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# Detecting Residual Cognitive Function in Persistent Vegetative State

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## Abstract

**Despite converging agreement about the definition of persistent vegetative state, recent reports have raised concerns about the accuracy of diagnosis in some patients, and the extent to which, in a selection of cases, residual cognitive functions may remain undetected. Objective assessment of residual cognitive function can be extremely difficult as motor responses may be minimal, inconsistent, and difficult to document in many patients, or may be undetectable in others because no cognitive output is possible. Here we describe strategies for using $H_2{}^{15}O$ positron emission tomography activation studies to study covert cognitive processing in patients with a clinical diagnosis of persistent vegetative state. Three cases are described in detail. Of these, two exhibited clear and predicted regional cerebral blood flow responses during well-documented activation paradigms (face recognition and speech perception) which have been shown to produce specific, robust and reproducible activation patterns in normal volunteers. Some months after scanning, both patients made a significant recovery. In a third case, blood flow data were acquired during a speech perception task, although methodological difficulties precluded any systematic interpretation of the results. In spite of the multiple logistic and procedural problems involved, these results have major clinical and scientific 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

Persistent vegetative state (PVS) was formally defined by Jennett and Plum (1972) and described as a state of 'wakefulness without awareness'. Aetiology is variable, although the condition may arise as a result of a road traffic accident, ischaemic attack, anoxia, encephalitis or viral infection. A diagnosis of PVS is not normally considered until between 1 and 3 months post-ictus at which point there must be no evidence of sustained, reproducible, purposeful or voluntary behavioural response to visual, auditory, tactile or noxious stimuli. There must also be no evidence of language comprehension or expression, although there is generally sufficiently preserved hypothalamic and brain stem autonomic functions to permit survival with medical care. Although PVS often follows coma, it is characterized by an irregular but cyclic state of circadian sleeping and waking. In contrast, patients in coma present with eyes closed and lack any consistent sleep–wake cycles.

The majority of imaging studies in patients with PVS have used either fluorodeoxyglucose (FDG) positron emission tomography (PET) or single photon emission computed tomography (SPECT) and have reported widespread reductions of up to 50% in (resting) cerebral blood flow and glucose metabolism (Levy *et al.*, 1987; DeVolder *et al.*, 1994; Tommasino *et al.*, 1995). In some cases, however, isolated 'islands' of metabolism have been identified in circumscribed regions of cortex, which may suggest residual cognitive processing in a subset of patients (Schiff and Plum, 1999). While metabolic studies are useful in this regard, they can only identify functionality at the most general level; that is, mapping cortical and subcortical regions that are potentially recruitable, rather than relating neural activity within such regions to specific cognitive processes (Momose *et al.*, 1989; Turkstra, 1995).

To some extent, electrophysiological studies do not suffer this same limitation and have been applied successfully to the problem of PVS (Turkstra, 1995), although with the exception of magnetoencephalography (MEG), these approaches lack sufficient spatial resolution to assess fully

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cognitive function in these patients. Unfortunately, MEG is still not widely available and, in any case, comparative data from healthy volunteers remain sparse.

So-called 'activation studies' using $H_2{}^{15}O$ PET or functional magnetic resonance imaging (fMRI) together with established sensory paradigms may provide a viable method for assessing cognitive processing in patients with PVS. In short, given the unique problem of assessing patients with PVS, 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. The technique does, however, pose a number of methodological, ethical and procedural problems. For example, motor responses are often minimal, inconsistent or absent in patients with PVS and by definition cannot be elicited directly (e.g. willfully) by external stimulation. In addition, even assuming that some level of residual cognitive processing does exist, there is no reliable mechanism for ensuring that the presented stimuli are 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). 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. Spontaneous movements during the scan itself may also compromise the interpretation of functional neuroimaging data, particularly scans acquired using fMRI. Where PET methodology is employed, issues of radiation burden must also be considered and may preclude longitudinal or follow-up studies in many patients. Finally, data processing of functional neuroimaging data may also present challenging problems in patients with PVS. For example, the presence of gross hydrocephalus or focal pathology may complicate co-registration of functional data (e.g. acquired with PET or fMRI) to anatomical data (e.g. acquired using structural MRI), and the normalization of images to a healthy reference brain. Under these circumstances statistical assessment of activation patterns is complex and interpretation of activation foci in terms of standard stereotaxic coordinates may be impossible.

