Functional Imaging and the Vegetative State

The vegetative state (VS) is one of a number of conditions of impaired consciousness (coma, vegetative state, minimally conscious state) resulting from either traumatic or non-traumatic neurological damage. In contrast to many neurological conditions the VS is defined by the behaviours exhibited by patients rather than a common underlying pathology. Consequently the clinical diagnosis is made on the basis of prolonged and extensive, but critically subjective, observations of a patient's behaviour in response to sensory and cognitive stimulation. To fulfil the diagnostic criteria a patient must (1) demonstrate no evidence of awareness of self or environment, (2) demonstrate no evidence of sustained, reproducible, purposeful or voluntary response to visual, auditory, tactile or noxious stimuli, and (3) demonstrate no evidence of language comprehension or expression.[12,8] The VS typically follows the acute comatose period in which the patient demonstrates no wakefulness (eye opening/sleep wake cycles) or response to command. This period typically lasts 2-4 weeks after the initial insult before the patient either regains consciousness or progresses to the vegetative or minimally conscious state. The minimally conscious state describes a spectrum of impairment.[2] At the lowest boundary and earliest sign of emergence from the vegetative state, a patient demonstrates visual fixation and/or evidence of tracking objects or people. At the upper boundary before emergence to a fully conscious but severely disabled state, the patient demonstrates inconsistent but reproducible response to command. Emergence to the severely disabled condition reflects consistent and reproducible communication either via movement or speech.

Pathophysiology, prevalence and prognosis

Although defined by the exhibited behaviour, post mortem work has identified three crude pathophysiological presentations in VS: (1) damage predominately to subcortical brainstem structures with an intact cerebral cortex, (2) damage predominately to cortico-cortical connections with a relatively preserved brainstem, and (3) damage to both the brainstem and cerebral cortex.[6] In reality, patients meeting the diagnostic criteria for the VS are extremely heterogeneous. Although precise figures for the incidence of this condition are not available, estimates have suggested up to 14 persons per million in the UK and 46 persons per million in the USA could exist in this condition 1 month post ictus.[5] It is also thought that three times this figure could exist in the minimally conscious state; each patient requiring 24 hour high dependency care, which is predominately met by the private sector. Although diagnosis does not take place until at least 6 weeks post presentation, decisions about long-term prognosis and in some cases withdrawal of nutrition and hydration can not be made until at least 6 months post non-traumatic and 12 months post traumatic brain injury. Although prognosis following non-traumatic brain injury is very poor, for those with traumatic brain injuries, up to 20% are estimated to recover consciousness within 6 months.[5]

Clinical assessment

A diagnosis of vegetative state is typically made by two independent doctors supported by the observations of all persons in regular contact with the patient, including family members. Observations are typically performed over a minimum period of 6 weeks at different times of the day and when the patient is in different postural positions or taking part in stimulatory activities. Behaviours are typically recorded using a range of purpose built scales such as the Sensory Modality Assessment and Rehabilitation Technique[4] (SMART), the JFK Coma Recovery Scale3 or the Wessex Head Injury Matrix[14] (WHIM). However, the interpretation and subsequent decision as to whether the patient demonstrates awareness of self or environment and/or purposeful response to sensory or cognitive stimulation is purely based on the subjective observation of the assessors. Critically, this approach relies upon the patient being capable of making

