# Neurofunctional imaging in differential diagnosis and evaluation of outcome in vegetative and minimally conscious state

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**Summary**

**Following severe brain injury, some patients will recover wakefulness without signs of consciousness, only showing reflex movements (the vegetative state), while others may show non-reflex movements but remain without functional communication (the minimally conscious state).**
**Functional neuroimaging is providing new insights into cerebral activity in patients with severe brain damage. The mapping of cognitive processes (mostly by measuring regional changes in blood flow, initially by PET and now also by fMRI) is shedding new light on the functional neuroanatomy of consciousness. This review focuses on neurofunctional imaging approaches recently introduced in the differential diagnosis and outcome assessment of patients with chronic disorders of consciousness.**

*KEY WORDS: functional magnetic resonance imaging, minimally conscious state, outcome, positron-emission tomography, vegetative state.*

## The vegetative state and the minimally conscious state: clinical findings

Consciousness is a multifaceted concept that has two dimensions: arousal, or wakefulness (the level of consciousness), and awareness (the content of consciousness).
An accurate and reliable assessment of arousal and awareness in severe brain damage is crucial, both for the differential diagnosis of low-level consciousness patients and for outcome evaluation.
Following coma, some patients permanently lose all brainstem function (brain death), some progress to "wakeful unawareness" (the vegetative state, VS), while others recover. The latter group typically progress through stages to partial recovery (a minimally conscious state, MCS) or to full recovery of consciousness. Patients in the VS can open their eyes and exhibit basic orienting responses, but show no conscious, purposeful activity. Reflex and other movements, mediated by brainstem, spinal cord, and brainstem-diencephalic arousal systems (1), are observed.
Patients can enter the VS on emerging from an acute catastrophic brain insult causing coma; the VS can also be seen in degenerative or congenital nervous system disorders. The two most common findings are necrosis of the cerebral cortex, thalamus and brainstem (usually after anoxic injury) and diffuse axonal injury (usually after trauma), although other pathological features can be found in degenerative and other disorders (2,3).
Patients in the MCS do not meet the diagnostic criteria for coma or VS because, by definition, they demonstrate some inconsistent but clear evidence of consciousness (2-4). In the MCS, the presence of variable degrees of functional impairment of the cerebral cortex, diencephalon and upper brainstem allows occasional conscious behaviours to occur; this does not happen in VS or coma. Patients may enter the MCS as they emerge from coma or the VS, or they may become minimally conscious as a result of an acute injury or chronic degenerative disease.

## The vegetative state and the minimally conscious state: functional neuroimaging

Positron emission tomography (PET) is a method used to investigate organ metabolism and blood flow. Using different compounds, this technique can, with equal resolution and sensitivity, assess regional blood flow, oxygen and glucose metabolism, and neurotransmitter and drug uptake in the tissues of the working brain. Until recent years, PET was the technique most widely used to assess the neural substrates of cognitive processes at macroscopic level, but now it has been superseded by functional magnetic resonance imaging (fMRI).
Functional magnetic resonance imaging can detect an increase in blood oxygen concentration occurring in an area of heightened neuronal activity. The basis for this capacity lies in the way neurons make use of oxygen. The most common form of fMRI is blood oxygenation level dependent (BOLD) imaging. The BOLD signal depends on the ratio of oxygenated to deoxygenated haemoglobin: in regions of neuronal activity this ratio changes as increased flow of oxygenated blood temporarily surpasses oxygen consumption, decreasing the level of paramagnetic deoxyhaemoglobin. These localised changes are used as markers of functional activation.
A comprehensive exploration of patients with disorders of consciousness should assess all the structures involved in arousal and awareness functions: the ascending reticular activating system located in the posterosuperior part of the brainstem (i.e. primary arousal struc-

ture) and a large set of supratentorial structures responsible for awareness, including the thalamus, basal forebrain, and frontoparietal association cortices. However, this kind of examination presents potential limitations, linked to patient motion, uncontrolled intracranial pressure, and the risks associated with the transportation of the sedated and ventilated patient from the intensive care unit to the MRI scanner.

