Clinical differentiation and outcome evaluation in vegetative and minimally conscious state patients: the neurophysiological approach

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Summary

The neurophysiological approach to patients with disorders of consciousness allows recording of both central and peripheral nervous system electrical activities and provides a functional assessment. Data obtained using this approach can supplement information from clinical neurological examination, but also from the use of morphological neuroimaging techniques: computed tomography and magnetic resonance imaging. Neurophysiological techniques, such as electroencephalography (EEG), evoked potentials, transcranial magnetic stimulation, and EEG in association with functional magnetic resonance imaging, allow monitoring of clinical conditions and can help in the formulation of a prognosis. The aim of this review is to describe the main neurophysiological techniques used in disorders of consciousness to evaluate residual cerebral function, to provide information on the neuronal dysfunction for outcome evaluation, and to differentiate clinically between the vegetative and minimally conscious states.

KEY WORDS: electroencephalogram, evoked potentials, minimally conscious state, outcome, transcranial magnetic stimulation, vegetative state

Introduction

Following coma, some patients permanently lose all brainstem function (brain death), some progress to "wakeful unawareness" (vegetative state, VS), while others recover. The latter group typically progress through stages to partial recovery (minimally conscious state, MCS) or to full recovery of consciousness. Patients who remain unresponsive to the environment even though their eyes may be open, are considered to be in a VS (1,2).

Theoretically, VSs are divided into transitory, persistent and permanent. A persistent VS (PVS) has been defined as a VS still present one month after acute traumatic or non-traumatic brain damage. It does not imply irreversibility. A permanent VS, on the other hand, is irreversible (3). According to guidelines published in the United States by the Multi-Society Task Force on PVS, a VS may be regarded as permanent when it is still present three months after non-traumatic brain damage, or 12 months after traumatic injury (4).

According to guidelines from the Royal College of Physicians, a VS is persistent when it lasts longer than a month, whereas it is deemed permanent when it lasts longer than six months following non-traumatic brain injury, or one year following traumatic brain injury (5).

A recent study has offered a new name for this challenging neurological condition: "unresponsive wakefulness syndrome". As this neutral descriptive term indicates, it refers to patients showing a number of clinical signs (hence syndrome) of unresponsiveness (i.e. absence of response to commands) in the presence of wakefulness (eye opening) (6).

Although the abbreviation "PVS" is often used to indicate both persistent and permanent vegetative states, the authors of a letter published in the *British Medical Journal* in 2000 suggested that, to avoid confusion, the abbreviation should be used exclusively to indicate a permanent vegetative state. In this paper, however, PVS is used to mean persistent vegetative state. The American Congress of Rehabilitation Medicine suggested that the cause of injury (traumatic, anoxic) as well as the time elapsed since onset of the condition should be documented, as both are important for prognosis (7).

Patients emerging from a VS often enter the MCS, which may be the end point of their improvement, or a staging post on the way to further recovery (4). Patients in the MCS show non-reflexive, i.e. purposeful, behaviors, but are unable to communicate effectively (8). To be diagnosed with MCS, patients are required to show limited but clear evidence of awareness of themselves, or their environment, on a reproducible or sustained basis, through at least one of the following behaviors: following simple commands, giving gestural or verbal yes/no responses (regardless of accuracy), producing intelligible speech, displaying purposeful behaviors.

Clinically, the differential diagnosis between these two patient populations is extremely challenging. Indeed, because there is no proper clinical scale, there is a high rate of misdiagnosis (9). Several studies have shown important differences in brain function (10,11) and prognosis (12) between VS and MCS patients.

The neurophysiological approach to patients with disorders of consciousness (DOC) allows the recording of both central and peripheral nervous system (CNS and PNS) electrical activities and provides a functional assessment, which can be integrated with data obtained mainly from morphological neuroimaging techniques: computed tomography (CT) and magnetic resonance imaging (MRI). Neurophysiological examinations, such as the electroencephalogram (EEG), evoked potentials (EPs), transcranial magnetic stimulation (TMS), and EEG in association with functional MRI (fMRI), contribute to the topographic and functional diagnosis of the CNS and PNS structures involved in the injury.

