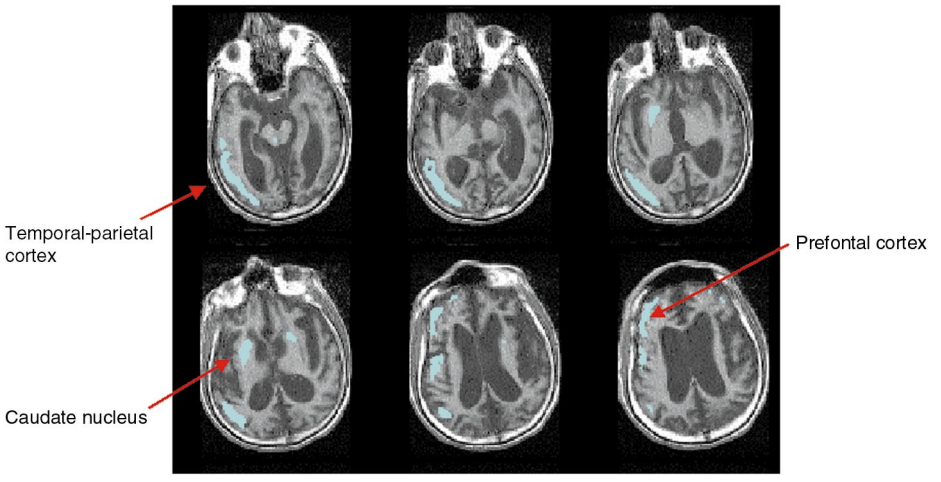

Fig. 1. Random prosodic processing in persistent vegetative state. FDG-PET data (measuring resting metabolism) coregistered onto MRI images. Average cerebral metabolism was reduced to ~30% of normal. The blue colored areas in the successive horizontal images represent regions of slightly increased activity, functioning between ~30–40% of normal. MRI images reveal marked atrophy consistent with progressive cerebral cell loss. (Adapted from Ref. 2.)

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most pressing issue focuses on their importance to global brain function. The hallmark of PVS as formulated by Jennett and Plum[7] emphasized its spontaneous arousal periods that fail to contain any discernible expression of consciousness. A natural clinical question is whether an absolute number of such preserved cerebral functional modules will, among themselves, generate varying levels of cognitive recovery from the vegetative state, or alternatively, whether selective and specific circuitry is indispensable for constructing the integrative brain functions that we associate with consciousness.

Evidence from human brain anatomy indicates that PVS can result not only from widespread cerebral injuries of indiscriminate severity, but also from damage to selective diencephalic and/or cortical regions. Previous reports giving autopsy findings in vegetative patients have provided anatomic evidence of dissociation between a relatively normal cerebral cortex and a severely damaged paramedian thalamus and mesencephalon[8,9]. We recently studied a young man with MRI evidence of bilateral paramedian thalamic injury and complete bilateral infarction of the tegmental mesencephalon. This patient had remained in a behaviorally unremarkable vegetative state for six years. Remarkably, he nevertheless had preserved a near-normal cerebral cortical metabolism measured by quantitative FDG-PET (N. Schiff *et al.*, 1998, Abstract in *Towards a Science of Consciousness III* Consciousness research abstracts, 154). The observation raises the possibility that the preserved metabolism correlates with multiple isolated modules as seen in Menon's patient and our own, but that lack integration. The finding further illustrates that in severe brain injuries, recovery beyond cyclic arousal, as seen in PVS, depends on the integrity of both thalamo-cortical and cortico-cortical connections.

Conclusions

Current attention is increasingly focused on ways to reduce the incidence and improve the epidemic of functionally poor outcomes following severe traumatic brain injury. Aside from the human tragedies that ensue, enormous societal costs accompany the brain damage of these patients as well as those with similar neurological outcomes resulting from non-traumatic injuries. The scope of the problem demands extension of the boundaries of clinical neuroscientific expertise[10] and mandates that the underlying cerebral dysfunction resulting from these disorders must be understood. The report from Menon and colleagues and other efforts in this direction represent the first steps toward such an understanding. These steps are critical in order to support decisions concerning patient dispositions and, ultimately, to develop rational therapeutic strategies that can improve cognitive disabilities.

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Response from Menon, Owen and Pickard

We thank Schiff and Plum for their lucid commentary on our article. They raise a number of important issues regarding the putative role of functional neuroimaging in the detection of covert cognitive processing in patients diagnosed as being in a persistent vegetative state (PVS).

