The Signs of Death
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THE MINIMALLY CONSCIOUS STATE: NEUROIMAGING AND REGENERATION*

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Background

The minimally conscious state (MCS) is a clinical manifestation of severe brain injury. While there are no evidence-based criteria, diagnostic guidelines were reached in a series of consensus development workshops [1]. The differential diagnosis of the minimally conscious state is important and includes the vegetative state (transient, persistent and permanent), coma and the locked-in syndrome (Table 1). Although sometimes confused in the lay media, none of these states indicate brain death. In recent years, neuroimaging studies have shed light on the underlying pathogenesis of both minimally conscious state and vegetative state and providing insights into the basis of the neural network subserving consciousness. These investigations are likely to have an increasing diagnostic role in severe brain injury.

Like the vegetative state, the minimally conscious state may be a long-term disorder of consciousness, but it may also represent a transition phase between coma, followed by the vegetative state and eventually normal consciousness. Animal studies and more recent human research have indicated, contrary to earlier understanding, that late restoration of functioning can occur due to underling axonal repair. These imaging studies, utilising positron emission tomography (PET scanning) and functional MRI (fMRI) have shed new light on this potential for neural recovery. These techniques may potentially provide a substrate for experimental interventional therapies, such as drugs and neurotrophic factors. Furthermore, a recent study has challenged the clinical criteria for the persistent vegetative state and underlined the importance of neuroimaging in assessment of disorders of consciousness [2].

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The Minimally Conscious State: Definition and Diagnostic Criteria

To develop consensus criteria for the definition of minimally conscious state, a series of Aspen workshops were held between 1995 and 2000 representing specialists in neurology, neuropsychology, neurosurgery, bioethics, allied health and nursing. The criteria were published in 2002 and have been endorsed by many groups, including the American Academy of Neurology [1].

Core criteria for the definition of minimally conscious state include a severely altered conscious state with minimal but definite behavioural evidence of self or environmental awareness. Key to the diagnosis is evidence of reproducibility, to distinguish responses from reflexive behaviour. Indeed the key distinction between minimally conscious state and vegetative state is some objective evidence of behaviour reflecting conscious awareness.

In the assessment of the minimally conscious state, adequate stimulation for arousal must be present. Potential confounding influences include sedative drugs, seizures, environmental distractions and focal neurological deficits such as hemiplegia or aphasia. Hence, the physician eliciting motor or other responses needs to be aware of the neurological capacity of the patient. A variety of behavioural responses are tested on serial occasions, ideally by independent observers. These might include the ability to follow simple commands, reproducible verbal responses and purposeful behaviour. Behavioural responses might include appropriate emotional reactions to linguistic or visual content, vocalisation or gestures in direct response to the linguistic content of questions, reaching for objects in a meaningful manner, touching or holding objects relevant to the size and shape of the object, pursuit eye movements or sustained fixation in direct response to a relevant tracking stimulus. In the assessment of the minimally conscious state, input from professionals, family and caregivers is valuable.

Duration of the minimally conscious state is not used in the definition, unlike vegetative state, where the persistent vegetative state indicates a duration of 1 month or longer and permanent vegetative state has been used for more than 3 months duration in non-traumatic cases and more than 1 year in traumatic cases. However, these terms are often used in an interchangeable manner (PVS).

Differential Diagnosis of Minimally Conscious State

The differential diagnosis of the minimally conscious state includes coma, vegetative state and the locked-in syndrome [3]. Whereas in coma and the vegetative state, consciousness is absent, there is partial consciousness in the minimally conscious state and full consciousness in the locked-in syndrome. Sleep/wake cycles are absent in coma, but present in the vegetative state, minimally conscious state and the locked-in syndrome. In the minimally conscious state, motor function is preserved to some extent, depend-

TABLE 1. DIFFERENTIAL DIAGNOSIS OF ALTERED CONSCIOUS STATE IN SEVERE BRAIN INJURY

Condition	Consciousness	Sleep/ Wake	Motor function	Auditory function	Visual function	Communication	Emotion
Coma	None	Absent	Reflex responses	None	None	None	None
Vegetative state	None	Present	Postures, withdraws to noxious stimuli	Startle	Startle	None	None
			Occasional nonpurposeful movement	Brief orienting to sound	Brief visual fixation	None	Reflexive responses
Minimally conscious state	Partial	Present	Localize noxious stimuli	Localizes sound	Sustained visual fixation	Contingent vocalization	Contingent responses
			Purposeful movements	May follow commands	Sustained visual pursuit	Inconsistent but intelligible verbalization or gesture	
Locked-in syndrome	Full	Present	Quadriplegic	Preserved	Preserved	Aphonic/ Anarthric	Preserved. May be labile
						Vertical eye movements, blinking intact	

