

Neurophysiological correlates of persistent vegetative and minimally conscious states

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The evaluation of patients after severe brain injury is a complex process for the clinician, even with the information provided by a detailed neurological examination. The clinical examination often does not provide sufficient information to fully evaluate these patients due to several factors. Limited and inconsistent motor responses may obscure expression of greater cognitive capacities. More importantly, evaluation of the functional integrity of the cerebral cortical, thalamic and basal ganglia system is poorly indicated by the clinical examination in many patients. Neurophysiological studies provide a complementary set of objective data for evaluating brain-injured patients, as well as predicting and following the course of their recovery. This additional information can be of great importance since vegetative patients may be difficult to distinguish clinically from those in the minimally conscious state. This is important because the latter category of patients may have a significantly better prognosis for recovery in the initial phase of injury. Electrodiagnostic and imaging studies can help the practitioner to determine the degree of preserved and recovering neurological function. In this review we will assess the various neurophysiological studies currently at our disposal to evaluate and follow the clinical course of patients who have suffered severe brain injuries.

In this review we discuss neurophysiological studies of patients in the vegetative state (VS) and preliminary studies of patients meeting diagnostic criteria for the recently defined minimally conscious state (MCS; Giacino et al., 2002). Neurophysiological correlates have been more comprehensively evaluated for VS than for MCS, at least in part due to the relatively recent definition of the latter state. Therefore, this review will be primarily focused on the neurophysiological studies of patients in the persistent

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vegetative state with the expectation that as corresponding studies of MCS patients become available, they will provide further insight into the pathophysiology of this condition. It is likely that the complementary information derived from different neurophysiological studies, such as electroencephalography (EEG) and evoked potentials (EPs), will enhance the determination of the neurological status, clinical course and outcome prediction of patients following severe brain injuries. Here, however, we will focus on the use of neurophysiological methods to improve the understanding of underlying pathophysiology of the severely injured brain.

NOSOLOGY

Patients in VS following a severe brain injury show a very limited recovery of cyclical arousal. VS patients remain unresponsive and their cyclical arousal pattern is limited to an eyes open “wakeful” appearance alternating with an eyes closed “sleep-like” state (Jennett & Plum, 1972). Otherwise, VS is identical to coma in that patients demonstrate no evidence of awareness of self or their environment. A VS that lasts more than one month is arbitrarily defined as a persistent vegetative state (PVS). It is estimated that the chance of further recovery after VS lasting longer than three months after an anoxic injury or one year after a traumatic brain injury is less than 1 in 1000, and is thus considered permanent (Jennett, 2002). The permanent vegetative state is often the clinical sequelae of diffuse anoxic cerebral injury or severe head trauma (Multi-Society Task Force on PVS, 1994).

The minimally conscious state (MCS) has been recently defined as a state of severely altered consciousness with demonstration of minimal, but definite behavioural evidence of awareness of self or the environment. It differs from PVS by the presence of inconsistent, but clearly discernible, behavioural evidence of consciousness (Giacino et al., 2002). MCS patients may exhibit intermittent behavioural fragments, such as simple verbalisation or context-appropriate gestures, or sustained visual fixation. It is essential to distinguish this condition from PVS due to the potential for a more favourable outcome in the initial stages of the illness (Giacino & Kalmar, 1997). When patients exhibit consistent, reliable functional communication (regaining more than the ability to follow simple commands), they are considered to have emerged from MCS. Due to the wide range of behavioural patterns of patients within MCS, there exists a need for further refinement of this diagnostic category and association with quantitative neurophysiological criteria.

EEG IN THE VEGETATIVE STATE

A variety of awake electroencephalography (EEG) patterns have been reported in patients in VS. These include focal or diffuse continuous

slowing in the theta (4–7.5 Hz) and/or delta (1–3.5 Hz) frequency ranges, intermittent delta rhythms, and attenuation of the EEG signal, which can be of a very severe degree such that the EEG is essentially isoelectric (Hansotia, 1985; Li, Wei, & Guo, 1993). In addition, epileptiform activity can occur, such as focal sharp waves, whether or not the patient has documented electrographic seizures. Alpha-theta coma and spindle coma EEG patterns are also reported in PVS. The EEG can provide prognostic information for severely brain-injured patients. Kane and colleagues found a highly significant correlation between the initial EEG grade (i.e., degree of abnormality) and clinical outcome (Glasgow Outcome Score) in comatose patients 6 and 12 months after brain injury (Kane, Moss, Curry, & Butler, 1998).