Despite converging agreement about the definition of PVS, recent reports have raised concerns regarding the accuracy of this diagnosis in some patients[1], and the extent to which, in some cases, residual cognitive functions might remain undetected[2,3]. While the investigation of such patients using resting blood flow and glucose metabolism[4,5] as markers of neural capacity (or its potential) is important, establishing that such activation is related to the presence of residual cognitive function is of greater significance. Objective assessment of residual cognitive function can be extremely difficult because motor responses can be minimal, inconsistent, and difficult to document in many patients, or undetectable in others because no cognitive output is possible. In the absence of such output, functional neuroimaging,

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or 'activation' studies with well-documented paradigms might allow the imaging of specific task-related cortical activation, and thus provide one means of assessing cognitive processing. In short, the power of this method, when applied to the problem of PVS, is the potential to demonstrate distinct and specific physiological responses (changes in regional cerebral blood flow, rCBF), to controlled external stimuli. In our article, we described, for the first time in this context, the use of a widely used paradigm that is known to produce robust and well-documented effects in functional imaging experiments. We used ^{15}O positron emission tomography (PET) to study covert cognitive processing in a single patient with a probable clinical diagnosis of PVS. Because this patient exhibited a clear and predicted rCBF response to familiar faces, and subsequently made a significant recovery, we interpreted our findings as evidence for covert cognitive processing.

As Schiff and Plum point out in their commentary, these studies are methodologically complex and the results are not always unequivocal. In this respect, the choice of paradigm to effect such a demonstration of covert cognitive processing requires careful consideration. It is essential that the cognitive stimulus is perceived by the subject. For example, abnormal brainstem auditory evoked responses in our patient made the use of auditory stimuli inappropriate. The decision to use visual stimuli was made partly 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. Our decision was reinforced further by non-reproducible reports in this patient of visual pursuit of familiar faces. Moreover, the choice of specific visual paradigm for testing cognitive processing (in this case, face recognition) was predicated by 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 that 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 patient's spontaneous sleep–wake cycles. Finally, it was essential that the paradigm used was known to produce well-documented, specific, robust and reproducible activation patterns in normal volunteers.

The activation patterns observed in our patient correlated closely with results from previous studies using similar paradigms[6,7]. For example, Haxby *et al.*[6] examined rCBF changes while healthy control subjects performed face-matching, dot-matching or sensorimotor control tasks. Face matching alone activated, bilaterally, occipitotemporal area 37, in a region very close to that activated in our patient. In a follow-up study, Haxby *et al.*[7] used a paradigm in normal control subjects that was very similar to the one used in our study. 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 midfusiform and mid-anterior fusiform gyri (areas 19 and 37); again, very close to those regions shown to be activated in the patient described in our study.

Data processing in patients with PVS can also present significant problems. The presence of gross hydrocephalus or focal pathology make it difficult to coregister PET data to anatomical data from magnetic resonance imaging, and it might be impossible to normalize the coregistered image to a reference brain, such as that provided in SPM software. Under these circumstances statistical assessment of activation patterns is difficult and coregistering foci of activation to stereotactic coordinates might be impossible. These problems, while not prominent in our reported study, have substantially hampered image analysis in other patients described in similar studies.

While the activation pattern that we observed in our patient with PVS is similar to that seen in normals[6,7], it is more difficult to be clear about its significance in the context of her residual cognitive abilities at the time of the study and during her subsequent recovery. While definitive judgments regarding 'awareness' or 'consciousness' are impossible based on these data, they do provide the basis for some inferences. It is clear that she was not merely perceiving visual stimuli, but also processing these stimuli in such a way as to recognize content that was not based on primary image attributes such as colour, luminance, size or movement. Schiff and Plum pose the question 'Would familiar faces versus unfamiliar faces have led to a significant subtraction image?'. This, of course, is an important and intriguing question, although not one that we felt to be more important than 'Is there a normal physiological response to faces *per se*?'

Schiff and Plum also express caution in interpreting the significance of 'isolated, regional cortical processing in a brain that failed to express any other hint of awareness or physical interactive behaviour'. They suggest that, in the absence of clinical cognitive improvement, this might simply have been the progression to a state of minimal awareness, or that it represented another example of limited, stereotyped activity in patients who otherwise fulfil criteria for the persistent vegetative state. We would hesitate to use the criterion of clinical recovery to judge whether the regional cortical processing was truly significant. This approach would appear to presuppose that residual cognition must always progress to be thought of as significant. We do not believe that this has necessarily been shown to be the case. We would use as an analogy the scenario of a computer with a nonfunctioning screen. While no conventional output is possible, the production of a printed page in response to a series of remembered and well-rehearsed keyboard strokes would provide eloquent proof that the computer still worked, even if the screen never functioned again. The face-recognition paradigm was our 'keyboard entry', the PET scanner our 'printer', and the subtraction image our 'printed page'.