Adapted from: Giacino J.T., Ashwal S., Childs N., Cranford R., Jennett B., Katz D.I., Kelly J.P., Rosenberg J.H., Whyte J., Zafonte R.D., Zasler N.D., The minimally conscious state: definition and diagnostic criteria, *Neurology*, 2002;58:349-53.

ing on neurological function. Hence, the patient may be able to exhibit purposeful reaching or touching of objects, depending on their motor ability. In contrast, patients in coma have only reflex responses and this is generally the case in the vegetative state, although there may be occasional non-purposeful movements. In patients with the locked-in syndrome (most commonly due to brainstem infarction at the level of the pons), there is motor paralysis due to quadriplegia. Because the midbrain is usually spared, vertical eye movements and blinking are typically preserved. Auditory and visual functioning may be partially preserved in minimally conscious state and patients may be able to localise sound and sustain visual fixation.

These functions are absent in coma, preserved in the locked-in syndrome, while only startle responses or very brief orientation to sound or vision are evident in the vegetative state. Some contingent vocalisation may be evident in the minimally conscious state, while there is no vocalisation in coma or vegetative state. Patients with a locked-in syndrome have bulbar paralysis and are unable to speak. Emotional responses are absent in coma and the vegetative state, although in the latter, reflexive crying or smiling may be evident. Contingent smiling or crying may be present in the minimally conscious state, while emotional responses are preserved in the locked-in syndrome.

At a more fundamental level, key to the understanding of the distinction between the minimally conscious state and these other disorders involves assessment of the two key components of consciousness, namely arousal (wakefulness) and awareness (of the environment and self). These are both absent in coma, while in the vegetative state there is normal arousal but absent awareness. They are both normal in the locked-in syndrome. In the minimally conscious state arousal is preserved (as in vegetative state) and awareness is impaired, but not absent. In summary, demonstration of some level of awareness is key to the diagnosis of the minimally conscious state.

Etiology and Pathogenesis of Minimally Conscious State

The etiology of the minimally conscious state is varied and may include trauma, hypoxic encephalopathy, stroke, neurodegenerative and neurometabolic disorders. Following acute brain injury, patients may emerge from coma with a variety of neurological states. These may include the vegetative state, protracted or chronic coma, the locked-in syndrome or the minimally conscious state [3, 4]. The minimally conscious state may be transient or permanent. Many patients gradually emerge from the minimally conscious state with a confusional state and varying degrees of independence.

In assessing recovery or emergence from the minimally conscious state, reliable and consistent demonstration of functionally interactive communication and functional use of objects is required [1]. Positive testing may include accurate yes/no responses to a number of basic situational questions on two consecutive evaluations. There should be evidence of appropriate use of at least two objects on two consecutive evaluations. Neurological confounders need to be excluded, including aphasia, agnosia, apraxia and sensorimotor impairment.

The natural history of minimally conscious state is poorly understood. While the condition may transient or permanent, generally outcomes are better than in the persistent vegetative state, particularly after traumatic brain injury.

Anatomical Basis of Vegetative State and Minimally Conscious State

The vegetative state is typically due to lesions that diffusely damage cortical neurones, thalami or white matter tracts that connect the thalamus and cortex, sparing the brainstem and hypothalamus.[3] Minimally conscious state is associated with less severe pathological changes, with a lower grade of thalamic injury and less severe high-grade diffuse axonal injury. Traumatic causes of both minimally conscious state and vegetative states predominantly affect the white matter (diffuse axonal injury), whereas in non-traumatic causes (classically hypoxic encephalopathy), grey matter is chiefly affected.