The normal diurnal and nocturnal EEG pattern fluctuations, as well as the reactivity of the EEG to stimuli can be affected by severe brain injury. In a study of 12 PVS patients, Isono and colleagues found that the diurnal EEG patterns typically did not vary significantly during the course of the day and that no changes were noted when PVS patients were subjected to noxious sensory stimuli (Hansotia, 1985; Isono et al., 2002). Behavioural arousal in VS indicates preservation of brainstem systems. The cyclic variability and reactivity of the EEG, however, are associated with the interaction of brainstem arousal systems and other cerebral systems supporting attention and other cognitive processes and, thus more directly reflects the integrity of corticothalamic systems. The upper brainstem-mesencephalic component of the reticular activating system and thalamus, where overwhelming injuries may lead to permanent VS (see Schiff et al., 2002), play a key role in these interactions. Many of the EEG changes, which normally occur during the different stages of sleep, are absent in PVS patients, such as rapid eye movements (REM), sleep spindles and vertex waves. In some PVS patients sleep EEGs show diffuse low voltage slow waves immediately following sleep onset. The slow waves can remain unchanged during the sleep period or gradually increase in amplitude with time. In other PVS patients there are no discernible fluctuations in the EEG during sleep compared with that during wakefulness (Isono et al., 2002). The diminution or absence of EEG fluctuation during the sleep–wake cycle, particularly when there is a coexisting evoked potential abnormality (see below), can serve as an indicator of the severity of brainstem dysfunction and VS patient's prognosis for recovery (Cheliout-Heraut, Rubinsztajn, Ioos, & Estournet, 2001).

Besides evaluating the EEG in the time domain, power spectrum and coherence analysis of the EEG has been used to evaluate various brain pathophysiological conditions. Power spectra analysis quantitates the relative amplitudes of the various frequencies that comprise the EEG signal. Changes in the EEG power spectrum after severe brain injury may have prognostic value. Kane et al. (1998) found highly significant correlations between six month and one year post-injury Glasgow Outcome Scores and left frontal-central

beta and left central-temporal alpha and beta activity power in comatose patients. Coherence is a measure of cross-correlation in the frequency domain. Coherence analysis of the EEG has been used to study patients with a variety of pathological conditions (Leocani & Comi, 1999). It is proposed that coherence provides an index of the integrity of inter-regional networks and communication between cortical areas, as well as with subcortical structures (e.g., thalamus and basal ganglia) that mediate this connectivity (Davey, Victor, & Schiff, 2000; Nunez, Wingeier, & Silberstein, 2001). Therefore, EEG coherence may serve as a better prognostic indicator for recovery after brain injury than power spectral analysis (Thatcher et al., 1991). Kane and colleagues (1998) found a significant reduction of the mean interhemispheric coherence of the EEG for all regions in comatose patients compared to normal healthy control subjects. However, they found no correlation between the degree of interhemispheric coherence and outcome scales at six months and one year post-injury. This is in contrast to the study by Thatcher and colleagues (1991) that identified coherence and phase measurements as the best predictors of functional outcome one year following closed head injury. Davey et al. (2000) performed power spectra and coherence analysis of the EEG in a PVS patient who had suffered severe damage predominantly to the right subcortical grey matter structures after a series of intraparenchymal haemorrhages from an arteriovenous malformation. EEG power spectra computed for each bilateral hemispheric region (frontal, central and parieto-temporal) showed only slight differences between the two hemispheres; there was relatively greater power of the lower frequencies and diminished power of the higher frequencies throughout the more damaged right cerebral hemisphere. In contrast, a marked reduction of coherence over the entire damaged right hemisphere was demonstrated, which was most evident frontally where the brain injury was most severe. This study provides a correlate of the impact of subcortical grey matter structures on the EEG as well as insight into the thalamic contribution to organised cerebral activity.

