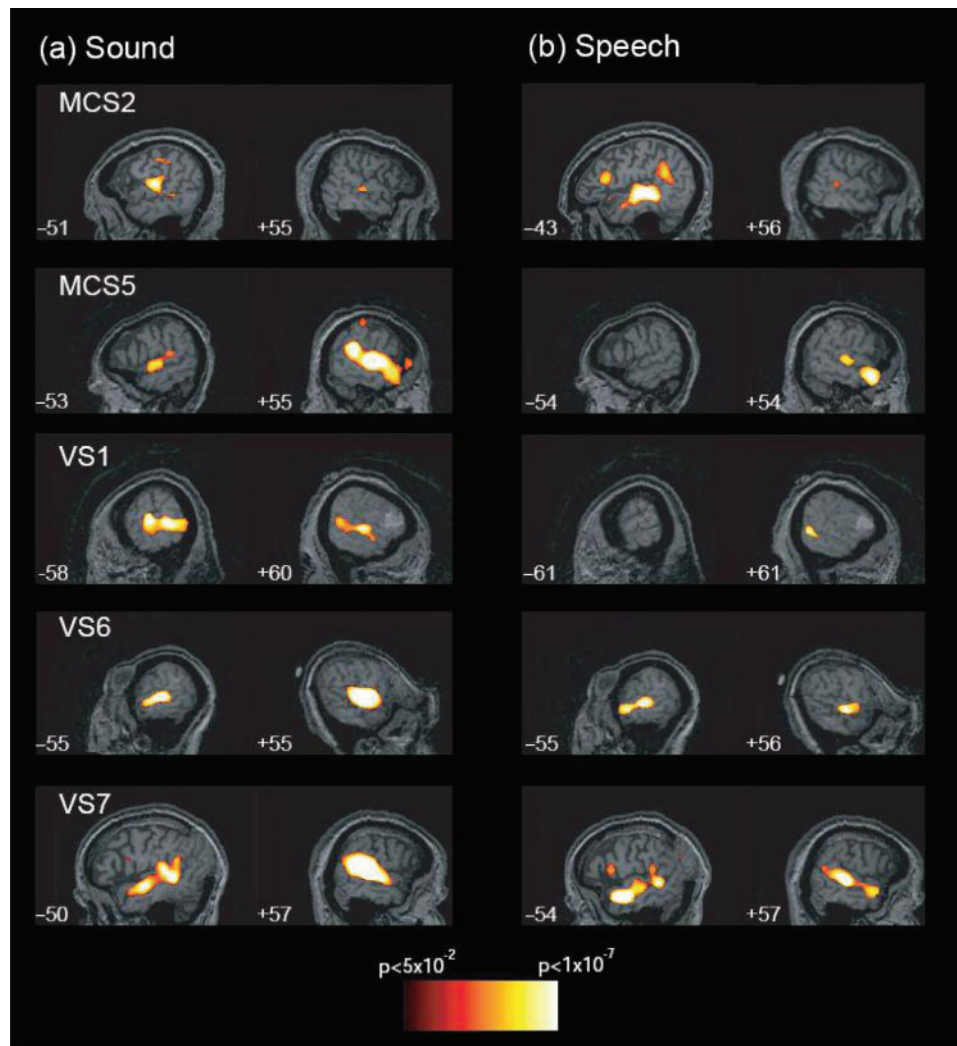
Fig. 4 Results for patients who met the diagnostic criteria for either the VS or the MCS, and who showed significant differences for all sound versus silence (**A**) and intelligible speech versus unintelligible noise (**B**). Activations are thresholded at $P < 0.05$ FDR corrected for multiple comparisons and shown on slices where the peak activation was observed.

auditory processing, neural responses are either too weak or too variable to be statistically reliable. None of these seven patients showed significant activation in the speech–noise contrast (all $P > 0.3$ FDR corrected).

It is also important to note that VS4 and VS5 produced substantial movement of their head during the scanning runs (displacements of up to 14 mm). Such head movement is well known to introduce substantial task-irrelevant noise into fMRI time series, reducing the power of statistical analyses. Note, however, that another patient (MCS2) did show highly significant effects despite similarly large magnitude movements. In addition, the statistical power of this contrast for MCS3 and MCS4 was reduced by the smaller number of silent scans included in the shorter version of the experiment that these patients performed (see Material and Method section), although again the presence of significant results for this contrast in three of the patients who performed this shorter version (VS1, VS7, MCS2) demonstrates that this version did include sufficient scans to produce significant results.

