

SCIENTIFIC COMMENTARY

Bringing neuroimaging tools closer to diagnostic use in the severely injured brain

In a vanguard study reported in this issue of *Brain*, Coleman *et al.* (page 2494) used hierarchically organized passive language tasks and functional magnetic resonance imaging (fMRI) to study 14 patients with severe brain injuries. Functional levels of the study subjects ranged across a spectrum from vegetative state to minimally conscious state, and severe disability following emergence from the minimally conscious state. The investigators assessed three levels of speech processing beginning with comparisons of auditory stimuli to a silent baseline, followed by comparisons of intelligible speech versus unintelligible noise, and finally advancing to high-level semantic contrasts using English sentences containing words with either high or low ambiguity of interpretation. Notably, their findings revealed evidence of preserved higher level language processing among a subset of three patients meeting the criteria for vegetative state. Taken together with an earlier single-subject study of one of the vegetative state patients (Owen *et al.*, 2006), the results support further developing these and other neuroimaging tools to aid the difficult diagnostic assessments of patients with severe brain injuries (Laureys *et al.*, 2004; Schiff, 2006).

Owen *et al.* (2006) earlier demonstrated at least minimally conscious state level function in one of the three vegetative state patients using another novel imaging technique that is operationally exchangeable with behavioural evidence of command following as judged clinically at the bedside. The patient demonstrated the ability to follow complex commands. Based on these earlier studies, it could be strongly argued that this vegetative state patient in fact reflects a novel category of ‘non-behavioural’ minimally conscious state (Fins and Schiff, 2006). This distinction may ultimately be of considerable importance as prospective studies have shown that the time course for further recovery from the minimally conscious state can be longer than vegetative state and associated in some instances with late recoveries above the level of severe disability (Lammi *et al.*, 2005). The comparison of activations with high versus low semantic ambiguity in the present study by Martin Coleman and colleagues does not, however, similarly provide a basis for potential diagnostic reclassification of the vegetative state patients who demonstrate selective responses. It is unclear whether such activations in response to passively presented linguistic stimuli reflect any element of active interpretation. Assessment of language comprehension in the absence of

a verifiable translation step such as the imaginal task so elegantly demonstrated in the paper by Owen *et al.* (2006) is inherently more ambiguous as it requires an identification of comprehension by fiat with neurophysiological correlates of higher level processing of linguistic content.

Although these studies and others (cf. Boly *et al.*, 2004; Schiff *et al.*, 2005) do suggest the potential utility of adding functional imaging tools to the comprehensive assessment of neurological disorders of consciousness, this remains a challenging task ahead. Among several caveats that must be noted at this early stage of work, it is essential to place the fMRI findings in vegetative state patients now reported within the context of what is known and what is not known about the natural history of different types of severe brain injuries. Uncertainties of outcome for individual patients differ considerably based on clinical findings obtained from bedside examinations and varying etiologies of injury. Critically important to the proper interpretation of these observations is the recognition that vegetative state is often a transitional state when no strong negative clinical predictors are identified (such as bilateral loss of both pupillary and corneal responses at the time of initial injury). Thus, it should be recognized that findings of otherwise unsuspected residual cerebral processing capacity in vegetative state patients who may yet recover within known timeframes could reflect the process of functional recovery. Importantly, the present findings do not cast doubt on known outcome probabilities over time for permanence of vegetative state following cardiac arrest or traumatic brain injury which have been established in large prospective studies (see Posner *et al.*, 2007 for review).

For the two major etiologies of the vegetative state, head trauma and anoxic/hypoxic ischaemic encephalopathy, there are strong prospective negative indicators based on early clinical assessments that are well correlated with natural history and anatomic pathology (Adams *et al.*, 2000; Posner *et al.*, 2007). Although there is a continuum of outcomes following an initial transition from coma to vegetative state in the setting of a severe brain insult, these outcomes are not equally distributed across that continuum. This is particularly true for anoxia where the mechanism of injury produces relatively sharp cutoffs associated with global neuronal death (in many instances leading to the vegetative state with underlying anatomic pathology closer to that of brain death than findings associated with outcomes within the low end of the

minimally conscious state category, see Jennett *et al.*, 2001) and where predictive signs and measurements can in some patients be established within 48–72 h (Posner *et al.*, 2007). All three of the vegetative state patients found to have preserved responses to high-level semantic contrasts in the study of Coleman *et al.* (page 2494) fall outside the large group of patients with such negative prognostic indicators. Accordingly, a greater uncertainty of outcome is present for these patients because of the less well-studied natural histories of outcomes for patients without negative predictors (or etiologies other than trauma or anoxia/hypoxia; importantly two of the patients suffered subcortical ischaemic injuries and were studied at 4 months or earlier). It is likely that neuroimaging assessments will find their greatest use where uncertainties of diagnosis and prognosis are present at onset of injury. Hopefully these tools will eventually help to distinguish vegetative state patients who may show further recovery, as did the patients studied by Coleman *et al.*, from the larger group of vegetative state patients encountered clinically with negative prognostic indicators in the setting of anoxia or traumatic coma.

It is perhaps most difficult to anticipate what impact such neuroimaging assessments will have on prognostic assessments for minimally conscious state patients. Recent studies have shown preservation of large-scale cerebral networks in patients remaining chronically in the minimally conscious state without further recovery (Schiff *et al.*, 2005). An interesting finding from the cohort of patients studied by Coleman and colleagues is the poor correlation of formal behavioural assessments with evidence for intact cerebral speech processing networks for the minimally conscious state patients as well as the vegetative state patients. It remains to be confirmed in additional studies of larger numbers of minimally conscious state patients whether this dissociation of low-level clinical evidence of responsiveness and retained integrity of large-scale cerebral network responses is generic. If so, these observations will support wider use of neuroimaging in chronic minimally conscious state patients and other brain-injured patients with higher functional outcomes to better characterize their residual cognitive capacities. Recent observations indicate that identification of preserved network function in minimally conscious state patients may help explain spontaneous late recoveries from this state (Voss *et al.*, 2006) and direct more efforts toward systematic exploration of pharmacologic (Brefel-Courbon *et al.*, 2007; Schiff and Posner, 2007) or other means of improving the response of such latent cerebral processing capacity (Schiff *et al.*, 2007).

Finally, there are at the moment several additional caveats and challenges ahead of bringing these fMRI and related neuroimaging techniques into use for diagnostic and prognostic assessment of patients with severe brain injuries. Few centres have the capability to carry out repeated careful clinical assessments of vegetative state and minimally conscious state patients over extended time periods

and neuroimaging research capabilities. As a result, as the investigators point out in their conclusions, at present there is insufficient experience with the application of fMRI or other functional imaging methods to outline their potential use in clinical decision making for disorders of consciousness. Moreover, the absence of brain activations may not rule out further recovery. Importantly, the sources of variance in response of these measurements in the severely injured brain are not known. Conversely, positive findings from these assessments, while demonstrating underlying functional connectivity of corticothalamic and other cerebral systems, remain ambiguous with respect to diagnostic or prognostic interpretation. Nonetheless, the present report represents a very important step towards the inevitable evolution of use of neuroimaging in the diagnosis and prognosis of disorders of consciousness.

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