EEG IN THE MINIMALLY CONSCIOUS STATE

A few reports of EEG findings in MCS patients are available. Observed EEG abnormalities depend on the location and type of cerebral lesions and include diffuse or focal slowing, often in the theta and delta frequency range, disorganisation (e.g., absence, diminution and/or decreased reactivity of the posterior dominant rhythm, and diminished or absent sleep spindles) (Boly et al., 2004). Bilateral, but predominantly ipsilesional polymorphic theta activity represented the most prominent abnormality in awake EEGs from two MCS patients we studied. This abnormal slow activity was most apparent in the electrodes nearest to the respective lesions. There was also disorganisation of the background, predominantly in the more severely injured

hemisphere, with an attenuated and slow posterior dominant (“alpha”) rhythm. Asleep EEG from our MCS patients showed continuous polymorphic slowing, which was more apparent near the cerebral lesions. The sleep spindles were also attenuated, less frequent and less well formed in the more severely affected hemisphere, particularly if the lesions involved the parasagittal regions (Kobylarz, Kamal, & Schiff, 2003).

We performed similar power spectra and coherence analyses of the EEG from an MCS patient to that utilised by Davey and colleagues (2000). For our MCS patients the EEG power spectra revealed generally few significant differences between corresponding hemispheric regions in the asleep and awake states (see Figure 1). Notably, there was slightly decreased EEG power for nearly all frequencies in the right frontal region during wakefulness. In the central-temporal regions there was slightly decreased EEG power on the right during wakefulness for several frequency ranges, most prominently from approximately 20–30 Hz and 40–50 Hz. These differences in

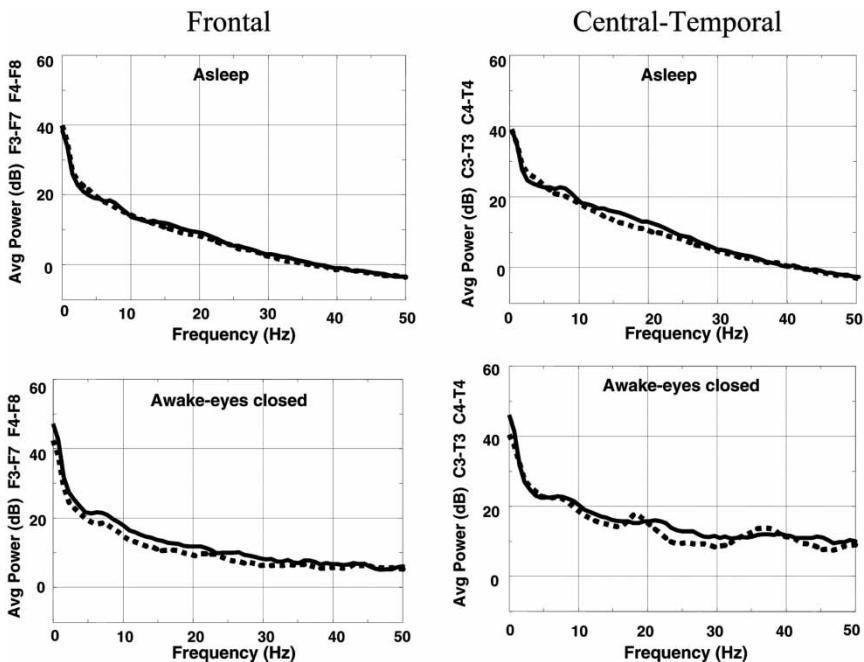


Figure 1. Regional asleep (above) and awake (below) EEG power spectra compared between the left (solid line) and right (dashed line) hemispheres from an MCS patient with post-traumatic right frontal lobe encephalomalacia and a right thalamic infarct. Frontal region, electrodes F3/F7 (left) and F4/F8 (right); central region, electrodes C3/T3 (left) and C4/T4 (right) (from Kobylarz, Kamal, & Schiff, 2003)

