Cortical function in the persistent vegetative state

Nicholas D. Schiff and Fred Plum

The recent article by Menon and colleagues might represent the first functional brain imaging of recovery of awareness identified in such a condition[1]. Menon *et al.* described a clinically diagnosed woman in a persistent vegetative state (PVS) whose right occipito-temporal regions demonstrated functional activity induced by visual stimuli. This finding, along with recent studies of preserved isolated cortical function in long-standing vegetative states[2–4], has potentially important implications for understanding neurological mechanisms that underlie the basis of consciousness. This commentary briefly discusses Menon's case as well as additional vegetative patients who express fragments of behavior over long periods without ever improving. Wider neurobiological and social implications of these findings are also considered.

Menon *et al.* studied a 26-year-old woman four months following an attack of acute disseminated encephalomyelitis which functionally impaired both cortical and subcortical (brainstem and thalamic) structures. Although consistently, clinically unconscious, the authors uncovered two early hints that might predict recovery of consciousness and interactive behavior. One was the presence, albeit abnormally delayed, of an auditory oddball response (P300). The other, obtained using a ^{15}O PET subtraction paradigm, was an activation of the right fusiform gyrus and extrastriate visual association areas in response to presentation of familiar faces. No other evidence of cortical processing was immediately reported but she 'became increasingly responsive' at six months and minimally perceptive and expressive at eight months post illness. The early finding at four months of isolated, regional cortical processing in a brain that clinically failed to express any other hint of awareness or physical interactive behavior generates one of two possibilities. The activity could indicate a recovery of minimal awareness. Alternatively, it might describe another example, reported previously in three chronic vegetative patients, of patients who show limited, repetitive and unchanging fragments of cerebral function dissociated entirely from any apparent evidence of self awareness[2–4]. In either case, it is necessary that overwhelming paralysis producing a locked-in state is excluded. The clinical context within which Menon *et al.*'s patient expressed quantitative cerebral activity is crucial. The strongest evidence that supports the concept of early recovery of awareness in Menon *et al.*'s patient is that she ultimately recovered consciousness. Had she never regained any additional expressed qualities of attention, recognition, or interactive behavior beyond the P300 and the PET findings after another eight months (i.e. a year after the initial illness) she would have been diagnosed as permanently vegetative by most observers. In this setting, the notion that the PET activation might confer a degree of awareness would be substantially less compelling.

Emphasis on selectivity of the response obtained in Menon *et al.*'s patient produces some additional concerns. The employed subtraction paradigm paired familiar face stimuli with images obtained by 'repixellating the photographs to remove structure from the images'. The ambiguity of separating faces from geometric non-faces prevents knowing the specificity or category of the response. For example, would familiar versus unfamiliar faces have led to a significant subtraction image? Is the response due solely to differences in spatial frequency content after the image-processing step? In any case, despite these ambiguities, the result marks a new and important observation using functional brain imaging to identify modular components in a severely brain-damaged patient. The abnormal P300 response in this patient is consistent with previous studies indicating that an intact P300 response improves the likelihood of recovery from coma or a vegetative state[5]. As discussed below, the preservation of the P300 may also reflect the integrity of important brainstem and diencephalic structures. Of note, the P300 response in Menon *et al.*'s case report might correlate with receding edema or inflammation in the brainstem and thalamus, heralding recovery of these injured regions in their patient[6].

Other evidence of preserved cortical processing in vegetative patients

During the past four years, our laboratory has collaborated with Drs Rodolfo Llinas and Urs Ribary of New York University Center for Neuromagnetism, and an inter-institutional brain imaging team, to study a group of highly selected vegetative patients[2–4]. Three particular patients, selected from 60 PVS cases, were reported to express remarkable behavioral fragments, not previously reported or observed by the authors. One of the three patients infrequently expressed isolated words (typically epithets) during a 20-year period of remaining in a PVS (Ref. 4). A second patient, over a period of many months without change, expressed continuous non-targeted movements during his wakeful periods, and a third patient explodes with sham rage responses to a multitude of non-noxious exogenous stimuli.