In this study we used $H_2{}^{15}O$ PET to study covert cognitive processing in three patients with a probable clinical diagnosis of PVS. In the first case, a decision was made to use visual (face) stimuli on the basis of a preliminary PET study that demonstrated activation in primary visual cortex (V1) in response to moving coloured visual stimuli on a computer screen. The decision was reinforced further by non-reproducible reports of visual pursuit in response to faces of family and friends. In the second patient, an auditory (speech) task was employed on the basis of anecdotal reports of occasional movement following verbal commands and intact brain auditory evoked responses on one side. In a third patient, speech recognition was also employed as the paradigm for investigation, but procedural complications during the scanning session precluded the acquisition of any useful data.

## Materials and methods

### *Case histories*

Case 1 (KB) was a 26-year-old female who presented with an acute febrile illness which culminated in a depression of her conscious state. MRI revealed widespread hyperintensity in the brain stem, both thalami, and anterior and medial temporal lobes. At first assessment, 4 months after admission, her eyes opened spontaneously and she exhibited sleep–wake cycles. Anecdotal evidence suggested that she occasionally followed family members with her eyes, but despite repeated examination, the patient showed no consistent spontaneous or elicited motor responses or eye movements to suggest that she could communicate. The pons and mid-brain components of brain stem auditory evoked responses were abnormal, but a delayed auditory oddball P300 could be detected. A diagnosis of probable PVS was made. Clinical findings and examination of cerebrospinal fluid were consistent with acute disseminated encephalomyelitis. MRI showed hyperintensity in the brain stem and small foci of hyperintensity in both thalami and in the medial right temporal lobe on T2-weighted images. When assessed the patient had a tracheotomy, was fed through a gastrotomy and was doubly incontinent.

The second patient (DE), a 30-year-old female bank manager, suffered severe head injuries during a road traffic accident involving a head-on collision with another vehicle. During a significant period trapped in the car, she probably suffered a period of hypoxia with hypotension. The Glasgow Coma Scale at the scene of the accident indicated a score of 4/15 with no improvement post-resuscitation. A long stay in intensive care was accompanied by episodes of pupillary unreactivity on more than one occasion. Fourteen weeks post-ictus, the pupils remained dilated and unreactive. The patient was weaned off a ventilator but still required a tracheotomy. Brain stem auditory evoked responses were intact on the right but abnormal on the left. Computed tomography (CT) findings at admission revealed a left frontal subcortical haemorrhagic contusion and a smaller frontoparietal contusion. A small haemorrhage in the inter-peduncular fossa with low-density areas in the adjacent mid-brain–pons region were also observed. A repeat scan on the same day showed fresh midline haemorrhage in the anterior mid-brain extending to posteromedial right thalamus. In addition, punctuate areas of high density in the right cerebellum and both cerebral hemispheres suggested diffuse axonal injury. The cerebral ventricles were noted to be normal in size. Over several weeks she developed a withdrawal to pain but showed no consistent evidence of volitional activity. In spite of this, the family felt that, when not tired, the patient occasionally

showed responses to commands. She was doubly incontinent, fed through a gastrotomy and required 24-h nursing care.

The third patient (JB) was a 28-year-old female with probable mixed connective tissue disease treated with immunosuppression. She suffered cardiorespiratory arrest during an episode of acute deterioration and was left in a PVS. Four months post-ictus the patient exhibited no signs of neurological awareness, was fed via a nasogastric tube and was incontinent with no voluntary movements or responses to external stimuli.

Informed written consent for participation was obtained for each 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.

### *Control subjects*

A healthy, 30-year-old, male (TM), control volunteer with English as his first language and no history of neurological or neuropsychiatric disturbance or substance abuse, was selected for comparison with patient KB. Local ethical considerations precluded the testing of a young female (i.e. gender-matched) volunteer. The control subject underwent precisely the same scanning conditions as patient KB (see below), and the data were analysed using an identical procedure (see Scanning methods). Informed, written consent for participation in the study was obtained after its nature and possible consequences had been explained to him.

It was unfortunately not possible to acquire single-subject matched control data for the two remaining patients within the context of this preliminary investigation. However, the paradigm employed in these two patients is very well established and has been used in previous studies in healthy control volunteers. Therefore, the data from these two patients were compared with that published previously on six normal healthy male control subjects (age range 26–58 years) using an identical paradigm (Mummery *et al.*, 1999). Full details of that study will not be replicated here, although all subjects had English as their first language and none had any significant history of neurological or neuropsychiatric disturbance or substance abuse.

