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Altered resting state effective connectivity in long-standing vegetative state patients: An EEG study

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HIGHLIGHTS

- Effective EEG connectivity was evaluated, using PDC, in long standing vegetative state patients.
- Compared to controls, chronic VS patients showed a widespread decrease in delta band connectivity.
- VS patients showed a significant increase in central and posterior alpha connectivity.
- The cortical de-afferentation in chronic VS patients leads to aberrant connectivity state.

ABSTRACT

Objective: Recent evidence mainly based on hemodynamic measures suggests that the impairment of functional connections between different brain areas may help to clarify the neuronal dysfunction occurring in patients with disorders of consciousness (DOC).

Objective: The aim of this study was to evaluate effective EEG connectivity in a cohort of 18 patients in a chronic vegetative state (VS) observed years after the occurrence of hypoxic (eight) and traumatic or hemorrhagic brain insult.

Methods: we analysed the EEG signals recorded under resting conditions using a frequency domain linear index of connectivity (partial directed coherence: PDC) estimated from a multivariate autoregressive model. The results were compared with those obtained in ten healthy controls.

Results: Our findings indicated significant connectivity changes in EEG activities in delta and alpha bands. The VS patients showed a significant and widespread decrease in delta band connectivity, whereas the alpha activity was hyper-connected in the central and posterior cortical regions.

Conclusion: These changes suggest the occurrence of severe circuitry derangements probably due to the loose control of the subcortical connections. The alpha hyper-synchronisation may be due to simplified networks mainly involving the short-range connections between intrinsically oscillatory cortical neurons that generate aberrant EEG alpha sources. This increased connectivity may be interpreted as a reduction in information capacity, implying an increasing prevalence of stereotypic activity patterns.

Significance: Our observations suggest a remarkable rearrangement of connectivity in patients with long-standing VS. We hypothesize that in persistent VS, after a first period characterized by a breakdown of cortical connectivity, neurodegenerative processes, largely independent from the type of initial insult, lead to cortex de-afferentation and to a severe reduction of possible cortical activity patterns and states.

1. Introduction

Brain injuries due to anoxic, hemorrhagic or traumatic events often give rise to severe disorders of consciousness (DOC). Interest in DOC has increased over recent year and this has led to an

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Abbreviations: VS, vegetative state; DOC, disorders of consciousness; ABI, anoxic brain injury; PDC, partial directed coherence; MVAR, multivariate autoregressive.

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increase in the “functional” evaluation of patients, mainly using fMRI-based techniques and to a lesser extent neurophysiological parameters. This is certainly partly because technological improvements now allow the better assessment of brain functions, but it is also due to the greater attention being given to the increasing number of patients who survive extreme brain damage as a result of improved emergency medicine and resuscitation techniques (Laureys and Boly, 2008). Unfortunately, a considerable proportion of such survivors enter a persistent vegetative state (VS) (Jennett and Plum, 1972), which is defined as a condition of wakefulness insofar as patients spontaneously open their eyes, but unawareness as their responses to the environment are inconsistent or absent.

Functional studies indicate that some severely impaired patients may retain some awareness and cognition (Boly 2011; Boly et al., 2011; Kotchoubey et al., 2005), and have shown the capability of fMRI-based passive paradigms (Monti et al., 2010) in revealing a decrease in large-scale cerebral connectivity related to the level of consciousness impairment (Soddu et al., 2012; Vanhaudenhuyse et al., 2010).

The spectral properties of EEG signals have been widely used to assess brain insult severity in analytical methods (Wu et al., 2011a; Gosseries et al., 2011). In comparison with metabolic signals, EEG and magnetoencephalography (MEG) have the advantage of better temporal resolution; moreover, they allow the assessment of the connectivity patterns in different frequency bands that have different functional significance.

Functional connectivity is a suitable means of evaluating network characteristics based on the statistical interdependence of physiological time series recorded in different brain areas (Aertsen et al., 1989; Friston et al., 2001). Previous studies have revealed alterations in various central nervous system disorders including cognitive dysfunction (Stam et al., 2009) and traumatic brain injury (Castellanos et al., 2010). Differently from functional connectivity, which is a symmetric measure of coupling between two signals, effective connectivity allows the evaluation of the influence that one neural system has over another (causal effects) and makes it possible to determine the direction of the information flow within a brain network.