Functional neuroimaging procedures are increasingly used in the clinical domain. Recent applications include protocols designed to monitor the natural history of recovery from acquired brain injury and to assess the effects of neurorehabilitation interventions. In this article, we discuss the role of functional neuroimaging procedures in characterising the integrity of residual cortical networks and in the search for neural evidence of cognitive function in patients with disorders of consciousness.

The first $^{15}$O-labelled PET study of the VS used an auditory paradigm. A post-traumatic VS patient showed activation in the anterior cingulate and temporal cortices while his mother told him a story, but not during the presentation of nonsense words (5). The authors hypothesised that this activation probably reflected an emotional response to speech or sound.

In cohort studies of VS patients, simple noxious somatosensory (6) and auditory (7,8) stimuli were associated with systematic activation of primary sensory cortices and a lack of activation of higher-order associative cortices, from which the primary cortices were functionally disconnected. However, secondary somatosensory, insular, posterior parietal, and anterior cingulate cortices, which were activated in all control individuals, did not show significant activation in any VS patient. In addition, in VS patients, the activated primary somatosensory cortex was functionally disconnected from the higher-order associative cortices of the pain matrix. Moreover, the observation, following auditory cortical stimuli, of a series of functional disconnections, from primary auditory areas to limbic areas (8), suggests that the residual cortical processing observed in the VS does not lead to integrative processes, which are thought to be necessary for awareness.

In another patient diagnosed as vegetative, Menon and colleagues (9) used PET to study covert visual processing in response to familiar faces. When the patient was presented with pictures of the faces of family and close friends, robust activity was observed in the right fusiform gyrus, the so-called human "face area".

External stimuli commonly produce stereotyped responses, such as grimacing, crying, or occasional vocalisation, in VS patients. These behaviours are assumed to derive from brainstem circuits and limbic cortical regions that are preserved. From a series of multimodal imaging studies of patients in the VS, three subjects with unusual behavioural fragments were identified. Preserved areas of high resting brain metabolism (measured with fluorine-18-labelled deoxyglucose PET) and incompletely preserved gamma-band responses (measured with magnetoencephalography) were fitted to structural MRI data and found to correlate with the behaviours of these patients (10).

Several fMRI activation studies in the VS (11-17) have confirmed the findings of previous PET studies that, employing auditory (8,18-20), somatosensory (18,21), or visual (9,20) stimulations, demonstrated preserved activation of lower level primary sensory cortices, which are disconnected from higher-order associative cortical networks.

Laureys et al. used $H_2{}^{15}O$ PET blood flow studies to evaluate pain processing in the VS. High intensity electrical stimulation – i.e. able to elicit pain in controls – was applied to the median nerve at the wrist in 15 non-sedated patients in the VS and in 15 healthy controls. The noxious somatosensory stimuli activated the midbrain, contralateral thalamus and primary somatosensory cortex in all the VS subjects, even in the absence of detectable cortical evoked potentials. The activated primary somatosensory cortex was functionally disconnected from higher-order associative cortical areas, including the anterior cingulated and the insular, prefrontal and posterior parietal cortices. Conversely, in healthy controls, these same stimuli activated the primary and secondary somatosensory cortices, and the bilateral insular, posterior parietal and anterior cingulate cortices (6).

Schiff et al. were the first to perform fMRI in the MCS (22). These authors demonstrated, in two minimally conscious patients, a residual capacity to activate large integrative networks. Similar studies using PET reported that minimally conscious patients showed a more widespread activation than patients in the VS; they also reported more efficient corticocortical functional connectivity in minimally conscious compared to vegetative patients (19). Moreover, in the MCS, the activation induced by stimuli with emotional valence (cries and names) was found to be much more widespread than that induced by meaningless noise (23). This evidence of context-dependent higher-order auditory processing shows that content does matter when talking to minimally conscious patients. Exceptionally, vegetative patients may also show higher level cortical activation and this was proposed to be a surrogate marker of good prognosis (24).

In a recent study, Coleman et al. (13), applied a hierarchical fMRI auditory processing paradigm to determine the extent of retained language processing in a group of 14 aetiologically heterogeneous patients who met the diagnostic criteria for either the VS or the MCS, or who were in a severely disabled condition having emerged from the MCS. As expected, the two severely disabled but conscious patients showed preserved speech processing at all the levels assessed (low-level auditory responses, mid-level speech perception, and high-level semantic aspects). However, contrary to the diagnostic criteria for the VS, three patients (1 traumatic, 2 non-traumatic aetiology) demonstrated some evidence of preserved speech processing. The remaining four patients (1 traumatic, 3 non-traumatic aetiology) with a diagnosis of VS showed no significant activation in response to sound compared with silence. These results seem to provide further evidence that a subset of patients fulfilling the behavioural criteria for the VS retain islands of preserved cognitive function.