Imaging in the Diagnosis of MCS and Vegetative State

Global cerebral metabolism (Fig. 1, see page 423) is depressed in states associated with depressed consciousness, but to varying degrees [5]. Hence, cerebral metabolism is depressed in deep sleep and anaesthesia, as well as coma and the vegetative state. In the vegetative state, cerebral metabolism is more severely depressed than in the minimally conscious state. By definition, cerebral metabolism is absent in brain death. In the vegetative state, cortical metabolism is reduced to about 30-50%, with preserved brain stem functions. External auditory and noxious stimuli can induce neuronal activation, but this is limited to primary cortices [3, 5]. Dissociation from higher order associative cortices (prefrontal, Broca's region, parieto-temporal, posterior parietal, and precuneus) is thought to underlie the absence of conscious perception and awareness. In rare cases of recovery, PET scanning has shown functional improvements in these regions, presumed due to resumption in functional connectivity [5].

In the vegetative state, residual cerebral activity can be shown using a variety of modalities including PET scanning and fMRI [6]. In a study of 5 patients with vegetative states, severe reductions in global metabolic rates were found, but there were islands of relatively preserved function with metabolic and functional integrity.

In the minimally conscious state, there have been fewer functional imaging studies [5]. In contrast to the vegetative state, the medial parietal cortex (precuneus) and the adjacent cingulate cortex (the regions most metabolically active in normal consciousness) are relatively preserved, compared to the vegetative state. This region is considered a critical part of the neural network for consciousness. Compared with the vegetative state, auditory stimulation produces more widespread activation of both primary and auditory association areas, indicating evidence of more cortical to cortical connectivity.

In summary, in healthy conscious individuals, the medial posterior cortex is the most active metabolic region of the brain and is the least active in those with the vegetative state who are awake. In the minimally conscious state, this region demonstrates an intermediate level of metabolism [5]. Recovery of consciousness in vegetative state has also been associated with partial recovery of glucose metabolism in this critical brain region and hence recovery of cortical/thalamic/cortical interactions [4].

In the minimally conscious state, large network activation has been shown using fMRI [7]. In these studies, personalised narratives elicited cortical activity in the superior and middle temporal gyri in patients and normal controls. The reversed signal, which was linguistically meaningless, produced markedly reduced responses in patients. In the minimally conscious state, patients may retain widely distributed cortical systems, despite an inability to reliably communicate or follow simple instructions. This may underlie rare cases of later recovery of verbal fluency.

Diffusion Tensor Imaging in Brain Injury

Diffusion tensor imaging (DTI) is an advanced MRI technique, evaluating direction of movement of water in the magnetic field. DTI uses 6 or more diffusion measures to characterise white matter structure. Because the brain has structure, movement of water is not free in all directions and is best represented as a diffusion ellipsoid. Motion is anisotropic. Reduced anisotropy, reflecting damage to myelinated axons, is typically seen in head injury or stroke, where barriers to translational motion of water are disrupted [8, 9]. In patients with even mild head injury, reduced diffusion anisotropy is evident within 24 hours. These signs of fibre pathway disruption have clinical prognostic value.

Use of DTI to Demonstrate Late Axonal Regrowth in the MCS

Recently, a remarkable patient has been reported with late neurological recovery from the minimally conscious state [10]. This 39-year-old male, with severe head injuries, developed reliable expressive language over a month, after 19 years of the minimally conscious state. At this late stage, he started to develop meaningful vocalisation. He was studied on two occasions, 18 months apart, using DTI techniques. During this interval, he exhibited striking improvement in his speech and some meaningful motor improvement, although still remained severely neurologically disabled. His imaging results were compared with another patient who remained in a stable minimally conscious state for 6 years and 20 normal controls.

In his first study, increased right-left fractional anisotropy, reflecting the density of myelinated fibres, was demonstrated in the posteromedial cortices and these had reduced to normal levels on the second study. These changes correlated with increases in right-left fractional anisotropy in the midline cerebellum and clinically with gains in motor and speech performance. His PET findings were concordant, with increased glucose metabolism in these regions. The changes were postulated to reflect late axonal regrowth and improving connectivity between brain regions.

This clinical example of late axonal regrowth has been supported by experimental studies. Hence, axonal sprouting has been seen surrounding strokes in animal models [11] and after motor cortical ischemic injury [12].