Electrophysiological techniques allow the assessment of a larger number of patients, including those who, for geographical, financial, or physical (i.e., metal plates or pins) reasons, do not have access to MRI.

Neurophysiological tests have the following advantages: they can be performed at the bedside; they can be performed many times along with the clinical examinations; they are independent of the efferent channel of motor behavior (intentional limb movements, verbalization, eye movements and emotional facial expressions) on which clinical evidence of consciousness is based.

Some of the neurophysiological tests that can be performed in the intensive care unit (ICU), e.g. EEG and somatosensory evoked potentials (SEPs), provide more information on the acute phase, while others [long-latency EPs/event-related potentials (ERPs)] inform on the post-acute phase in patients who are not yet responsive. It is important to point out that the EEG, indispensable for diagnostic purposes in the ICU, should be supplemented by SEPs, which are reliable indicators of the severity of acute brain injury (hypoxic-ischemic, traumatic and hemorrhagic). It is important to balance the high variability of the EEG and its sensitivity to neurosedation with the stability of SEPs, which are more resistant to sedation and have waveforms that are easily interpretable and comparable (13).

The aim of this review is to assess the main neurophysiological techniques useful for assessing and evaluating residual cerebral function in DOC patients. These techniques, which are non-invasive procedures and easily performed, support clinical neurological examination in the outcome evaluation and clinical differentiation of VS and MCS.

Electroencephalography

An EEG is a useful objective electrophysiological assay of cortical function in patients who do not respond to normal sensory stimuli (14).

EEG activity reflects the temporal synchronization of cortical pyramidal neurons as revealed by the summation of post-synaptic potentials at their apical dendrites (15). These processes of temporal synchronization at theta (about 4-7 Hz) and alpha (about 8-12 Hz) frequencies constitute an important neural substrate of human cognition (16). Cortical alpha rhythms are correlated with conscious awareness and are abnormal in patients with an impairment of awareness (17).

An EEG in a VS patient will show a marked general slowing of the electrical brain activity.

Instead, EEGs in PVS patients have shown a spectrum of abnormalities including changes during the wake-sleep cycle. Patterns have included delta and theta activity and spindle and alpha-like rhythms. These rhythms were more diffusely distributed, even though typically located in the posterior regions, and were not reactive to sound, pain, or light stimuli (17). Very-low-voltage EEG activity is all that can be detected in some patients. In others, persistent alpha activity is the most remarkable feature. In around 10% of VS patients, the EEG is nearly normal late in the course of disease but without evidence of vision-induced alpha blocking (18). There have been occasional reports of isoelectric EEGs in VS patients, although this has not been confirmed in larger studies (5). Typical epileptiform activity is unusual in PVS patients, as is seizure activity (19). Clinical recovery from a VS may be paralleled by diminished delta and theta activity and the reappearance of a reactive alpha rhythm. Indeed, Babiloni et al. (19) found that occipital source power in the resting EEG alpha band, when calculated with low-resolution electromagnetic tomography (LORETA), was correlated with recovery outcome at three-month follow-up in a group of VS patients; those who made a behavioral recovery had higher resting alpha band power than those who did not make a significant recovery. These results suggest that cortical sources of resting alpha rhythms are related to the outcome of PVS patients at three-month follow-up. Future research should seek to confirm that cortical sources of resting alpha rhythms might predict recovery in PVS patients (17). Based on multichannel surface EEG recordings, LORETA is a new method for localizing electrical activity in the brain. In contrast to the models presented to date, this new method does not assume a limited number of dipolar point sources nor a distribution on a given known surface, but directly computes a current distribution throughout the whole brain volume (20).

EEG reactivity can manifest itself not only as desynchronization or voltage reduction, but also as paradoxical reactivity, K-complexes, and prolonged bursts of delta waves (21).