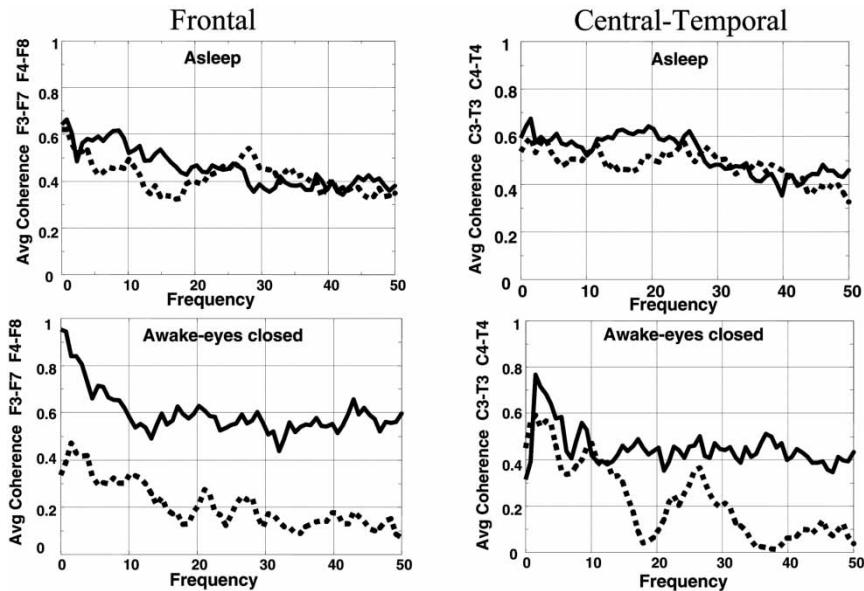


Figure 2. Regional asleep (above) and awake (below) EEG coherence compared between the left (solid line) and right (dashed line) hemispheres from an MCS patient with post-traumatic right frontal lobe encephalomalacia and a right thalamic infarct. Frontal region, electrodes F3/F7 (left) and F4/F8 (right); central region, electrodes C3/T3 (left) and C4/T4 (right) (from Kobylarz, Kamal, & Schiff, 2003)

regional power correlated with the underlying structural brain injury. There was also notably reduced coherence over the right hemisphere in this MCS patient (see Figure 2). The reduction was more marked across the entire right hemisphere for this patient in the awake state, but was also present to a lesser degree in the right frontal and central-temporal regions during sleep (Kobylarz et al., 2003).

EPs IN THE VEGETATIVE STATE

Evoked potentials (EPs) are affected to varying degrees in VS patients. Although brainstem auditory evoked potentials (BAEPs) can be normal in VS patients (Hansotia, 1985), the BAEP waveforms can also be attenuated, delayed or absent, depending on the location and degree of brainstem injury (Li et al., 1993). Isono et al. (2002) reported such abnormalities in waveforms III and V, corresponding to the superior olivary complex (pons) and lateral lemniscus-inferior colliculus (pons-midbrain) auditory responses for PVS patients.

Similarly, somatosensory evoked potentials (SEPs) have been found to be abnormal in PVS patients with delay and attenuation, or even absence of the

N20 cortical response to median nerve stimulation (Hansotia, 1985; Isono et al., 2002; Li et al., 1993). Rothstein and colleagues studied the prognostic value of EEGs and median nerve SEPs in patients with hypoxic-ischaemic coma lasting six or more hours (Rothstein, Thomas, & Sumi, 1991). They found that bilateral absence of median SEP cortical responses and/or a malignant EEG abnormality (e.g., low amplitude non-reactive delta slowing, burst suppression, alpha coma or isoelectric) predicted an unfavourable outcome or death without awakening in greater than 80% and 40% of patients with these neurophysiological abnormalities, respectively. However, comatose patients with normal or delayed central conduction time (CCT, time difference between cervical and cortical SEP responses) and benign (normal, theta slowing or frontal rhythmic delta) or uncertain (diffuse non-reactive or reactive delta slowing, epileptiform discharges) EEG patterns had an uncertain prognosis that included recovery of consciousness, entry into PVS or death without awakening. The spinal components of somatosensory evoked potential responses are remarkably resilient in amplitude and latency in comparison to the cortical responses, despite systemic changes that may occur due to metabolic derangements, anaesthesia and even brain death (Hansotia, 1985). Therefore, the cortical responses and, specifically the CCT are better indices of cerebral injury, recovery and prognosis after severe brain injury (Hume, Cant, & Shaw, 1979). For the patients who awakened after PVS, cortical SEP and EEG findings did not distinguish between patients who recovered completely from those who had varying degrees of motor or cognitive impairment.

Magnetoencephalography (MEG) is a unique functional imaging technique, which provides spatiotemporal identification of the sources of brain activation. Schiff and colleagues applied MEG to study auditory and somatosensory evoked responses in PVS patients (Schiff et al., 2002). They found that the auditory and somatosensory MEG responses were delayed, attenuated and incomplete, or absent for various frequency bands compared to those for normal subjects. These results correlated with the local abnormalities of the corresponding positron emission tomography (PET) imaging studies. The use of PET studies to evaluate brain-injured patients are described further below.