Simple auditory stimulation induced more widespread activation in the MCS than in the VS (7). In the former, the activation included primary areas as well as auditory associative areas suggesting more complex processing. In addition, corticocortical functional connectivity, between the auditory cortex and a large network of temporal and prefrontal cortices, was more efficient in MCS compared with VS patients.

The fMRI technique has also been used to study the response to natural language stimuli in the MCS. Patients and controls heard narratives that had personally meaningful content read forwards and backwards by a familiar voice (25). When the narratives were read normally, components of the cortical language networks showed selective activation in the two patients, while the controls showed the same pattern of activation when they heard the narratives read backwards as when they heard them read forwards. The fact that this did not occur in the MCS patients may be related to their low resting metabolic activity. The results of this study suggest that some MCS patients retain the capacity to activate large integrative networks.

Di et al. used fMRI to evaluate differences between VS and MCS patients in brain activation occurring in response to the presentation of the patient's own name, spoken by a familiar voice (24). These authors prospectively studied residual cerebral activation to a familiar voice in seven VS patients and four MCS patients. They found that only two of the VS patients, as opposed to all four MCS patients, showed activation not only in the primary auditory cortex but also in hierarchically higher-order associative temporal areas. These two VS patients showing widespread activation subsequently displayed a clinical improvement: three months after their fMRI examination they had progressed to the MCS. This study showed that fMRI measurement of cerebral responses to patient's own name spoken by a familiar voice might be a useful tool for pre-clinically distinguishing MCS-like cognitive processing in some patients behaviourally classified as vegetative.

In another recent study, Owen used fMRI in two patients in the VS. In one patient, a moving coloured grid (compared to darkness) elicited activation in the primary visual cortex, while in the second patient, noise stimulation (compared to resting state) activated the primary auditory cortex (20).

Moritz et al. studied a VS patient four days after the trauma and reported activation near the primary visual cortex induced by flashing light (compared to darkness) (16).

These studies support the view that simple somatosensory, auditory and visual stimuli typically activate primary cortices in patients with VS but fail to show robust activation in higher-order associative cortices.

## Concluding remarks

The results of these studies suggest that neurofunctional imaging techniques have a number of potential clinical and rehabilitation applications for VS and MCS patients. Although bedside clinical examination remains the standard diagnostic evaluation, PET and fMRI activation profiles may constitute useful adjunctive diagnostic methods when behavioural findings are very limited or ambiguous. fMRI activation profiles may also inform prognosis in patients who show no behavioural evidence of language or visual processing. As regards the future of diagnostic and prognostic assessment of patients with disorders of consciousness, it is possible to envisage the introduction of a battery of neurobehavioural and neuroimaging techniques serving as complementary clinical tools that may help to distinguish between the effects of underarousal, sensory impairment, motor dysfunction, and cognitive disturbance in the search for the potential causes of behavioural unresponsiveness.

Potentially, fMRI could serve as a good marker for differential diagnosis and prognosis. An active paradigm seems to be a valuable additional diagnostic tool in patients whose clinical diagnosis remains in doubt because of an atypical presentation. Negative results, however, must be interpreted cautiously in patients with severely altered levels of vigilance, who could show only transient activity in response to the presentation of instructions.

In summary, metabolic and molecular studies with PET and activation studies with PET and fMRI offer new possibilities in the assessment of patients with severe brain damage. However, all these techniques are methodologically complex and present numerous analysis and interpretation difficulties. Therefore, for the foreseeable future, functional imaging is destined to complement, rather than replace standardised, repeated clinical assessment by experienced and appropriately qualified personnel.

Novel applications of functional neuroimaging in patients with disorders of consciousness may aid in differential diagnosis, prognostic assessment and identification of pathophysiological mechanisms (26). Improvements in patient characterisation may open the way, in some cases, for restoration of function through interventional neuromodulation.

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