Normal diurnal and nocturnal EEG pattern fluctuations, as well as EEG reactivity to stimuli, can be affected by severe brain injury. In a study of 12 PVS patients by Isono et al., the typical diurnal EEG patterns did not vary significantly during the course of the day and no changes were noted when the PVS patients were subjected to noxious sensory stimuli (22).

While the EEG has proven useful for assessing arousal level and seizures, its spatial resolution is too low to allow investigation of specific brain functions.

In the MCS, the EEG seems to show diffuse slowing of brain activity (mainly of the theta and delta band) that in most cases is responsive to external stimuli. However, the available data are insufficient to establish a typical pattern.

In the few existing reports of EEG findings in MCS patients, the abnormalities observed depend on the location and type of cerebral lesions and include diffuse or focal slowing, often in the theta and delta frequency range, and diffuse disorganization (e.g., absence, diminution and/or decreased reactivity of the posterior dominant rhythm, and diminished or absent sleep spindles) (23).

Sleep EEG

The existence of normal sleep in VS patients is still a matter of debate.

Sleep is a behavior usually characterized by the adoption of a typical posture and the absence of response to external stimuli due to transient but reversible periods of unconsciousness which, in healthy individuals, are accompanied by well-defined EEG changes (24). In DOC, however, the operational electrophysiological definition of wakefulness and sleep is problematic as EEG-recorded oscillations no longer reflect the same cellular mechanisms as in normal physiological sleep. Large-amplitude slow waves do not necessarily indicate deep non-rapid eye movement (NREM) or ''slow-wave'' sleep, as they do in normal sleeping individuals. Sleep staging criteria for subjects affected by DOC are lacking and need to be explicitly defined (25).

Many of the EEG changes that normally occur during the different stages of sleep (e.g. rapid eye movements, sleep spindles and vertex waves) are absent in PVS patients. In some PVS patients sleep EEGs show diffuse low-voltage slow waves immediately following sleep onset. These slow waves can remain unchanged during the sleep period or gradually increase in amplitude over time. In other PVS patients there are no discernible fluctuations in the sleep EEG compared with that recorded during wakefulness (22). Reduction or absence of EEG fluctuation during the sleep-wake cycle, particularly when there is a coexisting evoked potential abnormality, can serve as an indicator of the severity of brainstem dysfunction and the VS patient's prognosis for recovery (26).

In most patients, the transition from wakefulness to sleep is accompanied by some desynchronization of the background activity. During sleep, fewer muscle twitches were observed, even if the patients were in a REM condition (27).

In an electrophysiological sleep study using high-density EEG sleep recordings, 11 patients with DOC (six in MCS, five in VS) were studied to look for correlations between electrophysiological changes associated with sleep and behavioral changes in vigilance (sustained eye closure and muscle inactivity). All the MCS patients showed clear EEG changes associated with decreases in behavioral vigilance. In the five MCS patients showing sustained behavioral sleep periods, several electrophysiological characteristics typical of normal sleep were identified. In particular, all MCS patients showed an alternating NREM/REM sleep pattern and a homoeostatic decline of EEG slow-wave activity through the night (28).

The EEG examination during sleep cycles in patients with DOC presents many limitations: difficulties in applying the American Academy of Sleep Medicine (www.aasmnet.org) rules for sleep staging, environmental limitations such as light and noise, and artifacts from hydration and nutrition pumps. Moreover, a further possible limitation is the variability of EEG patterns in patients with DOC, due to the different brain damage etiologies (Table I).

Evoked potentials

Evoked potentials (EPs) can be used to test the integrity of brainstem and forebrain pathways in DOC. Although they do not provide reliable information on the location of lesions in the brainstem, EPs (both auditory and somatosensory) and cortical event-related potentials can provide information on the prognosis of patients with DOC (29).

The term EPs generally refers to sensory processing responses, whereas ERPs are perceptual and cognitive processing responses. In terms of nomenclature, both tend to be named according to their polarity and latency (30).