### *Image acquisition and data analysis*

In patients KB, DE and JB and in the normal control volunteer TM, 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. Patient KB underwent two separate PET investigations (see below) comprising 12 and 15 scans, respectively, while DE, JB and TM were each scanned within a single PET session comprising 12 scans. Using the bolus $H_2{}^{15}O$ methodology, rCBF was measured during the 12 separate scans (or 15 in the case of the second session for patient KB, see below). For each scan, the subjects received a 20-s intravenous bolus of $H_2{}^{15}O$ through a forearm cannula at a concentration of 300 Mbq/ml and a flow rate of 10 ml/min. With this method, each scan provides an 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, normalized for global CBF value and averaged within each patient 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 (SPM 96, provided by the Wellcome Department of Cognitive Neurology, London, UK), with a condition effect for each of the conditions, using global CBF as a confounding covariate. For each patient, a three-dimensional MRI volume ($256 \times 256 \times 128$ pixels, 3 mm thick) was acquired and resliced so as to be co-registered with the PET data. The co-registered PET data were transformed into standard stereotaxic space using conventional algorithms within the SPM 96 analysis environment. The significance of a given rCBF difference was assessed by application of an intensity threshold to the SPM images (Worsley *et al.*, 1992, 1996). This threshold, based on three-dimensional Gaussian random field theory, predicts the likelihood of obtaining a false positive in an extended three-dimensional field.

### *Stimuli and testing conditions*

Across the patients and control subject, three separate paradigms were employed and are described below.

*Visual stimulation (patient KB only).* This task was used during a pilot study of patient KB, the purpose of which was to ascertain whether the logistic problems associated with PET scanning PVS patients could be overcome and, more importantly, whether any significant changes in rCBF could be detected. During six scans, a standard Windows 95 screen saver (Microsoft) involving rapidly moving coloured 'windows' was employed. The moving image was presented on a 20″ computer monitor mounted approximately 50 cm in front of the patient. The patient's eyes remained open for all six scans. During six further scans, no visual image was presented and the patient's face was covered with a light cloth to prevent any visual stimulation. All 12 scans (six experimental scans and six control scans) were presented in pseudo-random order. This preliminary PET study was carried out approximately 1 month before the second study of familiar face perception, described below.

*Familiar face perception (patient KB and control subject TM).* Ten photographs were obtained from the relatives of patient KB and control subject TM. In neither case was the participant aware of which photographs had been provided, although presumably they were all familiar. The photographs were chosen so as to include, as their main theme, faces of

**Fig. 1.** Example stimuli from the familiar face perception condition (left) and the corresponding control task (right). Control pictures were prepared by distorting and/or repixellating the experimental stimuli to remove any clear structure from the images.

friends, family, pets and the participant themselves. The photographs were digitized at high resolution and were presented in a large format (approximately 30 $cm^2$) against a black background on a high-resolution computer monitor. The monitor was suspended approximately 50 cm above the subject in the scanner and was therefore placed at a comfortable viewing distance. A set of 10 control pictures was also prepared by distorting and/or repixellating the same two sets of 10 photographs to remove any clear structure from the images (see Fig. 1). Specifically, the original photographs were altered such that the overall luminance, colour range, and solid angle subtended by the pictures and control images were identical. During the scans the photographs (experimental condition) or repixellated pictures (control condition) were presented on the computer screen for 12 s each, starting 30 s before tracer infusion was initiated and continuing until the end of data acquisition. During the experimental scans the patient and the control volunteer were told to look at each of the faces and to 'think about that person'. During the control scans the subjects were told to 'look at each of the images'.

Although 12 scans (six experimental and six control) were planned in patient KB (as in control subject TM), during three of the scans the patient appeared to close her eyes and fall asleep. Although the data acquired during these scans are plotted in Fig. 2 for reference, they were not used in the comparison of the familiar face perception condition with the control condition. Three additional scans (making 15 in total) were conducted in order that a balanced data set was available for analysis.

*Speech perception (patients DE and JB).* In the speech perception tasks the patients were scanned while being presented binaurally with either spoken words (experimental condition), or signal-correlated noise stimuli, or no auditory stimulus at all (rest condition). The presented words were disyllabic nouns matched for frequency (6–20 000), concreteness (400–700), and imageability (300–700) on the Medical Research Council Psycholinguistic Database (Coltheart, 1981), and were pre-recorded on a tape by a speaker, the rate being controlled by a metronome. The signal-correlated noise stimuli were made by selecting a sample of these spoken nouns with varying segmental durations and initial manners of articulation, digitizing them and then multiplying these with noise. The two sets of stimuli were matched for loudness by adjusting the amplification until they were subjectively similar. The task instruction was to 'pay attention to the stimuli without responding' or, in the rest condition, just to rest. In both stimulus conditions, the words were presented at rates of 30 per minute and presentations were started 30 s prior to tracer infusion and continued until the end of data acquisition.