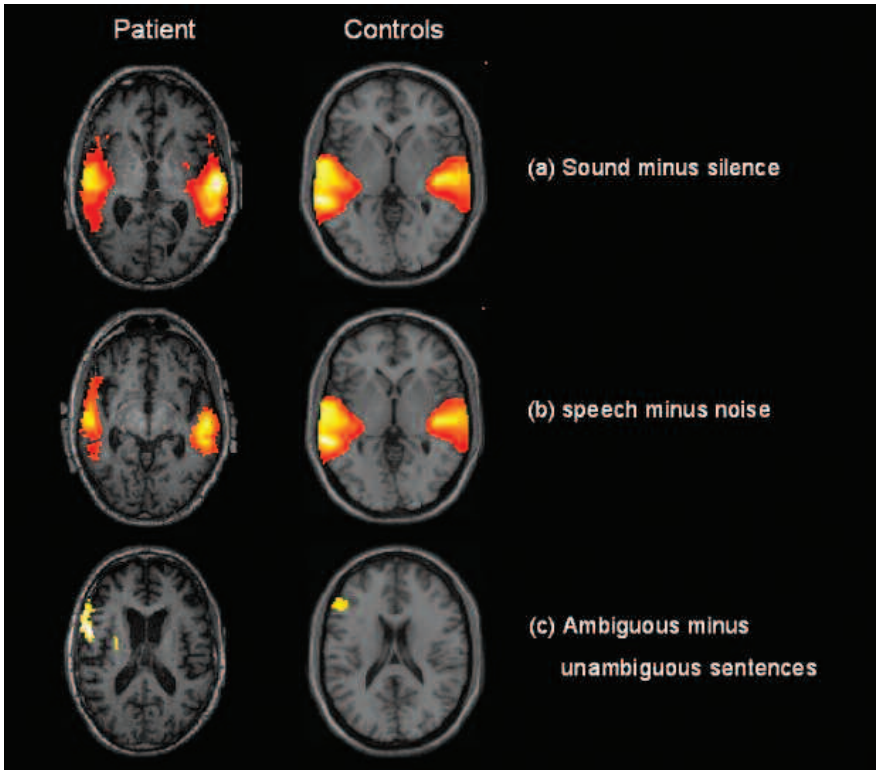

Figure 1: Auditory activations from a single patient meeting the behavioural criteria for the vegetative state and from a group of 12 healthy volunteers:
(a) Large bilateral temporal activation can be seen to hearing sound versus silence,
(b) intelligible speech minus signal correlated noise, in the superior and inferior temporal lobe, and
(c) discrete left inferior frontal activation can be seen to hearing sentences with ambiguous versus unambiguous content. All results are thresholded at FDR p<.05, corrected for multiple comparisons.

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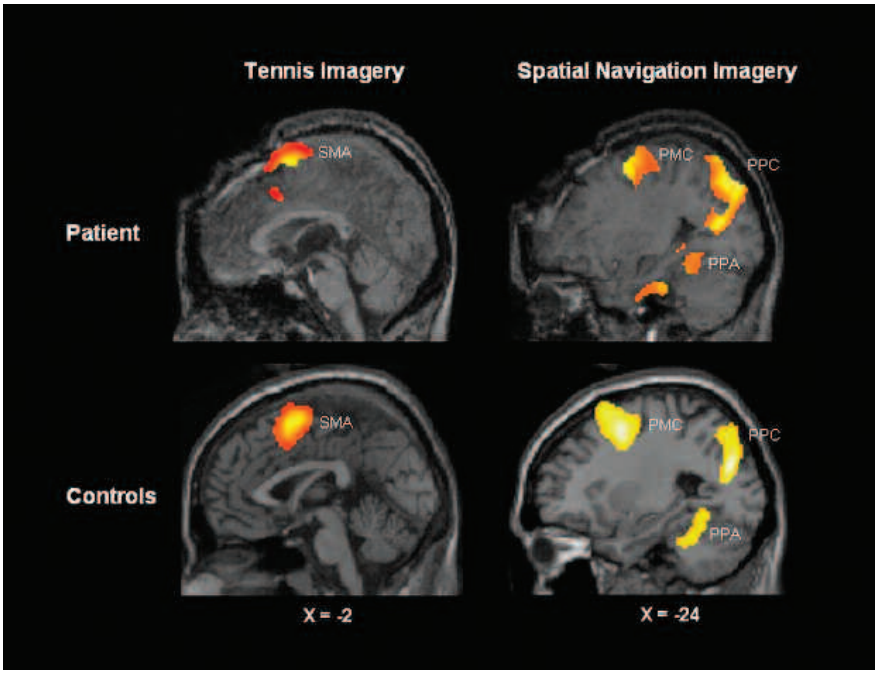

Figure 2: Supplementary motor area (SMA) activity in the comparison between tennis imagery and rest in both a VS patient and in a group of 12 healthy volunteers. Parahippocampal gyrus (PPA), posterior parietal-lobe (PPC) and lateral premotor cortex (PMC) activity in the comparison between imagining moving around a house and rest in both the patient and in the same group of volunteers. All results are thresholded at FDR p<.05, corrected for multiple comparisons.

an overt motor behaviour (movement or speech) to signal awareness and willingness to respond. However, a large number of patients progressing to the vegetative state also suffer complex peripheral nervous system changes. Many have extensive contractures, limited range of movement and muscle wastage preventing sufficient motor output to respond to command. Consequently, this difficulty is thought to be one of several contributing to the reported high rate of misdiagnosis.[1]

