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Residual auditory function in persistent vegetative state: A combined PET and fMRI study

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In recent years, a number of studies have demonstrated an important role for functional neuroimaging in the identification of residual cognitive function in persistent vegetative state. Such studies, when successful, may be particularly useful where there is concern about the accuracy of the diagnosis and the possibility that residual cognitive function has remained undetected. Unfortunately, functional neuroimaging in persistent vegetative state is extremely complex and subject to numerous methodological, clinical and theoretical difficulties. Here, we describe the strategy used to study residual auditory and speech processing in a single patient with a clinical diagnosis of persistent vegetative state. Identical positron emission tomography studies, conducted nine months apart, revealed preserved and consistent responses in predicted regions of auditory cortex in response to intelligible speech stimuli. Moreover, a preliminary functional magnetic resonance imaging examination at the time of the second session revealed partially intact responses to semantically ambiguous stimuli, which are known to tap higher aspects of speech comprehension. In spite of the multiple logistic and procedural problems involved, these results have

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major clinical and theoretical implications and provide a strong basis for the systematic study of possible residual cognitive function in patients diagnosed as being in a persistent vegetative state.

INTRODUCTION

An accurate and reliable evaluation of the level and content of cognitive processing is of paramount importance for the appropriate management of patients diagnosed with persistent vegetative state (PVS). Objective behavioural assessment of residual cognitive function can be extremely difficult in these patients, as motor responses may be minimal, inconsistent, and difficult to document, or may be undetectable because no cognitive output is possible. In recent years, a number of studies have demonstrated an important role for functional neuroimaging in the identification of residual cognitive function in PVS patients. Unlike resting blood flow and glucose metabolism, which provide markers of neural capacity and potential, activation methods such as $H_2{}^{15}O$ positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) can be used to link residual neural activity to the presence of covert cognitive *function*. In short, functional neuroimaging has the potential to demonstrate distinct and specific physiological responses (changes in regional cerebral blood flow, rCBF, or changes in regional cerebral haemodynamics) to controlled external stimulation in the absence of any overt response on the part of the patient. In the first of such studies, $H_2{}^{15}O$ PET was used to measure rCBF in a post-traumatic PVS patient during an auditorily-presented story told by his mother (de Jong, Willemsen, Paans, 1997). Compared to non-word sounds, activation was observed in the anterior cingulate and temporal cortices, possibly reflecting emotional processing of the contents, or tone, of the mother's speech. In another patient diagnosed as PVS, Menon et al. (1998) also used PET, but to study covert *visual* processing in response to familiar faces. During "experimental" scans, the patient was presented with pictures of the faces of family and close friends, while during "control" scans scrambled versions of the same images were presented which contained no meaningful visual information whatsoever. Previous imaging studies in healthy volunteers have shown such tasks to produce robust activity in the right fusiform gyrus, the so-called human "face area" (e.g. Haxby et al., 1991, 1994). The same visual association region was activated in the PVS patient when the familiar face stimuli were compared to the meaningless visual images (Menon et al., 1998; Owen et al., 2002). In other cohort studies, both noxious somatosensory stimuli (Laureys, Majerus, & Moonen, 2002) and auditory stimuli (Boly et al., 2004; Owen et al., 2002) have also been shown to systematically activate appropriate cortical regions in patients meeting the clinical criteria for PVS.

In this study we combined $H_2{}^{15}O$ PET with fMRI to study covert auditory processing in a patient with a probable clinical diagnosis of PVS. The decision to use auditory (language) stimuli was made, in part, on the basis of partially preserved brainstem auditory evoked responses (BAER). In an initial PET study, a hierarchical auditory processing test of graded complexity was employed (Davis & Johnsrude, 2003; Scott, Blank, Rosen, & Wise, 2000). This task allows neural responses to the processing of the linguistic content of spoken sentences (words and meanings) to be examined, relative to their more general acoustic properties. Preserved speech-related cortical responses were observed and on this basis a decision was made to reassess the patient following an interval of approximately nine months, during which time there was no significant change in his clinical condition. First, an identical PET study was carried out to ascertain whether the preserved cortical responses observed during the first session were still evident. Second, an fMRI study was conducted, using the phenomenon of semantic ambiguity to examine activity in regions of the brain that are involved in the semantic aspects of speech comprehension, in particular the processes of activating, selecting and integrating contextually appropriate word meanings (Rodd, Davis, & Johnsrude, in press). When words have more than one meaning, contextual information must be used to identify the appropriate meaning. For example, for the sentence "The boy was frightened by the loud bark", the listener must work out that the ambiguous word "bark" refers to the sound made by a dog and not the outer covering of a tree. This requires additional processing by those brain regions involved in activating and selecting contextually appropriate word meanings (Rodd et al., in press).