### *Determination of significance thresholds*

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. For example, Haxby *et al.* (1991) examined rCBF changes while healthy control subjects performed face matching, dot matching or a sensory motor control task. Face matching alone activated occipitotemporal area 37 in the posterior fusiform gyrus, bilaterally. In a follow-up study (Haxby *et al*., 1994), the subjects were required to match faces in one set of scans while in control scans scrambled patterns of equivalent visual complexity were shown. The most specific changes in rCBF associated with face perception (relative to both spatial perception and perception of scrambled visual stimuli) were observed in regions of the mid-fusiform and mid-anterior fusiform gyri (areas 19 and 37).

In spite of this background, single-subject studies using PET are rare and for this reason we elected to apply a standard face recognition paradigm, similar to that employed by Haxby *et al.* (1991, 1994), to the patient with PVS (KB) and to the control subject (TM) using an identical procedure in each case. Accordingly, a significant change in rCBF during face perception was predicted in the posterior section of the fusiform gyrus (area 19), particularly in the right hemisphere. Within this region a directed search was

conducted and the threshold for reporting a peak as significant was set at $P < 0.001$, 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 as significant was set at $P < 0.05$, corrected for multiple comparisons.

Unfortunately, within the constraints of the clinical investigation, it was not possible to scan any control subjects using the speech perception task. However, an identical investigation has been carried out previously and on the basis of published findings from that study (Mummery *et al.*, 1999) significant rCBF changes were predicted in our patients within the superior temporal cortex of both hemispheres. For these defined regions the significance threshold was set at $P < 0.001$, uncorrected. For all other regions, significance was set at $P < 0.05$, corrected. In all cases only regions satisfying these criteria are reported.

## Results

### *Visual stimulation (patient KB only)*

A comparison of the six control scans (eyes covered, no stimulation) with the six experimental scans (visual stimulation; 'flying windows' screen saver) yielded one significant focus of activation in primary visual cortex at coordinates 8, –92, 4 ($z = 4.59$, $P = 0.031$). Intriguingly, a second activation focus was observed within the right dorsolateral frontal cortex (45, 34, 21; $z = 3.91$, $P = 0.348$), although this failed to reach statistical significance according to our conservative criteria.

### *Familiar face perception (patient KB and control subject TM)*

In patient KB, subtraction of the six waking scans during which repixellated control images were presented from the six waking scans during which familiar faces were presented yielded just two significant peaks of activation that survived the statistical threshold described above. Specifically, two regions within the right fusiform gyrus (Brodmann area 37) were significantly activated at coordinates 38, –64, 0 ($z = 3.90$, $P = 0.001$) and 44, –66, –20 ($z = 3.65$, $P = 0.001$) (Fig. 2). The reverse subtraction yielded no significant foci of activation.

In control subject TM, the equivalent subtraction yielded a significant activation focus at very similar coordinates (see Fig. 2) within area 37 of the right fusiform gyrus (34, –76, –6; $z = 5.07$, $P < 0.001$). In addition, significant rCBF changes were observed in a similar region within the left fusiform gyrus (–36, –64, 0; $z = 5.08$, $P < 0.001$), as well as slightly more anteriorly in area 37 of the same hemisphere (–28, –44, –10; $z = 4.76$, $P = 0.016$) and in primary visual cortex (10, –94, 2; $z = 4.64$, $P = 0.026$). The reverse subtraction yielded no significant foci of activation.

### *Speech perception (patients DE and JB)*

In patient DE, the comparison of signal-correlated noise stimuli with rest revealed significant foci of activation bilaterally in the auditory region (–40, –6, –2; $z = 3.92$, $P < 0.001$ and 46, –30, 12; $z = 3.79$, $P < 0.001$), suggesting that basic auditory processes were at least somewhat functional. Knowing this, it is possible to compare speech with signal-correlated noise stimuli, in the hope of observing activation that is more specific to speech sounds. The comparison of speech sounds with signal-correlated noise stimuli revealed significant rCBF increases on the superior temporal plane bilaterally (68, –16, –10; $z = 3.59$, $P < 0.001$ and –60, –12, 2; $z = 3.01$, $P < 0.001$) and posterior to auditory cortex, in the region of the planum temporale, in the left hemisphere only (–54, –34, 10; $z = 3.30$, $P < 0.001$) (see Fig. 3). The reverse subtraction yielded no significant foci of activation. These findings correspond closely with PET results from a recent study of six healthy control subjects using identical stimuli (Mummery *et al.*, 1999). For example, in that study, significant activation was observed bilaterally on the superior temporal plane, including auditory areas, extending into the superior temporal sulcus (see Fig. 3). Although, from this figure, activation in the Mummery *et al.* (1999) study appears to be bilaterally symmetrical in its posterior extent, they report a unilateral left posterior temporal focus at –54, –38, 8, which is 4 mm from the posterior temporal focus in DE: this difference is not spatially resolvable with the PET technique. Zatorre *et al.* (1992), in another study comparing speech and noise, have also reported left posterior temporal activation, although 13 mm more anterior than the focus in DE and the study of Mummery *et al.* (1999).

