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Standard EEG in diagnostic process of prolonged disorders of consciousness

Anna Estraneo [a,*], Vincenzo Loreto [a], Ivan Guarino [a], Virginia Boemia [a], Giuseppe Paone [a], Pasquale Moretta [a], Luigi Trojano [b]

[a] Salvatore Maugeri Foundation, IRCCS, Scientific Institute of Telese Terme (BN), Via Bagni Vecchi 1, 82037 Telese Terme (BN), Italy
[b] Neuropsychology Lab., Dept. of Psychology, Second University of Naples, Viale Ellittico 31, 81100 Caserta, Italy

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HIGHLIGHTS

- Standard EEG can complement behavioral diagnosis of disorders of consciousness.
- EEG activity and reactivity differ in vegetative and minimally conscious state.
- In anoxic patients EEG features are more severely impaired and less discriminative.

ABSTRACT

Objective: This cross-sectional study assessed the ability of standard EEG in distinguishing vegetative state (VS) from minimally conscious state plus (MCS+) or MCS minus (MCS−), and to correlate EEG features with aetiology and level of responsiveness assessed by Coma Recovery Scale-Revised (CRS-R).
Methods: We analyzed background EEG activity and EEG reactivity to eye opening and closing and to tactile, acoustic, nociceptive stimuli and Intermittent Photic Stimulation (IPS) in 73 inpatients (VS = 37, MCS− = 11, MCS+ = 25), with traumatic (n = 21), vascular (n = 25) or anoxic (n = 27) aetiology.
Results: All patients, but one, showed abnormal background activity. EEG abnormalities were more severe in VS than in MCS+ or MCS−, and in anoxic than other aetiologies. MCS+ patients with normal or Mildly Abnormal background activity showed higher scores on CRS-R than patients with moderate to severe EEG abnormalities. Reactivity to IPS, and acoustic stimuli was significantly more frequent in MCS+ and MCS− than in VS patients.
Conclusions: EEG features differ between VS and MCS− or MCS+ patients and can provide evidence of relative sparing of thalamocortical connections in MCS+ patients. In anoxic patients EEG organization is more severely impaired and provides less discriminative diagnostic information.
Significance: Conventional EEG can help clinicians to disentangle VS from MCS patients.

1. Introduction

After a comatose state, severely brain-injured patients might remain in a vegetative state (VS; Multi-Society Task Force on PVS, 1994), and eventually evolve in a minimally conscious state (MCS; Giacino et al., 2002). On the basis of the complexity of patients' behaviors, a sub categorization of MCS patients into "MCS minus" (MCS−) and "MCS plus" (MCS+) has been recently proposed (Bruno et al., 2011). The distinction among the above diagnostic groups can be very difficult, because of fluctuations of clinical conditions and presence of severe sensori-motor deficits (Majerus et al., 2005). However, disentangling VS from low- and high-level MCS patients (i.e. detecting conscious behavior) is critical for definition of treatment and prognosis (Bruno et al., 2012; Giacino et al., 2012; Hirschberg and Giacino, 2011; Luauté et al., 2010).

Technologically advanced tools have been developed to detect not clinically recognizable responses (Cruse et al., 2012;

Abbreviations: DOC, disorder of consciousness; VS, vegetative state; MCS+, minimally conscious state plus; MCS−, minimally conscious state minus; CRS-R, Coma Recovery Scale-Revised; IPS, Intermittent Photic Stimulation; APG, anterior–posterior gradient; MiA, Mildly Abnormal; MoA, Moderately Abnormal; DS, Diffuse Slowing; LV, Low Voltage; CI, confidence intervals.

* Corresponding author at: Research Laboratory and Neurehabilitation Unit for Disorder of Consciousness, Salvatore Maugeri Foundation, IRCCS, Via Bagni Vecchi 1, 82037 Telese Terme (BN), Italy. Tel.: +39 0824 909521.
E-mail address: anna.estraneo@fsm.it (A. Estraneo).

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Demertzi et al., 2015; Fernández-Espejo et al., 2011; Perrin et al., 2006; Yu et al., 2013), or to complement behavioral assessment (Fernández-Espejo et al., 2015; Sitt et al., 2014; Trojano et al., 2012, 2013), but are not suitable for large-scale studies, since they are available only in specialized settings and are often expensive (Bekinschtein et al., 2011; Estraneo et al., 2013). Standard clinical EEG, instead, is widely used, easy to repeat and low-cost. Yet, visual analysis of EEG allows investigating integrity of thalamocortical connections, which are related to wakefulness and consciousness (Klimesch et al., 1998, Klimesch, 1999; Schiff, 2010). Nonetheless, to date the majority of studies did not focus on the diagnostic value of EEG in disorders of consciousness (DOC), but rather on its prognostic value (Bagnato et al., 2010, 2015; Boccagni et al., 2011; Logi et al., 2011). One recent study reported normal or near normal EEG background activity in MCS patients with fMRI signs of "covert" cognition not clinically recognized (Forgacs et al., 2014).

To date no study specifically estimated the value of visual analysis of standard EEG in disentangling VS from MCS+ or MCS− patients, and the possible differences in patients with traumatic, anoxic or vascular aetiology. We aimed to search for the possible association of EEG organization and reactivity with clinical diagnosis and aetiology in a cohort of DOC patients in relatively stabilized clinical conditions.