Caution has to be exercised in extrapolating from a single case report. The patient was already conscious and improving at the time of the first study and the neuroimaging changes reflected predominantly white matter injury, with relative preservation of neurones. However, this case report is provocative and does suggest late brain rewiring. This has implications for further neuroimaging research and therapeutic trials [10].

Challenging the Clinical Criteria of Vegetative State

A challenging case has been recently reported, with demonstration of presumed awareness in a patient with the presumed vegetative state [2]. A 25-year-old woman had been diagnosed with severe head injuries after a motor vehicle accident and fulfilled the clinical criteria for the diagnosis of the persistent vegetative state. Using fMRI, she was asked to imagine playing tennis and moving around her home. Neuroimaging studies indicated activation of cortical regions that were indistinguishable from normal controls. Again, it needs to be emphasised that this is only a single case report and that this patient may have been in a transition phase between the vegetative state and the minimally conscious state.

Future Research Direction

Although these recent publications indicate the potential for axonal regrowth in the very late stage after severe brain injury and provide diagnostic insight into both the minimally conscious state and persistent vegetative state, it needs to be emphasised that the amount of data is sparse. However, neuroimaging research has the potential to allow better characterisation of the differences between the minimally conscious state and persistent vegetative state, using larger number of patients with careful clinical correlations and serial studies.

Importantly, these neuroimaging studies provide potential surrogate endpoints for therapeutic trials in relatively small numbers of patients, compared with purely clinical endpoints such as functional rating scales. Modalities such as fractional anisotropy, tractography, fMRI and PET could be used in patients treated with experimental neurotrophic drugs and other therapies to measure functional and structural changes in the brain. This opens up exciting research opportunities. Finally, these recent studies have challenged our reliance on purely clinical criteria for delineation between the minimally conscious state and persistent vegetative state and shown the potential of the brain for very late recovery.

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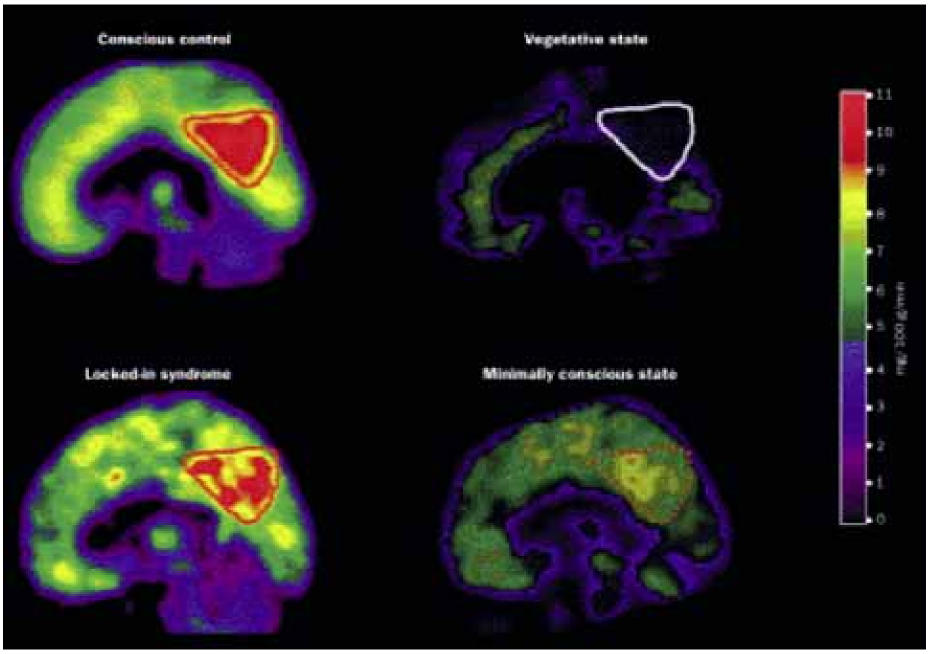

Figure 1. Resting cerebral glucose metabolism in healthy controls and patients in vegetative state, locked-in syndrome, and minimally conscious state. In healthy conscious individuals the medial posterior cortex is the most active brain region; in patients in VS who wake, this is the least active region. In MCS, there is an intermediate metabolism in this region, considered to be an important part of the neural network subserving consciousness. In locked-in syndrome, no brain region shows substantial metabolic suppression. From Laureys S. *et al., Lancet Neurology,* 2004;3:537-54.