Sensory EPs are most commonly used for clinical assessment of basic sensory functions. Brainstem auditory evoked potentials (BAEPs) occur in the 10 ms range

Table I - EEG studies in patients with disorders of consciousness.

Authors (ref. no.)	Summary
Hughes, 1978 (17)	This review showed that EEG evaluations in PVS have shown patterns of delta and theta activity and spindle and alpha-like rhythms, diffusely distributed in the typical posterior regions and not reactive to sound, pain, and light stimuli.
Oksenberg et al., 2001 (27)	During sleep, fewer muscle twitches were observed in 11 patients in VS, even if the patients were in a REM condition.
Danze et al., 1989 (18)	The authors studied 15 VS patients, following severe head injury. Around 10% of the patients, showed a normal EEG late in the course of disease but without evidence of vision-induced alpha blocking.
Babiloni et al., 2009 (19)	Occipital source power in the resting EEG alpha band in 50 PVS subjects was correlated with recovery outcome at three-month follow-up in a group of VS patients.
Guérit et al., 2009 (21)	This review showed that EEG reactivity can manifest itself as paradoxical reactivity, K-complexes, or prolonged bursts of delta waves.
Isono et al., 2002 (22)	Diurnal EEG patterns typically did not vary significantly during the course of the day and no changes were noted when 12 PVS patients were subjected to noxious sensory stimuli.
Landsness et al., 2011 (28)	11 patients with DOC (six in MCS, five in VS) were studied to correlate sleep-associated electrophysiological changes with behavioral changes in vigilance. All the MCS patients showed clear EEG changes associated with decreases in behavioral vigilance. In the five MCS patients showing sustained behavioral sleep periods, several electrophysiological characteristics typical of normal sleep were identified.

Abbreviations: VS=vegetative state; PVS=persistent vegetative state; EEG=electroencephalogram; MCS=minimally conscious state; DOC=disorders of consciousness.