Unfortunately, despite being well rested prior to the session, patient JB exhibited gross spontaneous (seemingly arbitrary) movements during the PET scanning session. Although 12 scans were obtained (six experimental, six control) and the data were analysed, the movement indices generated by SPM indicated that the results of any statistical analyses should be considered, at best, to be extremely unreliable. In any event, subtraction of control (signal-correlated noise stimuli) from test stimuli (speech) revealed no significant foci of activation.

## Discussion

In this exploratory study, we investigated how functional neuroimaging might be used to investigate residual cortical processing in patients diagnosed with PVS. Two established sensory paradigms, familiar face perception and speech recognition, were employed in three PVS patients who had otherwise shown no evidence of sustained, reproducible, purposeful or voluntary behavioural responses to visual, auditory, tactile or noxious stimulation. In two cases (KB and DE), rCBF responses were observed which closely resembled those seen in healthy control subjects carrying out identical tasks. In the third patient (JB), logistic complications

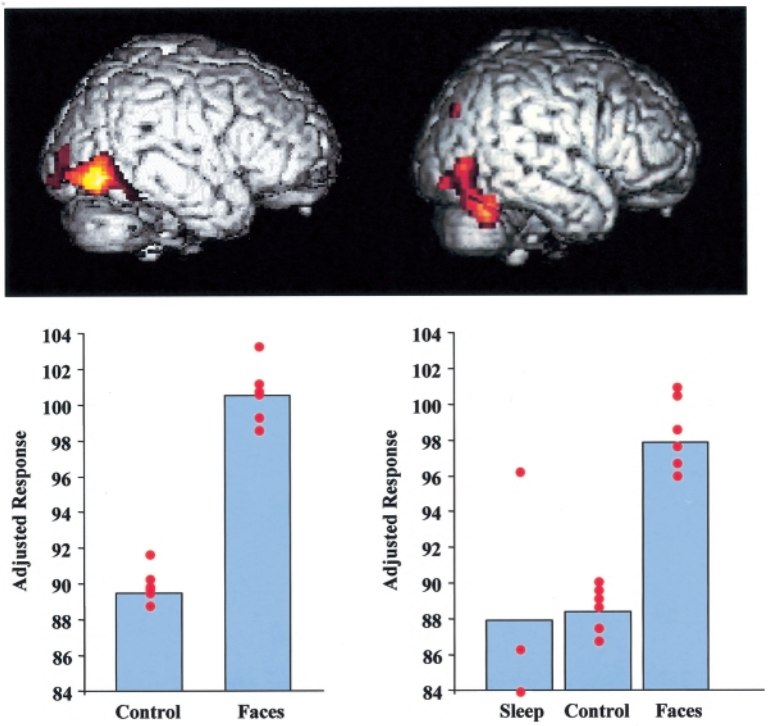


**Fig. 2.** Surface rendered normalized positron emission tomography (PET) data from the familiar face perception task superimposed on a standard three-dimensional magnetic resonance template (top). The subtraction shown is faces minus control stimuli for patient KB (right) and the control volunteer TM (left). In both cases, strong right hemisphere activation in the fusiform gyrus is clearly visible. The graphs below represent individual adjusted blood flow responses for each scan (dots) within each condition at peak coordinates within this region. Patient KB fell asleep during three scans (labelled 'sleep') and these data were not used in the comparison faces versus control.