MATERIALS AND METHODS

Case history

The patient was a 30-year-old male with a diagnosis of basilar thrombosis and a posterior circulation infarction. In early June 2003, he collapsed with a severe headache and quickly became unresponsive. By the following day, he was drowsy, with a left partial Horner's syndrome, horizontal nystagmus, right hemiparesis and bilateral upgoing plantars. An MRI scan revealed an infarction of the left pons, cerebellum and posterior thalamus, which was still clearly evident at the time of the first PET scan four months post-ictus (Figure 1). Consciousness fluctuated for the next few days until the patient became unconscious with absent dolls eyes movement. At that stage, one week post-ictus, angiography revealed severe basilar stenosis. Two recombinant tissue plasminogen activator infusions produced some improvement,

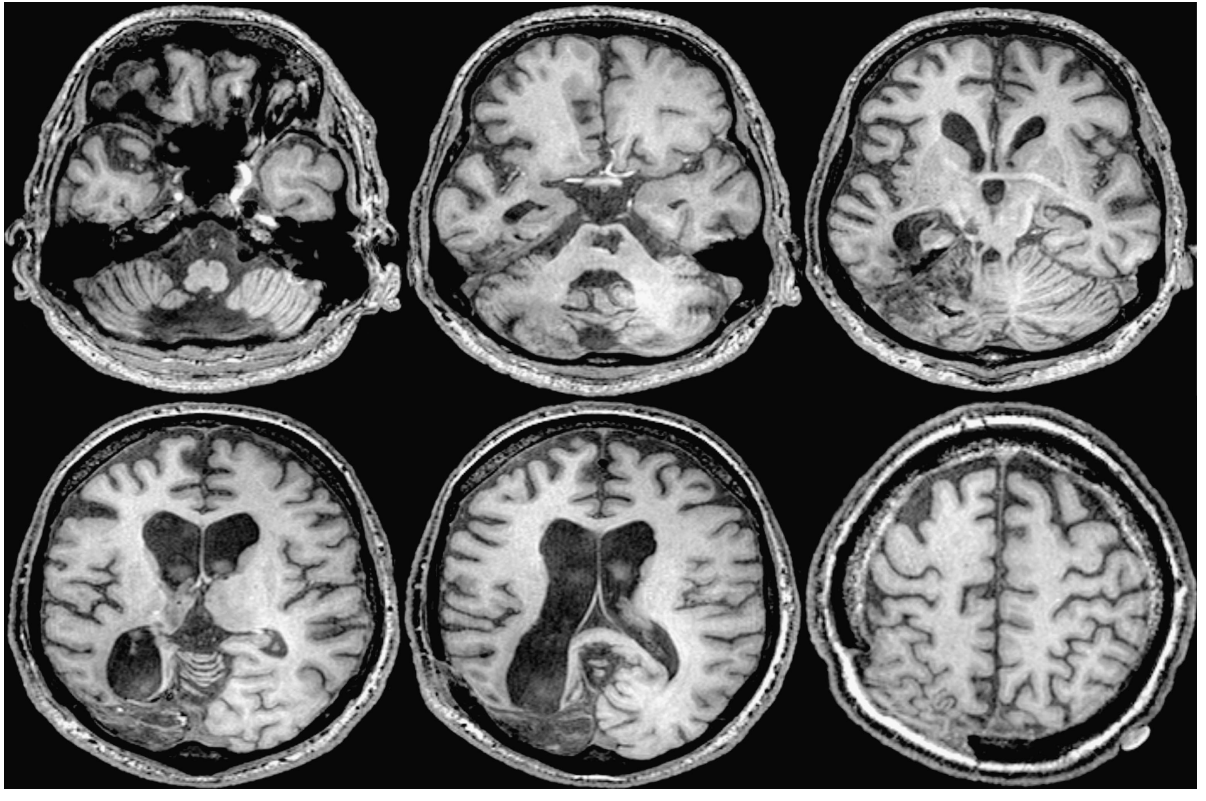

Figure 1. Structural MRI taken in October 2003 (4 months post-ictus) revealing an infarction of the left pons, cerebellum and posterior thalamus. The patient's left hemisphere appears left of figure.

although, following a brief spell of partial recovery after the anaesthesia had worn off, he deteriorated into a deep state of unconsciousness. Three weeks post-ictus the patient left the intensive care unit and to date he has not recovered. During the acute care period a BAER and a passive mismatch negativity (MMN) odd-ball paradigm were conducted. The BAER revealed preserved responses bilaterally from the pons and midbrain, although the onset of the midbrain component and consequently peak III–V interpeak interval was increased bilaterally. An MMN superior temporal N1 response was also observed, however, an N2 discriminating response was absent. Following sequential multidisciplinary assessment a diagnosis of PVS was made.