The issue of 'isolated' cortical activity is somewhat different. We did not make a full neuroimaging assessment of our patient's cognitive capabilities because we were limited both by logistics and by our ability to provide cognitive inputs that were not negated by sensory deficits and had clearly documented expected outputs. We therefore cannot comment whether the improvement observed in our patient occurred on a substrate of isolated modular activity or more generalized preserved cortical function. In a pertinent discussion, Schiff and Plum also address the importance of preserved integrative systems involving the tegmental mesencephalon, paramedian thalamus and cortico-cortical connections in the generation of self-awareness and consciousness.

The crucial question, however, is whether residual cognitive processing in one or more areas can be integrated enough to provide some level of self-awareness or 'consciousness', but still have no access to output. We do not, as yet, have activation data that might allow us to address these issues usefully. There are also no data from such patients that allow us to relate the level of resting metabolism (as measured by an ^{18}F-deoxyglucose PET study) to the capacity for activation by an appropriate cognitive stimulus (as measured by an activation study using ^{15}O PET).

Further elucidation of the precise level and mechanisms of preserved cognitive processing would require a carefully designed series of neuroimaging studies. If PET were used, the conduct of these would be limited by considerations of logistics, practicality and, most importantly, radiation burden. While conventional MR imaging has been thought to be unhelpful, one possible solution to this problem might lie in the use of functional MRI, which will allow the simultaneous acquisition of functional and anatomical data with high resolution and without any radiation exposure. The use of fMRI in this context will clearly present logistic and procedural problems. However, the

detection and elucidation of residual cognitive function in this group of patients has such major implications that we believe that such an effort is justified.

What, then, is the relevance of our case report? Our results raise the important (and somewhat disturbing) possibility that patients clinically diagnosed to be in a persistent vegetative state might still perceive and cognitively process at least some sensory inputs relatively normally. The scarcity of data and, as yet, unresolved methodological difficulties make it impossible for us to extend and/or generalize our inferences. However, we have highlighted the availability of a tool that enables the wider study of cognitive processing in a brain that does not have access to conventional cognitive outputs. This, we hope, will enable us better to understand and categorize patients who are currently lumped together under a single diagnosis, but possess widely different levels of cognitive processing, and hence have widely varying management requirements and prognoses. We would agree that our study is the first of many steps that 'are critical in order to support decisions concerning patient dispositions and, ultimately, to develop rational therapeutic strategies for cognitive disabilities'.

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Monitor

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Attentional suppression in human extrastriate cortex

What structures and processes mediate the operation of selective visual attention in the human brain? One hypothesis suggests that object representations at different locations compete for processing capacity in the visual system, and that attention works by biasing this competition in favour of the attended location. Recordings of single cells in awake monkeys have been consistent with this idea[1]. The response of a neuron to an optimal stimulus is reduced substantially when an irrelevant stimulus is presented simultaneously at another location in the receptive field. However, if the animal directs its attention to one of the competing stimuli in the receptive field, the responses are as large as when the stimulus is presented alone. Now, Kastner and colleagues[2] provide evidence that a similar mechanism might operate in humans. Using functional MRI, they examined cortical responses to four adjacent objects presented either simultaneously, or one at a time in rapid succession. Although the total amount of retinal stimulation (integrated over time) was the same in the two experimental conditions, cortical responses differed. Simultaneous presentation evoked less activity than successive presentation, and this difference was more pronounced in 'higher' cortical areas (those with larger receptive fields). Moreover, the reduction with simultaneous presentation was much less severe when attention was directed to one of the four peripheral stimuli. The authors argue that these findings are consistent with the notion that attention is 'protecting' a representation of the target item from competition. However, it is also possible that the difference between simultaneous and successive stimulation could have arisen as a result of other factors, such as the difference in presentation rate between the two conditions. In a control experiment to test this possibility, the authors presented stimuli at a constant rate and showed that the response to a single peripheral item presented alone was lowered when it was presented simultaneously with three other items. This suggests that the difference between successive and simultaneous stimulation is not simply related to different presentation rates and so could be a mechanism of attention that filters out unwanted information in cluttered visual scenes. Assessing the significance of these findings will come from directly addressing the mechanisms of directed attention – the intriguing parallels between single-cell and functional-imaging results warrant further investigation.

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