and are often employed in the assessment of coma. The absence of an intact brainstem response is indicative of a poor prognosis for recovery (31). Sensory EPs also include SEPs, middle-latency auditory evoked potentials, and visual EPs that occur in the 30 ms range and are used to evaluate the primary sensory cortices.
Evoked potentials are affected to varying degrees in VS patients. Although BAEPs can be normal in VS patients (32), BAEP waveforms can also be attenuated, delayed or absent, depending on the location and degree of brainstem injury (33). Isono et al. (22) reported such abnormalities in waveforms III and V, corresponding to the superior olivary complex (pons) and lateral lemiscus/inferior colliculus (pons-midbrain) auditory responses, in PVS patients.
Similarly, SEPs have been found to be abnormal in PVS patients, being characterized by delay and attenuation, or even absence of the N20 cortical response to median nerve stimulation (22).
Short-latency EPs have a high negative predictive value and bilateral absence of cortical BAEP or SEP responses is regarded as a reliable predictor of poor functional outcome. However, their presence does not necessarily indicate a good outcome.
Cognitive ERPs are used to evaluate higher-level functions like attention, memory and language, and their presence is indicative of recovery of consciousness (34). Auditory cognitive ERPs are useful to investigate residual cognitive functions, such as echoic memory (MMN), acoustical and semantic discrimination (P300), and incongruent language detection (N400). Vanhaudenhuyse et al. reviewed all studies that investigated cognitive ERPs (N100, MMN, P300, or N400) in comatose and post-comatose (VS and MCS) patients, and gave details regarding prognostic values (35).
Their review showed that ERPs are more useful than EEG in differentiating between VS and MCS. Recent data show that the P300 wave is not a reliable marker of awareness but rather an indication of automatic processing, given that it could be recorded in well-documented VS patients who never recovered.
Perrin et al. recorded auditory EPs to the patient's own name in 15 brain-damaged patients. A P300 component was observed in response to the patient's name in all patients with locked-in syndrome, in all MCS patients, and in three out of five patients in a VS. P300 latency was significantly delayed in MCS and VS patients compared with healthy volunteers. As remarked by the authors, these results suggest that partially preserved semantic processing can be observed in non-communicative brain-damaged patients, notably for the detection of salient stimuli, such as the subject's own name. This function seems delayed in MCS and (if present) in VS patients (36).
Schnakers et al. explored a new active evoked-related potentials paradigm as an alternative method of detecting voluntary brain activity. They presented patients with DOC with sequences of names containing the patient's own name or other names, in both passive and active conditions. The MCS patients showed a larger P300 for their own name, both in the passive and in the active conditions. Moreover, the P300 for target stimuli was higher in the active than in the passive condition. By contrast, no P300 differences between passive and active conditions were observed in the VS patients. These results suggest that active evoked-related potentials paradigms may allow detection of voluntary brain function in patients with severe brain damage who present a DOC (37).
The authors of another study set out to predict consciousness recovery in patients in a post-traumatic VS. They used a classical two-stimulus oddball task to elicit the P300 using the patient's own name as deviant and a pure tone as standard stimulus ("subject's own name" paradigm). There is evidence (36,37) that the amplitude of the P300 wave increases when more salient stimuli are used, such as the patient's own first name instead of visual or auditory deviants. The authors found that P300 was a strong predictor of future recovery of consciousness in VS. This finding is in line with several studies that have confirmed the usefulness of P300 evoked by deviant tones in predicting awakening and favorable outcome from coma and VS (38). In another study, the same authors, seeking to better differentiate patients in VS and MCS, again used the "subject's own name" paradigm but added an "other first name" paradigm. They instructed their patients to count the occurrence of deviant stimuli. In six out of 11 patients fulfilling the behavioral criteria for VS a reliable P300 component could be observed in both conditions. These findings corroborate earlier reports (36,37) showing that 38% of VS patients generate a P300 wave. Compared with the VS patients, the patients in MCS exhibited significantly longer P300 latencies for the "subject's own name" and the "other first name" paradigms. The finding of increased P300 latencies for more complex and salient paradigms in MCS but not in VS might help in the difficult differential diagnosis of MCS versus VS (39).
Moreover, Boly et al. measured effective connectivity during a mismatch negativity paradigm and found that the only significant difference between patients in a VS and controls was an impairment of backward connectivity from frontal to temporal cortices. This result emphasizes the importance of top-down projections in recurrent brain processing that involves high-order associative cortices for conscious perception (40).
Data from the literature show that patient-specific stimuli (well-known images or pictures of the patient, familiar sounds or the voice of a family member) are able to activate specific cerebral cortical systems (the primary sensory circuits, the attention and motor imagination circuits) (Table II).
Late-latency cognitive ERPs have a higher positive predictive value for conscious recovery that, however, ranges widely (from 30 to 100%).

Transcranial magnetic stimulation

Transcranial magnetic stimulation, on account of its high temporal resolution, has been proposed as an additional functional imaging technique for the study of cognitive function. To date, few studies have used this technique in the assessment of VS and MCS patients. Moosavi et al. applied TMS to the hand and leg motor area in 19 patients a few months after severe anoxic or traumatic brain injury. Eleven patients were in a VS, while eight were in MCS. The VS patient group differed from the MCS patient group, showing a higher threshold, longer duration, and greater irregularity in the form of the re-

Table II - Evoked potential studies in patients with DOC.