In October 2003, four months post-ictus, a decision was made to investigate the possibility of residual cognitive functions using PET and a novel language intelligibility task. Nine months later an identical PET activation study was performed, both to assess the reproducibility of the technique and to establish whether there had been any significant deterioration in cortical activity. On the same day, an event-related fMRI study was performed using the phenomenon of semantic ambiguity to examine activity in regions of the brain that are involved in the semantic aspects of speech comprehension. Informed written assent for participation was obtained for the patient from the next-of-kin after the nature of the study and possible consequences had been fully explained. The study was approved by the Cambridgeshire Local Research and Ethics Committee.

Stimuli and testing conditions

Auditory intelligibility (PET studies). In the two PET studies, the patient underwent a spoken language comprehension task. This involved the use of 189 declarative English sentences, on a range of topics, comprising 5–17 words (1.7–4.3 s in duration) taken from the test sentences used in a previous study (Davis & Johnsrude, 2003). A form of distortion (speech in noise) was generated by adding a continuous pink-noise background to these sentences at three signal-to-noise ratios (−1, −4, or −6 dB), using Praat software (www.praat.org). This form of distortion disrupts both the spectral and temporal properties of speech, while preserving the duration, amplitude and overall spectral composition of the original. In a previous study using the same stimuli (Davis & Johnsrude, 2003), participants' word report scores (calculated as the proportion of words per sentence that were reported correctly) and the rated intelligibility of stimuli were reliably correlated ($r = .99$, $p < .001$). Within each condition there were three trials. Thus, there were three "high intelligibility" trials, three "medium intelligibility" trials and three "low intelligibility" trials (totalling nine stimulus presentations in the experimental phase). Within conditions, the three trials varied *in content only*; the signal-to-noise ratio remained the same but the sentences differed.

Each trial comprised 21 declarative "speech in noise" sentences, with a 1 s gap between each sentence. The total time taken to play each trial was approximately 100 s. The study also contained a control condition (also undertaken three times) during which no stimuli were presented. In total therefore, 12 scans were performed (3×3 experimental conditions; 1×3 control condition).

Each PET scan lasted 90 s and the stimuli were initiated 5 s before scanning began. The scans were separated by 8 min and the order in which the conditions were administered was pseudorandomly arranged.

Semantic ambiguity (fMRI study). There were two experimental conditions (high-ambiguity sentences and low-ambiguity sentences) and a low-level noise baseline condition. There were 59 items in each of these three conditions. The high-ambiguity sentences all contained at least two ambiguous words (e.g., there were *dates* and *pears* in the fruit bowl). The ambiguous words were either homonyms (two meanings that have the same spelling and pronunciation; e.g., 'bark'), or homophones (two meanings that have the same pronunciation but different spelling; e.g., "knight"/"night"). 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 two sets of sentences were matched for the number of syllables, physical duration, rated naturalness, rated imageability, and the log-transformed mean frequency of the content words in the CELEX database (Baayen, Piepenbrock, & Gulikers, 1995). The imageability and naturalness scores came from pretests in which groups of healthy participants listened to the sentences and rated how imageable or natural they were on a 9-point Likert scale (Rodd et al., in press).

A set of 59 sentences that had not been used as experimental stimuli, but were matched for number of syllables, number of words and physical duration to the experimental sentences, were converted to signal-correlated noise (Schroeder, 1968) using Praat software. These stimuli had the same spectral profile and amplitude envelope as the original speech, but since all spectral detail was replaced with noise they were entirely unintelligible and they were used as a low-level baseline condition.

A sparse imaging technique was used (Hall et al., 1999), to minimise interference from scanner noise. The patient was played a single sentence (or noise-equivalent) in the 7.4 s silent period before a single 1.6 s scan. The timing of stimulus onset and offset was jittered relative to scan onset by temporally aligning the midpoint of the stimulus item (0.6 to 2.2 s after sentence onset) with a point that was 5 s before the mid-point of the subsequent scan.

There were 59 trials of each sentence type and an additional 21 silent trials for the purpose of monitoring data quality. The experiment was divided into

three sessions of 66 sentences. Sentences were pseudorandomised to ensure that the three experimental conditions and rest scans were evenly distributed among the three sessions, and that each condition occurred equally often after each of the other conditions. The sentences were presented diotically using a high-fidelity auditory stimulus-delivery system incorporating flat-response electrostatic headphones inserted into sound-attenuating ear defenders (Palmer, Bullock, & Chambers, 1998). To further attenuate scanner noise, the patient wore insert earplugs. DMDX software running on a Windows 98 PC (Forster & Forster, 2003) was used to present the stimulus items.