IMAGING STUDIES OF THE VEGETATIVE STATE

Imaging techniques can also provide useful information to study the neurophysiology of patients with severe brain injuries. Brain metabolism can be quantified by fluorodeoxyglucose-positron emission tomography (FDG-PET) imaging. Cerebral metabolic rates measured by FDG-PET correlate with neuronal firing rates in cerebral structures (Eidelberg et al., 1997). FDG-PET imaging has shown that glucose utilisation is significantly reduced in PVS patients globally (Levy et al., 1987; Rudolf et al., 1999)

and regionally (Tomassino et al., 1995) in comparison with age-matched controls. Levy and colleagues (1987) hypothesised that the decrease in glucose metabolism is evidence of a loss of cognitive function in PVS.

Studies employing ^{15}O -radiolabelled PET (^{15}O -PET) allow for measurements of brain activation in response to transient stimuli to be compared with baseline resting conditions. Laureys et al. (2002b) studied ^{15}O -PET cerebral activation patterns in response to noxious somatosensory stimuli in 15 PVS patients. PVS patients showed brain activations in the contralateral thalamus and primary somatosensory cortex, but not secondary somatosensory insular or anterior cingulate cortices activated in normal subjects presented with the same stimuli (Laureys et al., 2002b). In addition, Laureys and colleagues reported ^{15}O -PET abnormalities in the bilateral frontal and parieto-temporal association cortices in PVS patients using a similar strategy employing auditory click stimuli (Laureys et al., 2002a). The absence of activation of the sensory association regions and their functional connections with the higher level cortices is significant, since these are felt to be necessary for conscious perception.

IMAGING STUDIES OF THE MINIMALLY CONSCIOUS STATE

As with PVS, MCS patients often have PET imaging abnormalities related to their brain injury, although some characteristics of their studies appear more like those of normal subjects. Quantitative (FDG-PET) measurements of regional cerebral metabolic rates averaged 40–50% of normal values over the entire brain for both of our MCS patients (Kobylarz et al., 2003). However, Boly and colleagues (2004) determined similar ^{15}O -radiolabelled PET responses to auditory stimuli for patients in MCS compared to healthy control subjects. When subjected to auditory (click) stimulation, there was activation of the bilateral superior temporal gyri (Brodmann areas 41, 42, and 22). In contrast, for PVS patients activation was limited to bilateral Brodmann areas 41 and 42 (Laureys et al., 2000). The ^{15}O -radiolabelled PET responses to auditory stimuli with emotional valence (i.e., infant cries and patient's own name) in an MCS patient showed more widespread activation than that for meaningless noise (Laureys et al., 2004). The activation patterns were comparable to those from normal control subjects. Bekinschtein et al. (2004) recently reported evidence of emotion processing in an MCS patient who suffered a severe traumatic brain injury using functional magnetic resonance imaging (fMRI). When they played a recording of the patient's mother's voice, fMRI demonstrated activation of the amygdala and the insula, subcortical structures related to emotion, which later spread to the inferior frontal gyrus. In their study, stronger functional connectivity between the secondary auditory cortex and temporal and prefrontal cortices, and thus for higher order

integrative processes necessary for conscious auditory perception in MCS patients compared with those in PVS.

DISCUSSION

Severely brain-injured patients pose a unique set of diagnostic and management challenges to the clinician, both in the initial evaluation as well as during the subsequent course of recovery. The more traditional information provided by the neurological examination can be limited, given the physically debilitated state of these patients. Neurophysiological studies provide an additional set of useful, reliable indices to assess and follow patients with severe brain injury. In addition to using conventional parameters provided by the EEG and evoked potentials, quantitative analyses of these signals, such as in the frequency domain with power spectra and coherence, can also provide useful information. In conjunction with analyses of electrophysiological studies, more recently developed imaging techniques, such as PET and fMRI will provide additional information regarding preservation and recovery of brain activity and intracerebral networks both at rest and in response to stimulation. All of these neurophysiological techniques will enhance our understanding of the pathophysiology of the entire spectrum of severe brain injuries as well as mechanisms supporting or limiting further recovery.

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