Authors (ref. no.)	Summary
Hansotia, 1985 (32)	BAEPs were normal in 81 comatose patients (8 of these patients entered a PVS, of whom 4 died and 4 survived).
Li et al., 1993 (33)	BAEP waveforms can also be attenuated, delayed or absent, depending on the location and degree of brainstem injury, in five patients in PVS.
Isono et al., 2002 (22)	The authors reported, in 12 PVS patients, abnormalities in BAEP waveforms III and V, corresponding to the superior olivary complex and lateral lemniscus-inferior colliculus auditory responses. SEPs have been found to be abnormal in PVS, showing delay and attenuation, or even absence of the N20 cortical response to median nerve stimulation.
Vanhaudenhuyse et al., 2008 (35)	The authors reviewed Medline from January 1, 1980 to June 1, 2007 and selected all studies investigating cognitive ERPs in comatose and post-comatose patients, and which provided details of prognostic values.
Perrin et al., 2006 (36)	The authors studied auditory EPs to the patient's own name in 15 brain-damaged patients. The results suggest that partially preserved semantic processing can be observed in non-communicative brain-damaged patients, notably for the detection of salient stimuli, such as the subject's own name.
Schnakers et al., 2008 (37)	The authors presented patients (8 VS and 14 MCS) with sequences of names containing the patient's own name or other names, in both passive and active conditions. The results suggest that active an evoked-related potentials paradigms may allow detection of voluntary brain function in DOC patients.
Cavinato et al., 2009 (38)	34 patients in post-traumatic VS showed an increased P300 wave amplitude when more salient stimuli were used, such as the patient's own first name instead of visual or auditory deviants.
Cavinato et al., 2011 (39)	The authors studied 11 patients in VS and 6 in MCS. In 6 out of 11 patients fulfilling the behavioral criteria for VS a reliable P300 component could be observed in both conditions. 38% of patients in VS were found to generate a P300 wave. Compared with the VS patients, those with MCS exhibited significantly longer P300 latencies for the "subject's own name" and the "other first name" paradigms.
Boly et al., 2011 (40)	The authors measured effective connectivity during a mismatch negativity paradigm and emphasized the importance of top-down projections in recurrent brain processing that involves high-order associative cortices for conscious perception.

Abbreviations: BAEPs=brainstem auditory evoked potentials; PVS=persistent vegetative state; ERPs=event-related potentials; EPs=evoked potentials; SEPs=somatosensory evoked potentials; VS=vegetative state; MCS=minimally conscious state; DOC=disorders of consciousness.

sponse, while the threshold, form, and latency of motor evoked potentials (MEPs) in the MCS group were similar to those recorded in healthy control subjects (41). In another study, TMS was used to monitor recovery. The authors examined MEPs from upper and lower limbs in 27 patients in the subacute period and then at six and 12 months post-ictus. During the study period, the authors observed an overall trend toward an increase of amplitude and a decrease of latency of MEPs. MEPs from upper and lower limbs progressively normalized in all patients and, at one year after trauma, only 12% of patients had mild abnormalities in MEP responses (42). Nevertheless, a concomitant increase in MEP amplitude and clinical recovery has been observed in a single case study. Crossley investigated the relationship between cognitive and behavioral ability and TMS-elicited MEPs. In their patient, clinical and TMS examinations were performed at four weeks post-injury, when the patient showed signs of arousal and alertness, and again at 12 months, when she was reported to be fully awake and conscious. TMS conducted at 12 months showed an increase in MEP amplitude in comparison to the recording at four weeks, consistent with the clinical improvement (43).

Despite the absence of voluntary movements, TMS elicited MEP responses in the majority of severely brain-damaged patients, and a trend toward an increase of amplitude and decrease of latency of MEPs could be observed during the recovery period (Table III, over).

The measurement of effective cortical connectivity may make it possible to differentiate between MCS and VS. Using TMS/high-density EEG, Rosanova et al. (44) demonstrated, in VS patients, a breakdown of effective cortical connectivity similar to that seen during NREM sleep in healthy subjects. By contrast, MCS patients showed a widespread TMS-evoked response of the kind recorded in locked-in, conscious patients. Interestingly, longitudinal data in patients who gradually recovered consciousness showed that this change in the breakdown of effective cortical connectivity preceded significant modification of the spontaneous EEG. Moreover, this clear-cut modification of effective connectivity was detected before the patient recovered the capacity for functional communication.

Table III - Transcranial magnetic stimulation studies in patients with disorders of consciousness.