Image acquisition and data analysis

PET scans were obtained with the General Electrics Advance system, which produces 35 image slices at an intrinsic resolution of approximately $4.0 \times 5.0 \times 4.5$ mm. The patient underwent two separate PET investigations, comprising 12 scans each. Using the bolus $H_2{}^{15}O$ methodology, rCBF was measured during the 12 separate scans. For each scan, the patient received a 20 s intravenous bolus of $H_2{}^{15}O$ through a forearm cannula at a concentration of 300 Mbq ml^{-1} and a flow rate of 10 ml min^{-1}. With this method, each scan provides a static image of rCBF integrated over a period of 90 s from when the tracer first enters the cerebral circulation. The 12 PET scans were realigned using the first scan as a reference, normalised for global CBF value and averaged within each session for each activation state (experimental task and control task). The images were then smoothed using an isotropic Gaussian kernel at 16 mm. Finally, a simple ANCOVA (analysis of covariance) model was fitted to the data at each voxel, as implemented by the method of Statistical Parametric Mapping (SPM99, Wellcome Department of Imaging Neuroscience, London, UK), with a condition effect for each of the conditions, using global CBF as a confounding covariate. A 3D MRI volume ($256 \times 256 \times 128$ pixels, 3 mm thick) was acquired and resliced so as to be coregistered with the PET data. The significance of a given rCBF difference was assessed by application of an intensity threshold to the SPM images (Worsley, Evans, Marrett, & Neelin, 1992; Worsley et al., 1996). This threshold, based on 3D Gaussian random field theory, predicts the likelihood of obtaining a false positive in an extended 3D field.

The fMRI imaging data was acquired using a Bruker Medspec (Ettlingen, Germany) 3-Tesla MR system with a head gradient set. A total of 198 echo-planar image volumes were acquired over three 12-min sessions. 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.

The data were pre-processed and analysed using Statistical Parametric Mapping software (SPM99, Wellcome Department of Imaging Neuroscience, 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 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. 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) as well as a constant term for each of the three scanning runs.

Determination of a priori defined regions of interest. Each study was designed to test anatomically specific hypotheses as both of the tasks used are known to produce well-documented, specific, robust and reproducible activation patterns in normal volunteers (Davis & Johnsrude, 2003; Rodd et al., in press). The graded complexity speech task used in the PET studies has been shown previously to produce activity, related to the intelligibility of the presented stimuli, in the left anterior and superior temporal lobe (Davis & Johnsrude, 2003; Scott et al., 2000). Importantly, this task also includes a "silence" baseline condition, making a more general comparison of speech (collapsed across different levels of background noise) versus silence possible. Many previous studies in healthy volunteers have shown that such comparisons produce bilateral activity in an extensive region of the superior temporal gyrus, incorporating Heschel's gyrus and the planum temporale (Davis & Johnsrude, 2003; Mummery, Ashburner, Scott, & Wise, 1999; Scott et al., 2000). The semantic ambiguity task has been used previously in healthy volunteers to investigate the network of brain regions that is involved in computing the meaning of speech (Rodd et al., in press). Relative to low-ambiguity sentences, high-ambiguity stimuli produce increases in signal intensity in the left posterior inferior temporal cortex and inferior frontal gyri bilaterally. Again, this task also incorporated two baseline conditions involving either silence or signal correlated noise, making the more general comparison of speech perception (irrespective of ambiguity) versus acoustically-controlled non-speech stimuli as well as silence possible. Previous studies in healthy volunteers have shown that such comparisons produce bilateral (although commonly stronger in the dominant hemisphere), activity in the superior and middle temporal gyri (Davis & Johnsrude, 2003; Mummery et al., 1999; Rodd et al., in press; Scott et al., 2000).

In spite of this background, single subject studies using PET or fMRI are rare and, compared to the commonly used group designs, are very under-powered. Accordingly, for the comparisons described above, a directed search was conducted within the regions identified by the studies in healthy volunteers and the

threshold for reporting a peak was set at $p < .001$, uncorrected for multiple comparisons. For the rest of the brain an exploratory search involving all peaks within the grey matter (volume 600 cm^3) was conducted and the threshold for reporting a peak was set at $p < .05$, corrected for multiple comparisons.

RESULTS

Auditory intelligibility (PET studies)

During the first PET study, 4 months post-ictus, the comparison of speech (collapsed across the three levels of intelligibility) with the silence baseline condition revealed significant foci of activation over the left and right superior temporal planes (see Figure 2, top left) suggesting that basic auditory processes were probably functional.