This last patient, a 41-year-old man, was also noted over the seven years of his PVS to be calmed occasionally by soothing sounds or music. The average metabolism in this patient's brain was reduced to ~30% of normal as measured by fluorodeoxyglucose (FDG)-PET. However, there were some brain areas with a slighly increased activity, with between 30–40% of normal metabolism (Fig. 1). An MRI scan revealed marked atrophy consistent with progressive cerebral cell loss during the seven years since the traumatic injury. During those seven years careful and repeated examinations failed to identify any recognition of self or environment in the patient. The regions of relatively increased metabolism identified by FDG-PET reveal a close, reciprocal correspondence with the cortical and subcortical regions that when lesioned produce human aprosodia. We interpret the responses to the soothing sounds to be the random expression of prosodic processing in a remnant circuit linking the cortico-cortical connections of the temporal–parietal–occipital junction with prefrontal cortex seen in Fig. 1. The capacity to activate the cortical processing, however, must depend equally on the relative integrity of the related basal ganglia–thalamocortical loops of the right hemisphere[3,4]. In this patient, auditory evoked MEG responses existed only in the right hemisphere and localized to Heschl's gyrus, thereby indicating the unilateral preservation of a thalamocortical relay[3]. We conclude that the presence of such an isolated processing module in this patient and the others we have studied, which may persist indefinitely as the disused brain atrophies, cannot be taken by themselves to enable any degree of self-awareness.

Among the many questions generated by identifying preserved functional modules in the vegetative state, the

N. Schiff is at the Department of Neurology and Neuroscience, New York Presbyterian Hospital Cornell, 1300 York Avenue, NY 10021, USA.
F. Plum is University Professor at the Department of Neurology and Neuroscience, New York Presbyterian Hospital Cornell, 1300 York Avenue, NY 10021, USA.

tel: +1 212 746 2372
fax: +1 212 746 8532
e-mail: nschiff@mail.med.cornell.edu

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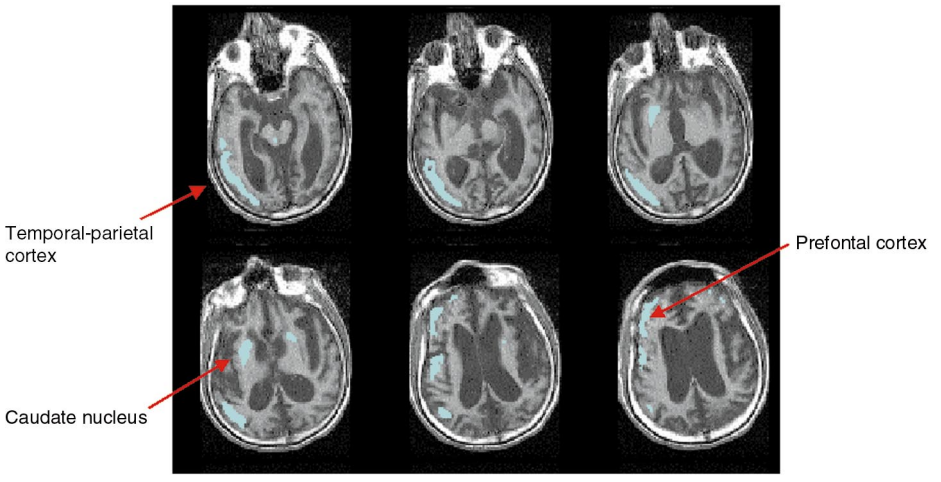

Fig. 1. Random prosodic processing in persistent vegetative state. FDG-PET data (measuring resting metabolism) coregistered onto MRI images. Average cerebral metabolism was reduced to ~30% of normal. The blue colored areas in the successive horizontal images represent regions of slightly increased activity,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

D.K. Menon is at the Wolfson Brain Imaging Centre and Department of Anaesthesia, University of Cambridge School of Clinical Medicine, Addenbrooke's Hospital, Cambridge, UK CB2 2QQ.

tel: +44 1223 217889
fax: +44 1223 217223
e-mail: dkm13@wbic.cam.ac.uk

A.M. Owen is at the MRC Cognition and Brain Sciences Unit, 15 Chaucer Road, Cambridge, UK CB2 2EF.

tel: +44 1223 355294 ext. 700
fax: +44 1223 359062
e-mail adrian.owen@mrc-cbu.cam.ac.uk

John D. Pickard is at the Wolfson Brain Imaging Centre and Department of Neurosurgery, University of Cambridge School of Clinical Medicine, Addenbrooke's Hospital, Cambridge, UK CB2 2QQ.

tel: +44 1223 336946
fax: +44 1223 216926

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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