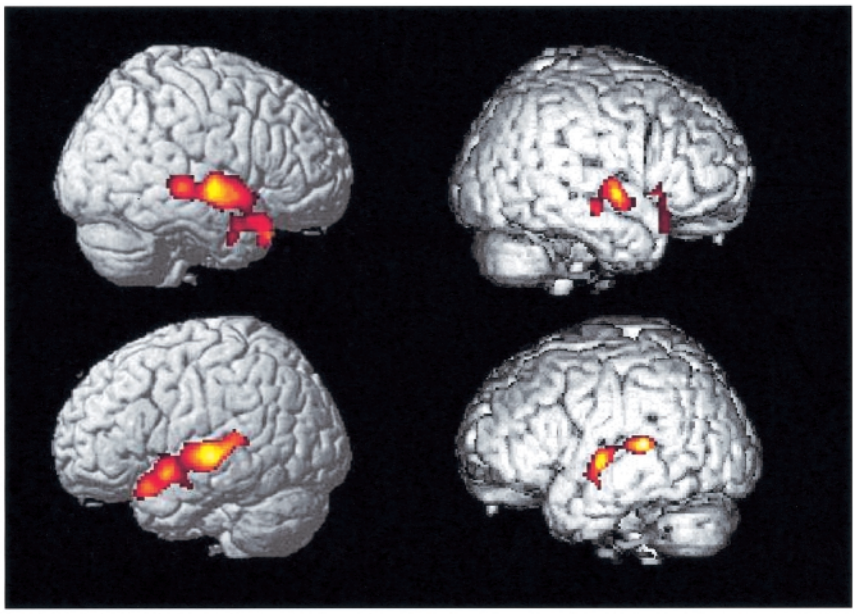

**Fig. 3.** Surface rendered normalized positron emission tomography (PET) data from the speech perception task superimposed on a standard three-dimensional magnetic resonance template. Left (bottom) and right (top) hemispheres are shown for patient DE (right) and average data from six control volunteers (left) published previously by Mummery *et al.* (1999). The subtraction shown is speech minus signal-correlated noise. In both the patient and the control subjects, strong bilateral activation in the superior temporal gyrus (anterior and posterior sectors) is clearly visible.

during the scan acquisition period could not be overcome and no reliable data were obtained.

In patient KB, subtraction of the control stimuli from the familiar face stimuli yielded two significant foci of activation, both in the right fusiform gyrus of the occipitotemporal region (area 37). Neuropsychological evidence from brain-damaged patients has long since suggested a role for this region in face recognition; patients suffering from prosopag-

nosia (the inability to recognize faces) are usually found to have focal damage in this cortical area. Activation in what has often been referred to as 'the human face area', has also been observed in many PET studies that have required participants to view face stimuli (e.g. Haxby *et al.*, 1991, 1994) and has been shown to be distinct from those cortical regions associated with location perception, as well as those mediating the perception of colour and motion. For example, Haxby *et al.* (1991) examined rCBF changes while healthy control subjects performed face matching, dot matching or a sensory motor control task. Face matching activated occipito-temporal area 37, bilaterally, in a region very similar to the one activated in patient KB in the current study. In a follow-up investigation, Haxby *et al.* (1994) used a paradigm even more similar to that used in the current study in healthy control subjects; volunteers were required to match faces in one set of scans, while in control scans 'scrambled' patterns of equivalent visual complexity were shown. The most prominent changes in rCBF during face perception (relative to both spatial perception and perception of 'scrambled' visual stimuli) were observed in regions of the mid-fusiform and anterior fusiform gyrus (areas 19 and 37), again, very close to those regions shown to be activated in the patient described in our study.

Although none of these studies, nor recent confirmatory studies using fMRI (Puce *et al.*, 1995, 1996), actually prove that the right fusiform gyrus is involved in face processing *per se* (for example, similar signal changes might well have been observed with any class of three-dimensional object), they do confirm that this region is more involved in the processing of meaningful objects than in the processing of nonsense visual patterns or letter strings. Kanwisher *et al.* (1997) extended these findings by identifying a cluster of voxels in the right middle fusiform gyrus that was consistently more active in 80% of participants when they were viewing photographs of faces than when they were viewing photographs of common objects. Crucially, both sets of stimuli used were similar along many dimensions that are probably important for low- and mid-level vision, including that they both depicted interpretable, meaningful three-dimensional entities. The face > object comparison was then used to define functionally a putative 'fusiform face area' in each of the participants and activity in this region was examined during additional tasks that involved different kinds of stimuli. For example, the hypothesis that the fusiform face area might be involved in distinguishing between exemplars of a homogeneous object set was examined by comparing responses to faces with responses to houses. Despite the fact that both faces and houses are single basic-level object categories, the fusiform face area response to faces was much greater. Similarly, the fusiform face area response to pictures of faces was found to be significantly greater than the response to pictures of hands, confirming that the fusiform face area does not simply respond equally to any part of the body [see also Kanwisher *et al.* (1999)]. When considered together, these studies provide convincing evidence that the region of the right fusiform gyrus activated in patient KB is selectively involved in 'face perception', and concurs fully with results derived from neuropsychological data in patients.

More importantly, perhaps, the pattern of activation observed in KB was both qualitatively and quantitatively similar to that observed in a single, healthy control volunteer (TM) selected for comparison with KB and scanned during an identical paradigm. Although anatomical and global blood flow factors precluded direct statistical comparisons between the two subjects, examination of Fig. 2 reveals a startling similarity between the activation observed in the right fusiform gyrus in both cases. Significant activation foci were also observed in control subject TM in a similar region of the left fusiform gyrus as well as in primary visual cortex. While these additional changes in rCBF might indicate less widespread recruitment of regions involved in face perception in patient KB, one should be cautious about drawing such strong conclusions based on qualitative comparisons between two individuals. For example, while the fusiform face area was identified on the right side in 12 of the 15 healthy volunteers studied by Kanwisher *et al.* (1997), activation in a similar region in the left fusiform gyrus was observed in six of these subjects.