With this in mind, a second comparison was made comparing low intelligibility sentences with high intelligibility sentences in order to isolate any residual activity related specifically to the comprehension of spoken language. This comparison revealed two peaks in the superior and middle temporal gyri of the left hemisphere (see Figure 2, bottom left). Although neither of these peaks approaches whole-brain conventional levels of corrected significance, they are well within the region that has been shown to be activated in healthy volunteers during this same task (Davis & Johnsrude, 2003). The results of additional comparisons, between the high and medium intelligibility conditions, for example, were entirely consistent with, but did not add to, these results, yielding peaks of activation that were weaker, but at similar co-ordinates.

During the second PET study, 13 months post-ictus, the comparison of speech (collapsed across the three levels of intelligibility) with the silence baseline condition revealed several foci of activation over the superior and middle temporal gyri of the left and right hemispheres (see Figure 2, top right), suggesting again that basic auditory processes were probably functional.

The second comparison, comparing low intelligibility sentences with high intelligibility sentences revealed two peaks in the brain in the superior and middle temporal gyrus of the left hemisphere (see Figure 2, bottom right). Although not significant, these peaks are well within the region found to be activated in healthy volunteers during this same task (Davis & Johnsrude, 2003). Similarly, the activation foci are extremely close to those regions that were activated by the same comparison in the patient, nine months earlier (see Figure 2, bottom left).

In the semantic ambiguity fMRI study, the contrast between all the speech conditions (irrespective of ambiguity) plus the signal correlated noise versus silence baseline yielded a pattern of activation very similar to the speech versus silence contrast of the initial PET investigation, although all of these

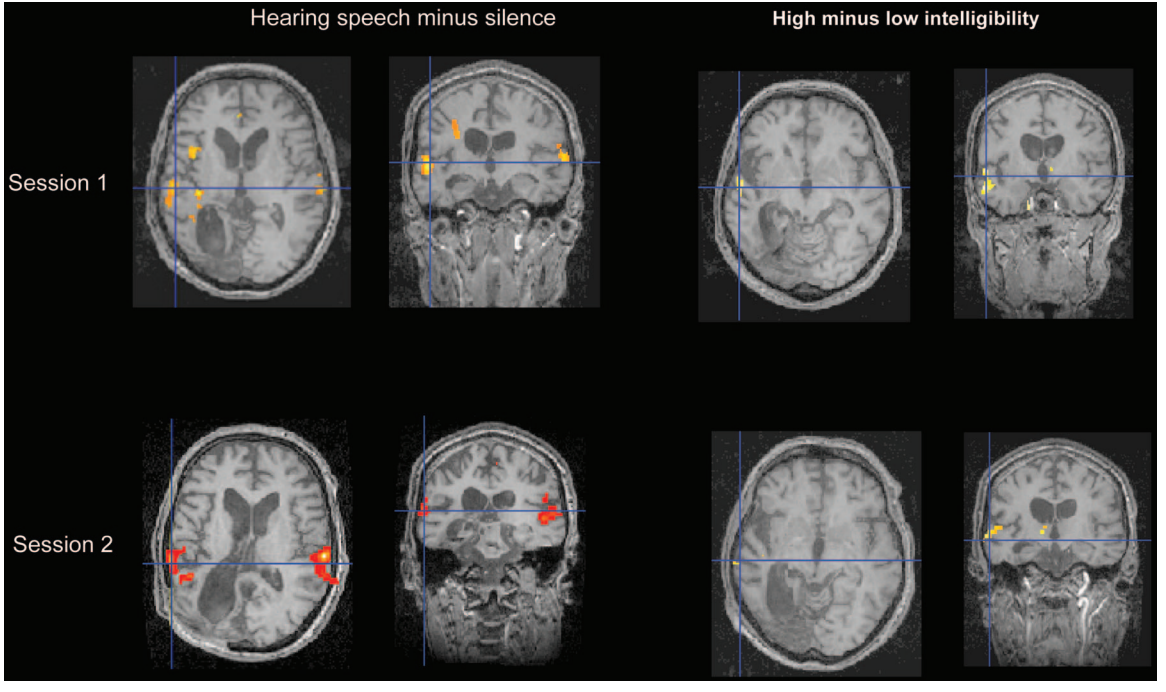

Figure 2. Activation data from the two PET sessions, nine months apart. (1) Hearing speech minus silence during the first PET session (top left) reveals activity bilaterally in the superior temporal gyrus. (2) Hearing speech minus silence during the second PET session (bottom left) reveals very similar activity bilaterally in the superior temporal gyrus. (3) High intelligibility speech minus low intelligibility speech during the first PET session (top right) reveals activity predominantly in the left superior temporal gyrus. (4) High intelligibility speech minus low intelligibility speech during the second PET session (bottom right) reveals very similar activity predominantly in the left superior temporal gyrus. The patient's left hemisphere appears left of figure.