Discussion

In this study, we used a hierarchical fMRI method to measure auditory, speech perception and semantic responses from a group of 14 brain-injured patients with a clinical diagnosis of VS ($n = 7$), minimally conscious state ($n = 5$) or severe disability ($n = 2$). A range of patterns of activations were seen: while some patients did not show any significant responses to the auditory stimuli, others, including patients clinically diagnosed as being in a VS, showed significant auditory, speech perception and semantic responses that were anatomically appropriate and comparable to the results of healthy volunteers (Rodd *et al.*, 2005).

These results provide further evidence that some vegetative patients retain islands of preserved function and that in the absence of behavioural evidence, functional imaging provides a valuable tool to the assessment team.
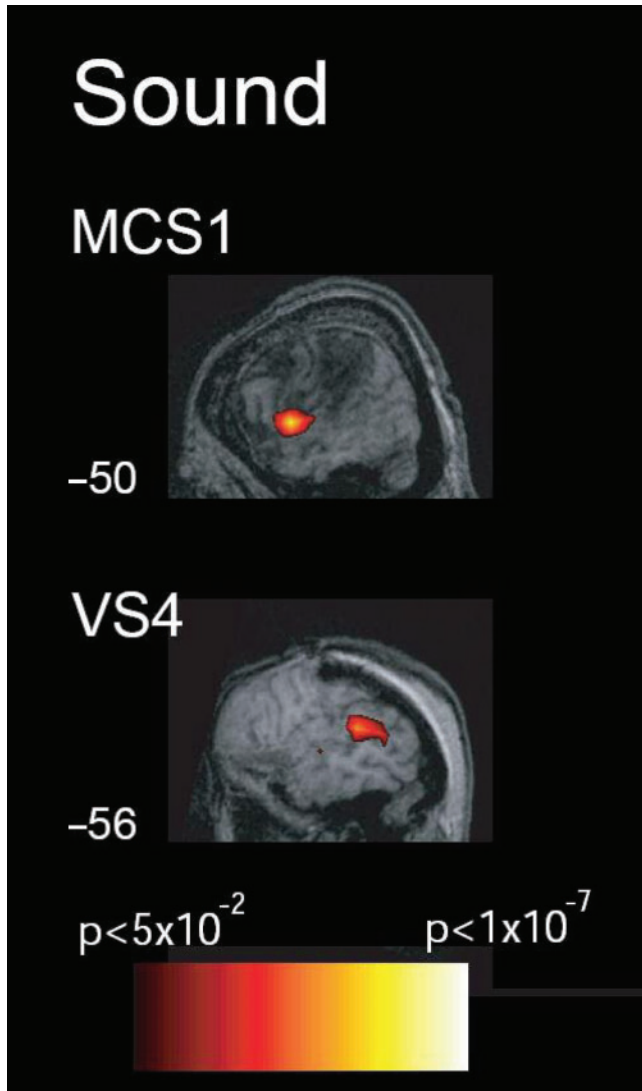
Fig. 5 Results for patients who met the diagnostic criteria for either the VS or the MCS, and who showed no significant differences for all sound versus silence, but who did show some anatomically appropriate activation at a lower statistical threshold. Activations are thresholded at $P < 0.0I$ uncorrected and shown on slices where the peak activation was observed.

Indeed, we believe the hierarchical fMRI speech-processing paradigm employed here represents a robust and reliable assessment tool at the single subject level. First, this paradigm has been extensively used with groups of healthy awake and sedated volunteers in which consistent cerebral responses at corrected statistical significance have been found (Rodd *et al.*, 2005; Davis *et al.*, 2006). Second, our findings acquired from two patients classified as severely disabled also demonstrates the validity of this paradigm at the single subject level. These patients showed appropriate temporal and frontal activations in both the low-level auditory contrast and mid-level speech perception contrast. In addition, the high-level semantic contrast also produced anatomically appropriate responses, although in one case

this result only approached statistical significance. Further work may be needed to improve the power to detect semantic effects in all single subjects for this linguistically subtle contrast. Nonetheless, we are confident that the strict methodology and corrected statistical threshold we have applied to the analysis of this data, using regions of interest created from the healthy control activations (Rodd *et al.*, 2005), provides a useful tool to aid the assessment of the speech processing abilities of patients with peripheral motor impairments or atypical aetiological presentation.