In patient DE, subtraction of the signal-correlated noise stimuli from the speech sounds revealed significant activation bilaterally along the superior temporal gyrus including auditory areas and the planum temporale in the left hemisphere. These regions have been consistently activated in previous PET rCBF studies of conscious, healthy control subjects performing similar tasks that require the perception of speech sounds relative to non-speech stimuli. For example, Mummery *et al.* (1999) performed a PET study with six neurologically normal volunteers, using a stimulus paradigm very similar to that used with patient DE. The stimuli were identical, but these researchers used six different presentation rates with each subject. When speech was compared with signal-correlated noise, across all presentation rates, they found a broad swathe of activation along both superior temporal gyri, including auditory regions, extending ventrolaterally into the superior temporal sulcus, as shown in Fig. 3. Although, at first glance, activation in DE appears to be less intense and less extensive, this is probably not the case. DE was scanned four times in each condition; the normal data comprise 36 scans per condition, with a correspondingly greater chance of a voxel achieving significance. Given residual variations in normal structural and functional anatomy after spatial normalization, we would expect that activation would be more extensive when averaged across several subjects, compared with within a single subject. When these factors are taken into account, the activation observed in the patient is very similar to that seen in normal individuals. Furthermore, the sole unilateral activation, in the left posterior temporal region, was in a location indistinguishable from the unilateral left posterior focus observed in the Mummery *et al.* (1999) study. Furthermore, Mummery *et al.* (1999) demonstrated a speech-specific pattern of activation at this site: activation in this area correlated with the number

of speech stimuli presented, but not with the number of signal-correlated noise stimuli presented. Importantly, this was the only unilateral focus that exhibited such speech-specific behaviour, strongly implicating this area in higher-order, language-specific functions.

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 patients KB and DE was similar to that observed in healthy awake control volunteers while performing identical tasks. The question therefore arises as to whether the presence of 'normal' activation in these two patients indicates some level of 'awareness' similar to that which presumably existed in the control volunteers during their scanning session. Two possibilities present themselves; the first, which must be considered, is that neither patient KB nor DE warranted the diagnosis PVS, but were 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 was the case, then the possibility of 'minimal awareness' as an accompaniment to the rCBF changes observed cannot be ruled out. In this regard it is notable that both patients made a significant recovery in the months following their imaging session. Patient KB, for example, started to become responsive 6 months post-ictus (2 months after the second PET scan) and 2 years after her illness performed well on many cognitive tests and was able to communicate effectively using an electronic communication aid. Fifteen months later KB's cognitive functioning was well within the normal range for most functions assessed and she was able to enjoy reading, playing simple games and listening to music. At that time she had no memory for events at the time of her two PET scans.

An alternative possibility for the apparently 'normal' patterns of rCBF responses observed in KB and DE, is that these patients represent two further examples of vegetative patients who show limited, repetitive and unchanging fragments of cerebral function dissociated entirely from any apparent evidence of self-awareness [Plum *et al.*, 1998; Ribary *et al.*, 1998; Schiff *et al.*, 1999; for a discussion, see Schiff and Plum (1999), Menon *et al.* (1998, 1999)]. For example, one of three patients discussed by Schiff *et al.* (1999) infrequently expressed isolated words during a 20-year period of remaining in a PVS. A second patient expressed continuous non-targeted movements during wakeful periods, while a third exhibited occasional sham rage responses to a multitude of non-noxious exogenous stimuli (Schiff *et al.*, 1999). More importantly perhaps, one young man studied by the same group remained in a behaviourally unremarkable vegetative state for 6 years despite exhibiting near normal cerebral cortical metabolism measured by quantitative FDG PET. Based on cases such as these, Schiff and Plum (1999) concluded that the presence of isolated modules of processing in patients diagnosed as PVS cannot be taken by themselves to enable any degree of self-awareness.