changes were statistically significant. Thus, large areas of activity were observed bilaterally in the middle and superior temporal gyri all of which survived correction at $p < .05$. When the combined high and low ambiguity sentences were compared to signal correlated noise, significant changes in signal intensity were again observed, bilaterally, in the middle and superior temporal gyri (see Figure 3, upper panel), a pattern which is very similar to that observed in healthy volunteers (see Figure 3 lower panel; see also Rodd et al., in press). This activity, although distributed over a larger area of the temporal cortex, incorporates that region that was activated in the comparison between high and low intelligibility sentences in both of the previous PET studies in this same patient (see Figure 2). In addition to the temporal lobe foci, an area of significantly increased activity was also seen in the left inferior frontal gyrus (see Figure 3).

For the high-ambiguity sentences compared to low-ambiguity sentences no statistically significant increases in signal intensity were observed anywhere in the brain when a conservative whole brain correction method was employed. A directed search within the predicted left posterior inferior temporal cortices and the inferior frontal gyrus, bilaterally, was then conducted

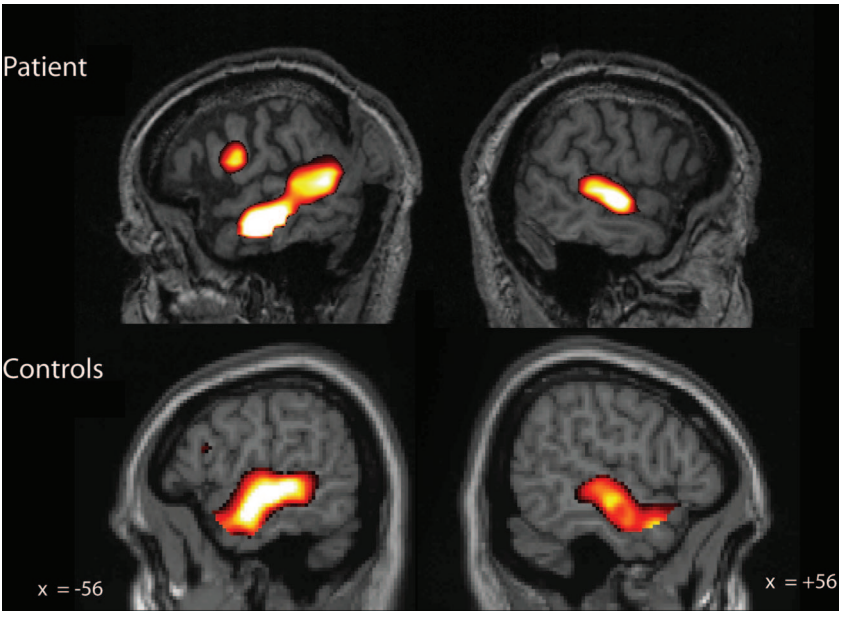

Figure 3. fMRI data from the hearing speech (ambiguous plus unambiguous sentences) minus signal correlated noise contrast. In both the patient (top) and a group of healthy volunteers (bottom; from Rodd et al., in press) a very similar pattern of signal intensity changes is observed in the superior temporal lobe, bilaterally.

using a regions of interest (ROI) generated from an independent data set obtained previously in healthy volunteers (Rodd et al., in press). Because the data from the patient were not spatially normalised, it was necessary to use anatomical landmarks identified by one member of the research team (DKM) who was blind to the hypothesis, to identify the appropriate regions for analysis in the patient. The ROI analysis revealed responses in the patient that were well within the normal range in the left posterior inferior temporal region, but there was no evidence for the predicted changes in the inferior frontal gyrus in either hemisphere (Figure 4).

DISCUSSION

In this exploratory study, we investigated how longitudinal functional neuroimaging might be used to investigate residual auditory processing in a single