Authors (ref. no.)	Summary
Moosavi et al., 1999 (41)	TMS was applied to the hand and leg motor area in 19 post-coma patients with severe brain injury following anoxia or physical trauma (11 patients in VS and 8 in MCS). The VS group differed from the MCS group, showing a higher threshold, longer duration, and greater irregularity in the form of the response, while the threshold, form, and latency of MEPs in the MCS group were similar to those recorded in healthy control subjects.
Mazzini et al., 1999 (42)	The authors examined MEPs from upper and lower limbs in 27 patients with severe traumatic brain injury in the subacute period and then at 6 and 12 months post-ictus. MEPs from the upper and lower limbs progressively normalized in all the patients, and at one year after trauma, only 12% of patients had mild abnormalities in MEP responses.
Crossley et al., 2005 (43)	TMS conducted at 12 months after traumatic brain injury, in an 80-year-old patient, showed an increase in MEP amplitude in comparison to the recording at 4 weeks, consistent with the clinical improvement.
Rosanova et al., 2012 (44)	In 7 VS patients, TMS triggered a simple, local response indicating a breakdown of effective connectivity, similar to that previously observed in unconscious sleeping or anesthetized subjects. In contrast, in 8 MCS patients, TMS invariably triggered complex activations that sequentially involved distant cortical areas ipsi- and contralateral to the site of stimulation.

Abbreviations: TMS=transcranial magnetic stimulation; VS=vegetative state; MCS=minimally conscious state; MEPs=motor evoked potentials.

Thus, TMS/high-density EEG might be used as an indicator of consciousness independently of the patient's ability to communicate, and may serve as a diagnostic tool for the differentiation between VS and MCS in the individual patient (44).

Concluding remarks

Electroencephalography and EPs are considered the most reliable neurophysiological methods for outcome evaluation and differential diagnosis. However, neurophysiological studies provide useful and reliable indices for the assessment and monitoring of patients with severe brain injury, and quantitative analysis of neurophysiological signals can provide useful information to supplement that provided by conventional EEG and EP parameters.

Furthermore, in conjunction with analyses of electrophysiological studies, more recently developed imaging techniques, such as fMRI, can provide additional information regarding preservation and recovery of brain activity and intracerebral networks, both at rest and in response to stimulation.

In recent years, there has been growing interest in the use of neurophysiological investigations (EEG and EPs) in association with fMRI: combination with this neuroimaging technique makes it possible to study different components of the brain's activity (e.g., neurovascular coupling, electromagnetic activity) with high temporal and spatial resolution (45).

All of these neurophysiological techniques will enhance our understanding not only of the pathophysiology of the entire spectrum of severe brain injuries, but also of the mechanisms supporting or limiting further recovery.

Clinical neurophysiology provides functional evaluation of the nervous system. Therefore, its domain is similar to that of clinical examination and complementary to that of imaging techniques (CT, MRI).

The well-known advantages of EEG recording include its high temporal resolution and its non-invasive nature, along with its portability and low cost. EEG is also useful in excluding non-convulsive status epilepticus and in providing a rough but objective idea of the degree of cortical and subcortical dysfunction in DOC (46). Its main limitation is its lack of specificity (e.g., diffuse slowing of background rhythms is seen in various encephalopathies regardless of etiology). Another limitation of EEG is its low spatial resolution. With the possible exception of high-density EEG, source reconstruction is possible but it never equals the spatial resolution of fMRI and the technique remains more difficult for the evaluation of deep brain structures.

However, the neurophysiological approach offers two main advantages over clinical examination: it can be employed in sedated and/or curarized patients, and it provides quantitative data for comparison with follow-up studies.

The prognostic accuracy of neurophysiological tests is estimated by calculating the relationship between presence or absence of an evoked potential and patient outcome. The positive predictive value is the percentage of patients who will awaken from a VS when a specific potential is present, while the negative predictive value is the percentage of patients who will not recover from a VS when a specific potential is absent.

Clinical neurophysiology procedures are useful as they are easily performed, non-invasive and repeatable at the bedside. These methods provide irreplaceable data about the extent and evolution of neuronal dysfunctions and their evolution, and also information useful for clinical differentiation and outcome evaluation in DOC patients.

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