2. Methods

2.1. Subjects

We screened for the present cohort study all patients consecutively admitted to the Neurorehabilitation Unit for DOC patients, Salvatore Maugeri Foundation (Telese, Italy), from January 2012 to January 2015. Inclusion criteria for the present study were: diagnosis of VS or MCS on repeated clinical evaluation (see below); severe traumatic, anoxic or vascular brain injury; time from onset $\geqslant$3 months, age $\geqslant$18 years. We excluded patients with mixed aetiology (e.g., both traumatic and anoxic brain injury), with premorbid history of psychiatric or neurodegenerative diseases, with severe medical conditions potentially influencing EEG (e.g., hepatic insufficiency, chronic renal failure), or with sub continuous or abundant focal or generalized and rhythmic epileptiform discharges on EEG recordings. Patients were also excluded if their diagnosis had changed in the week before the examination.

The study was approved by the local Ethics Committee, and performed according to the ethical standards laid down in the 1964 Helsinki Declaration and its later amendments.

Written informed consent was obtained from the legal guardians of the patients.

2.2. Clinical evaluation

All patients underwent repeated evaluations to establish diagnosis of VS or MCS according to standard diagnostic criteria (Giacino et al., 2002; Multi-Society Task Force on PVS, 1994). Before and after EEG recordings, skilled hospital staff evaluated the level of consciousness on the Coma Recovery Scale-Revised (CRS-R; Kalmar and Giacino, 2005), including six subscales to assess auditory, visual, motor, oromotor/verbal, communication and arousal functions. The presence of intentional (non-reflexive) responses on a single subscale can suffice to identify MCS from VS patients. We also applied the recent clinical criteria (Bruno et al., 2011) to sub-categorize MCS into MCS− patients (i.e., patients with low-level intentional behavior, such as visual pursuit or localization of noxious stimulation) and MCS+ patients (i.e., patients with high-level behavioral interactions, such as command following). In the present study we used the Italian validated version of CRS-R (Estraneo et al., 2015).

2.3. EEG acquisition

We used a portable EEG device (Nicolet video-EEG system) to record a 35-min (at least) standard EEG from 19 electrodes placed on the scalp according to the international 10–20 system (O1, O2, P3, P4, Pz, T5, T6, C3, C4, Cz, T3, T4, F3, F4, Fz, F7, F8, Fp1, and Fp2). Standard procedure of eye-closed recording during a waking resting state was used with filter settings 1–70 Hz, and notch filter on. Synchronous video recordings were acquired to remove artefacts due to subjects' movements. For the analysis of predominant activity we forced eyes closing by cotton wool applied by paper patch in condition of patients awake (spontaneous eye opening) and at the end of EEG recording we ensured that patients had their eyes spontaneously open (after removal of paper patch). In case of appearance of drowsiness or clear sleep activity on EEG (e.g., K complexes, sleep spindles), EEG recording was stopped and CRS-R vigilance protocol was administered to ensure patients' vigilance. The EEG was recorded at patients' bed in the morning after customary nursing procedures and after a 15-h washout from myorelaxants and sedative drugs (e.g., benzodiazepines, neuroleptics), in order to ensure patients' best vigilance state. Long-term antiepileptic treatment was not discontinued.

EEG acquisition was repeated after two days, and the best recording was taken into account for analysis in order to reduce influence of possible arousal fluctuations. In the presence of artefacts in more than 50% of EEG recording time, EEG acquisition was repeated after one week. When no EEG of sufficient quality could be obtained, the patient was excluded from the study.

In order to analyse EEG reactivity, five kinds of stimuli were randomly administered during EEG recording: (1) eye opening and (forced) eye closing; (2) tactile stimuli (wiping on the back of right and left forearm with cotton wool); (3) noxious stimulation (pressing fingernail beds on each hand); (4) acoustic stimulation (hand clapping); (5) Intermittent Photic Stimulation (IPS) by 1, 3, 6, 12 and 20 Hz flashes in 5-s trains presented through closed eyelids with 5-s interval between two trains. Each stimulus was presented 3 times, for a total of 15 stimuli in each EEG recording. Inter-stimulus interval between two kinds of stimulation lasted about 1 min; resting periods of about 3 min were given before and after the stimulation sequence, and after having administered about half sequence.

2.4. Definition of predominant background EEG activity

Two skilled clinical neurophysiologists (blinded to patients' aetiology, clinical diagnosis and CRS-R score) reviewed EEG recordings using a conventional 16 longitudinal bipolar channels (double banana montage) and 3 midline channels. The predominant posterior EEG background activity was analyzed on occipital bipolar channels (O1–O2), and defined as frequency band of alpha, theta, or delta rhythms recorded in almost 50% of EEG recording at rest with eye closed, according to traditional neurophysiological criteria for EEG interpretation (Hirsch et al., 2013). In case of Diffuse Slowing or Low-Voltage patterns, we considered EEG predominant rhythms recorded over most of the brain areas. We classified predominant EEG background activity adapting recent classification criteria proposed for prolonged DOC patients (Forgacs et al., 2014). With respect to the original set of criteria (Forgacs et al., 2014), the present classification also took into account percentage of alpha rhythm and EEG amplitude, thus distinguishing the following five categories, instead of the four proposed by Forgacs and colleagues: (1) normal EEG activity, in presence of predominant posterior alpha rhythm and of the anterior–posterior gradient