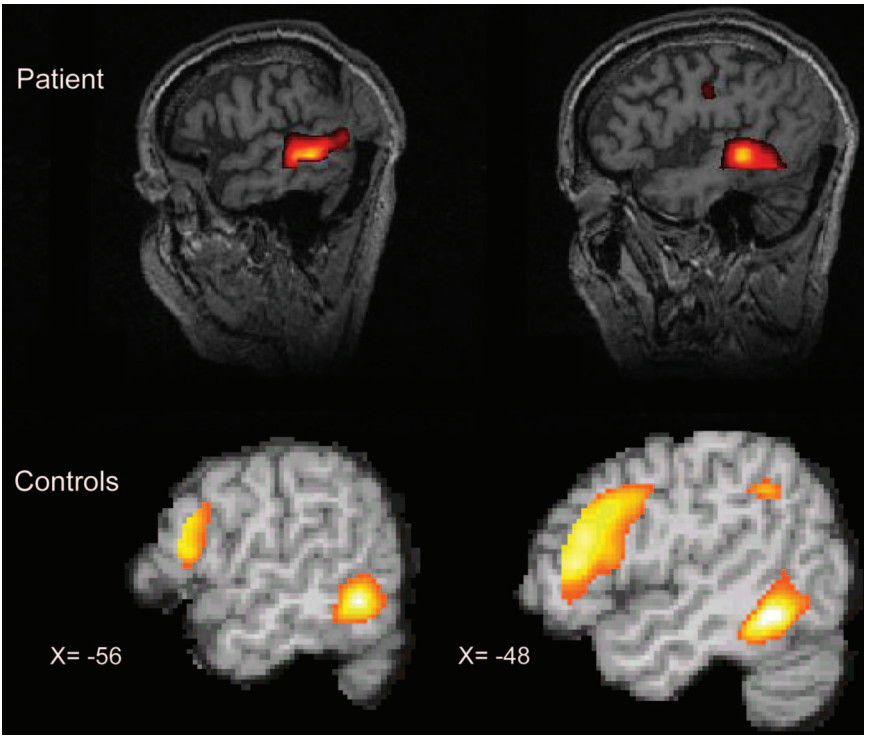

Figure 4. fMRI data for the ambiguous sentences versus unambiguous sentences comparison. Like controls (bottom; from Rodd et al., in press), the patient exhibited significant signal intensity changes in the left posterior inferior temporal cortex, but (unlike controls), not in the inferior frontal gyrus.

patient meeting the clinical criteria for PVS. Two established auditory paradigms, involving speech intelligibility and semantic ambiguity, respectively, were employed during two (repeated) PET activation studies and one fMRI investigation. The results clearly illustrate that functional neuroimaging has the potential to demonstrate distinct and specific physiological responses to controlled external stimulation in the absence of any overt response on the part of the patient. They also clearly demonstrate, however, that the technique poses a number of unique methodological, ethical and procedural problems. For example, like most patients diagnosed as PVS, motor responses were minimal in the patient studied here and by definition could not be elicited directly (e.g., wilfully) by external stimulation. In addition, even if we had assumed *a priori* that some level of residual cognitive processing did exist, there was no reliable mechanism for ensuring that the presented stimuli were actually *perceived* by the patient. Many PVS patients suffer serious damage to auditory and/or visual input systems, which may impede performance of any 'higher' cognitive functions (e.g., voice discrimination), which place demands on these "lower" sensory systems (e.g., hearing). In both of the paradigms selected here (speech intelligibility and semantic ambiguity), the various levels of processing assessed were designed to have broadly similar basic acoustic and sensory properties; thus, any differences observed *between* those levels could not be attributed to a basic lack of perception on the part of the patient. Like patients with any form of serious brain damage, PVS may also be accompanied by a significant reduction in attention span (assuming some level of cognitive processing remains), which may further complicate the assessment of higher cognitive functions. Again, in the current study, the paradigms were chosen such that different levels of each task made similar demands on attention. For example, in healthy volunteers, the ambiguity in the sentences used in the fMRI study goes largely unnoticed (Rodd et al., in press). The additional semantic processes that are required for the comprehension of ambiguous sentences are invoked relatively "automatically", without healthy participants reporting that they were aware of the increased difficulty of comprehension. Thus, semantic ambiguity appears to recruit additional comprehension processes that may be dependent on the inferior temporal and frontal regions without these processes being deliberately and consciously invoked.

Finally, data processing of functional neuroimaging data may also present challenging problems in patients with PVS. In the current study, for example, the presence of focal pathology did not complicate co-registration of functional data (PET and fMRI) to anatomical data (e.g., acquired using structural MRI), but it did preclude the spatial normalisation of the patient's images to a healthy reference brain. Under these circumstances statistical assessment of activation patterns is anatomically imprecise and activation foci could not be localised in terms of standard stereotaxic coordinates.