Emerging objective tools to aid the clinical assessment

Since 1998 work using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) has slowly facilitated a change in attitude to and understanding of this complex condition. Although by definition a vegetative patient should demonstrate no sustained or purposeful response to sensory or cognitive stimuli a number of imaging studies have demonstrated 'islands' of preserved cerebral function in a small number of patients otherwise behaviourally unresponsive.[7,13,9,10] Founded on the belief that the assessment of patients should require no overt action on the part of the patient, functional imaging has the ability to tap discrete covert cognitive processes – something the behavioural observation of a patient is entirely unable to do. In 1998 a landmark paper by Menon and colleagues identified preserved face processing in a VS patient behaviourally unresponsive to command. This was later expanded to auditory processing of intelligible versus unintelligible sound[9] and more recently to speech comprehension.[10] Indeed, Owen and colleagues have developed and subsequently advocated a hierarchical approach to the assessment of these patients using functional neuroimaging.[10] Having established the integrity of sensory pathways using electrophysiology, a number of paradigms using PET and fMRI are used to tap the residual cognitive function of the patients. In the auditory domain the group have developed a paradigm to determine whether (a) the patient is able to detect sound versus silence, (b) is able to discriminate speech from non speech, and (c) retrieve semantic information in order to comprehend sentences with ambiguous content (Figure 1). Although this paradigm is able to determine whether a patient is able to comprehend language, it does not tell us definitively whether the patient is aware of the information presented to them. To address this issue Owen and colleagues have recently developed an fMRI paradigm where the participant is asked to imagine playing tennis or moving around the rooms of their home.[11] In this scenario the subject is asked to create a vivid mental picture of the movement associated with hitting a ball with a racket and critically to maintain this picture for 30 seconds until told to relax. This request is then repeated 5 times and alternated with an equal number of rest periods. Therefore, in performing this task the participant not only demonstrates understanding of the command to perform the mental imagery task, but also the will and therefore awareness of the command to actually perform the task. To date four patients meeting the International criteria defining the vegetative state have been asked to perform these tasks. Two of these patients (one unpublished) have not only demonstrated appropriate activation consistent with retrieving semantic information to comprehend speech, but have also demonstrated cerebral activation consistent with volunteers asked to perform the mental imagery tasks (Figure 2). This has further suggested that despite negative behavioural markers a small subset of VS patients do in fact retain awareness of self and environment.

Conclusion

Despite the emerging and promising utility of functional imaging in this area there are a number of very important caveats. Firstly, only positive findings on functional imaging can be interpreted since false negatives are known to occur in conscious and healthy volunteers. Secondly, even if a negative finding is observed it is impossible to exclude the fact that at another time or in another cognitive task a patient might respond. Indeed, only a limited number of functional imaging paradigms currently exist to tap specific cognitive networks – for instance we know very little about whether these patients are able to learn or feel emotions. This work will undoubtedly continue over the coming years, but what is certain is that functional imaging is likely to play an increasingly important part in the accurate assessment of patients with impaired consciousness following brain injury.

References

1. Andrews K, Murphy L, Munday R & Littlewood C. *Misdiagnosis of the vegetative state.* British Medical Journal. 1996;313:13-16.
2. Giacino JT, Ashwal S, Childs N, Cranford R, Jennett B, Katz DI, Kelly JP, Rosenberg JH, Whyte J, Zafonte RD & Zasler ND. *The minimally conscious state: Definition and diagnostic criteria.* Neurology. 2002;58:349-53.
3. Giacino JT, Kalmar K & Whyte J. *The JFK Coma Recovery Scale – revised: Measurement characteristics and diagnostic utility.* Archives of Physical Medicine and Rehabilitation. 2004;85(12):2020-9.
4. Gill-Thwaites H & Munday R. *The Sensory Modality Assessment and Rehabilitation Technique (SMART): A comprehensive and integrated assessment and treatment protocol for the vegetative state and minimally responsive patient.* Neuropsychological Rehabilitation. 1996;9:305-20.
5. Jennett B. *Thirty years of the vegetative state: clinical, ethical and legal problems.* In Laureys S (Ed). Progress in Brain Research: The boundaries of consciousness; Neurobiology and neuropathology. 2005;150:537-43.
6. Kinney HC & Samuels MA. *Neuropathology of the persistent vegetative state: a review.* Journal of Neuropathology and Experimental Neurology. 1994;53:548-58.
7. Menon DK, Owen AM, Williams EJ, Minhas PS, Allen CMC, Boniface SJ & Pickard JD. *Cortical processing in the persistent vegetative state.* Lancet. 1998;352:200.
8. Multi-Society Task Force on PVS. *Medical aspects of the vegetative state (in two parts).* New England Journal of Medicine. 1994;330:1499-508, 1572-9.
9. Owen AM, Menon DK, Johnsrude IS, Bor D, Scott SK, Manly T, Williams EJ, Mummery C & Pickard JD. *Detecting residual cognitive function in persistent vegetative state.* Neurocase 2002;8:394-403.
10. Owen AM, Coleman MR, Menon DK, Johnsrude IS, Rodd JM, Davis MH, Taylor K & Pickard JD. *Residual auditory function in persistent vegetative state: A combined PET and fMRI study.* Neuropsychological Rehabilitation. 2005;15(3/4):290-306.
11. Owen AM, Coleman MR, Boly M, Davis MH, Laureys S & Pickard JD. *Detecting awareness in the vegetative state.* Science. 2006;313:1402.
12. Royal College of Physicians. *The vegetative state: Guidance on diagnosis and management.* London: Royal College of Physicians, 2003.
13. Schiff N, Ribary U, Moreno DR, Beattie B, Kronberg E, Blasberg R, Giacino J, McCagg C, Fins JJ, Llinas R & Plum F. *Residual cerebral activity and behavioural fragments can remain in the persistently vegetative brain.* Brain. 2002;125:1210-34.
14. Shiel A, Horn SA, Wilson BA, Watson MJ, Campbell M & McLellan DL. *The Wessex Head Injury Matrix (WHIM) main scale: A preliminary report on a scale to assess and monitor patient recovery after severe head injury.* Clinical Rehabilitation. 2002;14(4):408-16.