The aim of this study was to evaluate effective connectivity in different EEG frequency bands in a population of chronic VS patients using partial directed coherence (PDC), a frequency-domain measure derived from the multivariate autoregressive (MVAR) modelling of multichannel EEG signals (Baccalà and Sameshima, 2001).

2. Methods

2.1. Patients

The study involved 18 brain-injured patients with a clinical diagnosis of persistent VS: 9 had experienced a global post-hypoxic brain insult (the ABI group), and nine a hemorrhagic or traumatic insult (the non-ABI group) insult. Table 1 shows their age, the time from the brain insult, the damage revealed by means of MRI, and the mean scores of the Revised Coma Recovery Scale (Giacino et al., 2004) and the Coma Near Coma Scale (Rappaport et al., 1992), which were repeatedly administered by trained neuropsychologists and neurologists. The patients were not sedated, but 13 were receiving low doses of various anti-epileptic drugs. The control group consisted of 10 healthy adults matched for sex and approximately for age (37.3 ± 10.9 years) to the groups of patients.

The study was approved by the Ethics Committee of Carlo Besta Neurological Institute Milan, Italy, and written informed consent was obtained from the controls and the patients’ legal representatives.

2.2. EEG recordings

EEG and polygraphic channels (EOG, ECG, sub-mental EMG) were recorded in a dimly lit room using Ag/AgCl surface electrodes (impedance $<5\ \text{k}\Omega$) placed in accordance with the 10–20 International System, and acquired at a sampling rate of 256 Hz (Micromed SpA, Mogliano Veneto, Treviso, Italy). The analysis was based on artifact-free EEG representative epochs recorded immediately after the end of arousal stimuli, when the patients had closed their eyes but there were no changes in the EEG or polygraphic parameters that suggested “sleep” behaviour. The EEG traces with significant epileptiform activities (e.g. periodic lateralised epileptiform discharges) were excluded from the analysis.

2.3. EEG power spectrum density

To compute the power spectrum density, the selected EEG epochs were reformatted against the linked ear-lobe reference, and analyzed using an autoregressive (AR) parametric model. The model order was selected using the Akaike criterion (AIC) as a guideline (Akaike, 1974), and the goodness of the identification was verified by checking the whiteness of the model’s residual noise using a ‘portmanteau’ chi-squared test (Box and Jenkins, 1970). One minute of EEG activity was analysed by dividing it into 30 non-overlapping 2-s segments. Each spectrum was divided into spectral components using the spectral decomposition method based on residual integration (Zetterberg, 1969; Johnsen and Andersen, 1978), and the frequency and power of the associated peaks were evaluated for each component. Relative power was evaluated in the delta (1–4 Hz), theta (4–8 Hz), alpha (8–13 Hz) and beta bands (13–30 Hz), and averaged among the segments. The gamma band was excluded from the analysis because of possible contamination with high-frequency muscle activity.

2.4. EEG connectivity

The connectivity pattern was studied using the same EEG epochs as used for the spectral analysis. Before computing PDC, the EEG data were normalised by subtracting the mean value and dividing the result by the variance. All of the 19 EEG derivations were simultaneously used as inputs for the multivariate autoregressive (MVAR) model. Once the MVAR coefficients had been adequately estimated, the PDC spectra (Baccalà and Sameshima, 2001) were estimated (see Varotto et al., 2012, for further details about the method). The statistical significance of the non-zero PDC values at each frequency was estimated using a bootstrap approach (Zoubir and Iskander, 2004) based on phase randomisation and the Theiler algorithm (Theiler et al., 1992). All of the data were pre-processed and analysed using a custom-written toolbox in Matlab (Mathworks Inc., Natick, MA, USA), which also contained modified functions from the Biosig toolbox (Schlögl et al., 2007).

PDC amplitude and degree were calculated for each subject and frequency band. These measures, calculating respectively the strength and the number of connections from or toward all of the other nodes, constitute the most common measures of centrality (Boccaletti et al., 2006). In order to evaluate local and long-distance connectivity patterns, the electrodes were grouped into five regions of interest (ROIs: frontal F3, F4, Fz, Fp1, and Fp2; central C3, C4 and Cz; posterior P3, P4, Pz, O1 and O2, right temporal T4, T6 and F8; left temporal T5, T3, F7), and the degree and mean PDC amplitude within each ROI were averaged. Finally, in order to take into account the different number of nodes in each region, the average degree value was normalised by dividing it by the number of possible connections between each pair of regions in order to consider the density values of the nodes.