What aspects of speech processing are intact in vegetative patients?

The most interesting aspect of the data collected is that there is no clear relationship between these patient's fMRI responses to speech and non-speech stimuli and their referred diagnosis of either vegetative or minimally conscious. That is, both vegetative and minimally conscious patients in our cohort showed similar neural markers of speech processing. The distinction between the vegetative and minimally conscious state relies upon a number of key behavioural distinctions: (i) awareness of self or environment, (ii) evidence of sustained, reproducible, purposeful or voluntary behavioural response to visual, auditory, tactile or noxious stimuli and (iii) evidence of language comprehension (MSTF, 1994; Royal College of Physicians, 2003). The differential diagnosis is currently made following prolonged and extensive behavioural assessment by at least two independent doctors supported by the patient's clinical history and the observations of all persons in regular contact with the patient. Of the seven vegetative patients included in the study we found three who showed some evidence of intact speech processing abilities. These patients all showed significant temporal lobe responses in both the low-level auditory contrast and the mid-level speech perception contrast. In two cases, these activations were very similar to the control subjects with extensive, bilateral superior temporal activation accompanied by activation in the LIFG. Most strikingly, two of these patients showed a significant response in the high-level semantic ambiguity contrast, consistent with volunteer activation associated with processing the semantic aspects of speech. These findings suggest that some patients meeting the clinical criteria defining the VS may retain critical speech-processing networks that contribute to language comprehension in healthy volunteers.

However, these findings do not necessarily imply language comprehension *per se*. Even in the case of healthy volunteers, a positive ambiguity result does not unequivocally confirm successful comprehension in the absence of confirming behavioural data. It is possible that healthy participants 'try' to resolve ambiguity but ultimately fail to comprehend the sentence, even though they produce the 'correct' fronto-temporal activation pattern. The same is true for patients. We cannot infer

successful comprehension, only that comprehension was attempted to a sufficient degree so as to (i) engage the same systems as normal volunteers and (ii) to produce similar patterns of activity as normal volunteers.

By extension, although comprehension is not necessarily confirmed by this activation, the activations observed do confirm that most of the preceding stages of speech processing are intact. In order for a difference between sentences containing ambiguous and unambiguous words to be observed it is necessary (i) that speech sounds are perceived, (ii) that words in speech are recognized and (iii) that the meaning(s) of those words are activated. All of these stages are necessary for successful comprehension, and go well beyond those processes that could be inferred from existing data (e.g. Di *et al.*, 2007) which contrast speech and rest, or speech and non-speech sounds.

As should be apparent from the above discussion, the present data do not, on their own, permit strong conclusions concerning whether those patients showing intact fMRI responses were consciously aware of speech. However, some evidence that would lead us to associate frontal responses to ambiguity with both intact speech comprehension and conscious awareness comes from a study with healthy volunteers scanned using the same fMRI paradigm while progressively sedated using the GABA$_A$ potentiating anaesthetic agent Propofol (Davis *et al.*, 2006). The results of this study showed that low-level auditory and temporal lobe responses to speech were preserved at two levels of sedation (Ramsay II and III; Ramsay *et al.*, 1974), including a deep level of sedation which prevented conversational responses to speech. However, in contrast to these temporal lobe responses, inferior frontal responses to speech compared to non-speech, and for high- versus low-ambiguity sentences were sensitive to the declining levels of awareness produced by sedation. Indeed, high-level semantic responses detected by the ambiguity contrast were only observed in non-sedated, fully awake participants. Such findings suggest that an additional neural response to ambiguous sentences may be associated with awareness.

Implications for diagnosis

The findings reported here, in addition to those previously published (Owen *et al.*, 2005, 2006), suggest that a small number of patients with a diagnosis of VS may retain islands of residual cognitive function that cannot be observed using methods that rely on the patients' ability to make overt motor responses. It is matter of debate however, whether if such findings were acquired during the clinical assessment of these patients they would support a diagnosis of minimally conscious state (acknowledging the lack of any behavioural indicators), or whether these findings suggest that, contrary to existing definitions, the vegetative state (VS) represents a spectrum of impairment, similar to the more recently defined minimally conscious state (Giacino *et al.*, 2002).