Notwithstanding these methodological and theoretical caveats, the current study yielded compelling evidence for high level residual auditory processing in the PVS patient. Thus, at four months post-ictus, a comparison of speech sounds with silence yielded activity bilaterally in a region of the superior temporal gyrus very similar to that which has been activated using similar comparisons in healthy volunteers. More importantly, a comparison of high intelligibility sentences with low intelligibility sentences designed to isolate any residual activity related specifically to the comprehension of spoken language revealed two foci in the patient in the superior and middle temporal gyri of the dominant (left) hemisphere. While it was not possible to relate these foci to control data within standard stereotaxic space (because spatial normalisation of the damaged brain was not possible) a qualitative comparison with data from healthy volunteers revealed remarkable similarity between the two (Davis & Johnsrude, 2003). More importantly perhaps, the pattern of activation observed during the first PET study was both qualitatively and quantitatively similar to that observed nine months later when an identical procedure was carried out. Although anatomical and global blood flow factors preclude direct statistical comparisons between the two sessions, examination of Figure 2 reveals a startling similarity between the activation patterns observed in temporal-lobe auditory areas in both cases. In short, notwithstanding qualitative differences that are well within the range that would be expected given normal inter-subject variability, the pattern of activation observed in the patient during the two PET sessions was similar to that observed in healthy awake control volunteers while performing identical tasks.

This finding has a number of important theoretical and clinical implications. First and foremost, it suggests that whatever level of residual cognitive activity existed in the patient, it was persistent across time and remains, at least until 13 months post-ictus. Second, the results suggest that some level of speech comprehension is preserved in this patient; the different activation patterns observed could not simply be due to the perception of sounds in general as the basic acoustic properties of the stimuli were well matched across conditions. However, whether the responses observed reflected speech comprehension per se (i.e., understanding the contents of spoken language), or a more basic response to the acoustic properties of intelligible speech that distinguish it from less intelligible speech could not be determined on the basis of this data alone.

The fMRI study in the same patient both confirmed and extended the PET investigations. Thus, a comparison of speech with signal correlated noise revealed bilateral changes in signal intensity in the middle and superior temporal gyri that, unlike the PET data, survived statistical correction for multiple comparisons (Figure 3). This finding suggests that in future, fMRI may provide a statistically more robust approach to the assessment of PVS

patients using functional neuroimaging. The findings also add to the corpus of data in this patient suggesting that some level of speech comprehension was intact despite the clinical diagnosis. The comparison of ambiguous versus unambiguous sentences in this patient partially confirmed this suggestion still further and, in addition, suggests that some of the semantic aspects of speech comprehension are partially preserved. Thus, signal intensity changes within the normal range were observed in the posterior inferior temporal lobe when ambiguous sentences were compared with unambiguous sentences, although (unlike healthy volunteers), consistent activation was not observed in the inferior frontal gyrus. These results suggest that some of the processes involved in activating and selecting contextually appropriate word meaning may be intact in the patient, despite his clinical diagnosis of PVS.

The question therefore arises as to whether the presence of some "normal" activation in this patient indicates some level of "awareness" similar to that which (presumably) exists in healthy volunteers when performing similar tasks. One possibility, which must be considered, is that the diagnosis of PVS was unwarranted in this case and the patient was in fact at a stage of recovery which, while eluding conventional diagnosis, nevertheless yielded patterns of activation that were similar to those seen in healthy control volunteers. If that were the case, then the possibility of "minimal awareness" as an accompaniment to, and partial explanation for, the neural changes observed cannot be ruled out. Notwithstanding this possibility, definitive judgements regarding "awareness" or "consciousness" in this and similar patients are difficult based on the data presented here, although a number of clear conclusions can be drawn. For example, it is clear that the patient was perceiving something more complex than pure sound (as indexed by the significantly increased activity in response to speech relative to signal correlated noise), confirming that some component of the *perception* of speech was relatively preserved. Second, the fact that a significant response was observed to speech of increasing intelligibility suggests that these perceptual processes are recruited more strongly for speech that can be more readily understood. These results could be interpreted as suggesting that *comprehension* may also have been relatively preserved. One piece of evidence that supports this final conclusion was our observation of a significant response to ambiguous sentences, showing that some *semantic* aspect of sentences can alter neural activity; in other words, not only did the patient's brain recognise speech as speech, but it was also being processed at a level sufficient to detect when words with multiple meanings were presented. Whether this semantic activity can also be elicited in other situations in which sentences are not consciously perceived (e.g., during sleep) remains a critical issue for future investigations with normal volunteers.

In summary, there is a clear need to improve our characterisation of the clinical syndrome of PVS, not only to redefine diagnosis, but also to stratify

patients in terms of the depth and breadth of residual cognitive functioning. This has major implications, not only for prognosis, but also for possible responses to novel therapies that may emerge in the future. The use of functional neuroimaging in this context will clearly continue to present logistic and procedural problems. However, the detection and elucidation of residual cognitive function in this group of patients has such major clinical and scientific implications that such an effort is clearly justified.

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