On balance, definitive judgements regarding 'awareness' or 'consciousness' in these patients are impossible based on the data presented here, although they do provide clear directions for future work in this area. For example, it is clear that patient KB was not merely perceiving visual stimuli, but also processing them in such a way as to recognize content that was not based on primary image attributes such as colour, luminance, size or movement. Similarly, patient DE was clearly perceiving something more complex than pure sound (as indexed by the significantly increased rCBF in response to speech relative to signal-correlated noise stimuli); in this sense, it is clear that her brain recognized speech as speech, although the extent to which she was 'aware' or 'conscious' of familiar, meaningful words is entirely unclear. Schiff and Plum (1999) have recently posed the question with reference to patient KB, 'would familiar faces versus unfamiliar faces have led to a significant subtraction image?'. By analogy, one might ask of patient DE, 'would she have been able to (neurally) ''recognize'' (associate semantics with) words in English, as opposed to words in a language that she does not speak?'. These questions, of course, are important and intriguing and suggest a systematic strategy, by which the ladder of cognitive hierarchy could be climbed sequentially via a series of different studies in individual patients, leading ultimately to a clearer understanding of the extent to which each patient is 'aware' of the stimuli to which they are exposed.

Unfortunately, for the two patients scanned successfully in this study, multiple studies were not possible due primarily to considerations of radiation burden. With this in mind, in the case of patient KB we felt that the question of whether she could distinguish between familiar and unfamiliar faces was less important than 'is there a normal physiological responses to faces *per se*?' One possible solution to this problem may lie in the use of fMRI, which will allow the longitudinal acquisition of functional and anatomical data sets with high resolution and without the need for radiation exposure. While any single study (using PET, for example) may not allow us to address whether or not a given patient is 'conscious', an incremental approach using fMRI may permit us to infer more definitively the limits or otherwise of residual neural capacity. Unfortunately, at the present time, there are still significant logistical problems that will need to be overcome before patients with PVS can be scanned routinely with high-field MRI.

The results of the current study clearly illustrate many of the difficulties inherent in imaging patients with PVS. In particular, the choice of paradigm appears to be crucial, although this choice may be dictated largely by the clinical profile of individual patients. For example, abnormal brain stem auditory evoked responses in patient KB made the use of auditory stimuli inappropriate. The decision to use visual stimuli was made partly on the basis of a preliminary PET study, which demonstrated activation in primary visual cortex (V1) in response to moving coloured visual stimuli on a computer screen. Our decision was reinforced further by non-

reproducible reports in this patient of visual pursuit of familiar faces. In patients DE and JB the decision to use a speech perception paradigm was based on a number of factors, including anecdotal reports of occasional movement following verbal commands (in both patients) and intact brain auditory evoked responses on one side (in patient DE). Moreover, in all three patients, the choice of specific relatively low-level visual or auditory paradigms for testing cognitive processing was predicated on three considerations. First, the paradigm had to be sufficiently complex to exercise processes that were not simply involved in stimulus perception. Conversely, it was essential to avoid the use of too complex a paradigm, which might overload limited residual cognitive function and fail to demonstrate activation. Second, it was important to present the paradigm during periods of arousal in the spontaneous sleep–wake cycle of the patient. In this respect, auditory stimulation proved to be the most effective as the fact that patient KB fell asleep during three of her scans involving visual stimulation clearly precluded interpretation of those data sets. Finally, it was essential that the paradigm used was known to produce well-documented, specific, robust and reproducible activation patterns in normal volunteers.

In summary, there is a clear need to improve our characterization of the clinical syndrome of PVS, not only to redefine diagnosis, but also to stratify patients in terms of prognosis and 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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# Detecting residual cognitive function in persistent vegetative state

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## Abstract

Despite converging agreement about the definition of persistent vegetative state, recent reports have raised concerns about the accuracy of diagnosis in some patients, and the extent to which, in a selection of cases, residual cognitive functions may remain undetected. Objective assessment of residual cognitive function can be extremely difficult as motor responses may be minimal, inconsistent, and difficult to document in many patients, or may be undetectable in others because no cognitive output is possible. Here we describe strategies for using $H_2{}^{15}O$ positron emission tomography activation studies to study covert cognitive processing in patients with a clinical diagnosis of persistent vegetative state. Three cases are described in detail. Of these, two exhibited clear and predicted regional cerebral blood flow responses during well-documented activation paradigms (face recognition and speech perception) which have been shown to produce specific, robust and reproducible activation patterns in normal volunteers. Some months after scanning, both patients made a significant recovery. In a third case, blood flow data were acquired during a speech perception task, although methodological difficulties precluded any systematic interpretation of the results. In spite of the multiple logistic and procedural problems involved, these results have major clinical and scientific 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.

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## Primary diagnosis of interest

Persistent vegetative state

## Author's designation of case

KB, DE, JB

## Key theoretical issue

- Detecting residual cognitive function in patients with persistent vegetative state

*Key words*: positron emission tomography; magnetic resonance imaging; cognition; imaging

## Standardized assessment

Glasgow Coma Scale

## Lesion location

- Brain stem

## Lesion type

Various

## Language

English