The favoured opinion is that these results do not change the diagnosis of the patients; it is well known that responses measured with functional brain imaging only provide 'neural correlates' of critical cognitive processes and such data are therefore insufficient to conclude that the brain areas activated in normal participants are necessary for successful performance. Similarly, in the vegetative and minimally conscious states, observation of neural activity in brain regions which have been previously associated with specific cognitive processes (such as perceptual or semantic processing of speech) may be insufficient to conclude that these cognitive processes are intact. However, in opposition we would suggest that although intact speech comprehension is not necessarily entailed by our observations, our data is most parsimoniously explained by assuming that certain neural responses to speech do provide evidence for intact comprehension. This conclusion is perhaps most appropriate for those patients that showed additional frontal and temporal lobe responses for high- versus low-ambiguity sentences. One vegetative patient (VS6) who showed speech perception responses that were very similar to the control subjects as well as a response to semantic ambiguity also showed a volitional response when given spoken instructions to perform mental imagery tasks (Owen *et al.*, 2006). This latter response is contingent on comprehension and would therefore suggest, in her case at least, that the observed speech perception and ambiguity responses are a reliable indicator of comprehension. It remains to be seen whether other patients will show a similar association, when assessed on both the semantic ambiguity paradigm described here and the volition paradigm described by Owen *et al.* (2006).

Correspondence with previous findings

The fMRI findings described here provide further insight into the integrity of auditory processing and the higher perceptual and cognitive processes that integrate auditory information in brain-injured patients. Boly *et al.* (2004) performed a PET study looking at the cerebral responses in vegetative versus minimally conscious versus healthy controls in response to simple auditory stimuli (clicks) and the functional connectivity and integration of this information within the secondary auditory cortex. Boly *et al.* (2004) found auditory stimulation produced increased regional cerebral blood flow (rCBF) bilaterally in cortical areas involved in auditory processing: transverse temporal (Brodmann area 41) and superior temporal gyri (areas 42 and 22) in healthy controls. VS patients activated bilateral area 41/42, but did not show higher order associative area 22 activation. In contrast, MCS patients activated similarly to controls. Although we did not normalize our patients brains to a healthy template, the extent of activation seen in three of our vegetative patients undoubtedly exceeds the higher associative auditory activation explored by Boly *et al.* (2004). The most important finding from the

Boly *et al.* (2004) study was that the higher cognitive integration of auditory information was absent across her 15 vegetative patients. This integration formed by a frontal–parietal cognitive matrix, is thought to be necessary for awareness.

Further work by Laureys *et al.* (2004) using more complex auditory information with and without emotional valence, has suggested some patients may be capable of extended cerebral processing of auditory stimuli. Laureys *et al.* (2004) only found this in MCS patients, but more recently Staffen *et al.* (2006) have demonstrated increased cerebral activity to hearing ones own name, versus control names in a vegetative patient. This finding has also been found in MCS patients by Schiff *et al.* (2005) and Bekinschtein *et al.* (2004). Di *et al.* (2007) has recently shown primary auditory cortex activation in three VS patients to hearing the patients own name versus scanner noise (equivalent to our low-level contrast). Reviewing the functional imaging investigations conducted to date, Giacino *et al.* (2006) concluded that the vegetative patients investigated by Laureys *et al.* (2000) and Boly *et al.* (2004) did not demonstrate the higher order multimodal integration of auditory data within the posterior parietal cortex, anterior cingulate and hippocampus, thought to be necessary to attain a normal level of consciousness. While this might be true for many patients meeting the criteria for the VS, our results do suggest that at least in a small number of patients, some cortical integration within associative cortices might be preserved. Moreover, Owen *et al.* (2006) have suggested in at least two cases (one as yet unpublished) that such integrative processes necessary to achieve some level of awareness of self and environment do exist. The challenge is now to determine how prevalent such retained function is and to develop paradigms capable of accurately determining this.

Prognostic value of fMRI responses to speech

Our anecdotal observations suggest that fMRI responses to higher level speech contrasts might have some significance in terms of prognosis or retained function that the patient demonstrates. Although we only have three vegetative patients with fMRI evidence of speech processing to compare, it is these patients who have gone on to make the most marked behavioural recovery. At 6 months post fMRI VS6 showed fixation and inconsistent tracking, progressing at 14 months to score 17 on the JFK coma recovery scale (original score of 7 at the time of fMRI), demonstrating reproducible movement to command and operating a mechanical switch to discriminate between objects. Patient VS7 at 6 months post fMRI, demonstrated visual fixation, orientation, tracking (head and eyes) and reproducible movement to command, operating a brain–computer interface using head movement (CRS total score 13). Patient VS1 at 6 months post fMRI, demonstrated visual fixation, orientation, tracking (head and eyes) and

inconsistent response to command (CRS total score 11). Those patients (VS2, VS3, VS4, VS5) who did not show any significant auditory responses with fMRI showed no change in their JFK coma recovery score at 6 months post fMRI (CRS scores 6–7).

Although these findings are encouraging, it is a matter of debate whether they changed the prognosis of these patients: First, VS1 and VS7 both had atypical aetiologies for VS with less published information regarding their expected natural history. Second, all three patients subsequently demonstrated key behavioural markers before critical time points for permanence (6 months non-traumatic, 12 months traumatic). Hence our fMRI findings acquired relatively early after their injuries may have simply preceded the natural recovery pattern for these less well-studied aetiologies. Nevertheless, it is our belief that such information was still helpful and could be used to stream early rehabilitative interventions that capitalize upon the patient's retained/strongest functional attributes. For example, VS6 who, despite a behavioural diagnosis of VS, showed evidence of retained speech comprehension and has been shown to volitionally respond to command using mental imagery rather than overt motor output (Owen *et al.*, 2006), subsequently benefited from the use of brain–computer interface technology. Furthermore, the information acquired using fMRI facilitated a dramatic change in motivation towards the patient from her care staff, whom prior to our investigations had a very negative outlook.

Using fMRI to inform clinical decisions

There is one very important caveat to the use of functional imaging that cannot be emphasized enough, particularly where media interpretation and legal cases are concerned. That is, only positive findings from brain imaging can be interpreted and a negative result does not exclude the possibility that the patient at another time might demonstrate appropriate responses. For example, even a healthy volunteer might not produce a neural response if they are asleep at the time of the scan or were unable to hear or understand the instructions or the stimuli. This is also likely to be the case for both vegetative and minimally conscious patients, the latter group by definition demonstrating inconsistent, but reproducible responses to command. The fluctuating and impaired wakefulness and/or awareness of these patients, means that an fMRI investigation on one day or even in the morning versus the afternoon, may produce a different result. For instance, of the five minimally conscious patients investigated, three (MCS1, MCS3, MCS4), showed no cerebral response to sound despite positive behavioural observations preceding the fMRI investigation supporting a diagnosis of minimally conscious state. Indeed, MCS1, showed reproducible movement to command. One solution might be to conduct repeated fMRI investigations at different times of day or to use EEG technology to stimulate the patient at the time

of maximal wakefulness. However, wakefulness fluctuations could have a high frequency and repeated presentation of stimuli is well known to cause habituation even in healthy volunteers. The optimal solution is to monitor the patient carefully with behavioural and electrophysiological assessments for a prolonged period prior to fMRI investigation and to document during this time whether there exists a pattern of heightened wakefulness, which might provide the best opportunity for the patient to respond. Second, it is highly desirable to be able to assess the patient with a hierarchical battery of paradigms in both the visual and auditory domain—exploring key cognitive processes that might be used to target further rehabilitative efforts if detected.

On the wider issue of adopting such paradigms to inform clinical decision making, there is a general belief that although this may happen in time, we are currently not at the point where we have sufficient data to support this as a routine measure. First, there are currently no practice guidelines or consensus statements covering the use of fMRI in clinical decision making. Second, there is currently insufficient population data to warrant convening an expert panel to create these guidelines. Third, the application and analysis of these paradigms requires an experienced multi-disciplinary team potentially restricting the use of such paradigms to a limited number of research units at the present time. Finally, although it is accepted only positive findings on fMRI can be interpreted, the data published to date remains ambiguous with respect to the diagnostic and prognostic benefits of such information.

Acknowledgements

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