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The value of spontaneous EEG oscillations in distinguishing patients in vegetative and minimally conscious states

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Abstract

Objective: The value of spontaneous EEG oscillations in distinguishing patients in vegetative and minimally conscious states was studied.

Methods: We quantified dynamic repertoire of EEG oscillations in resting condition with closed eyes in patients in vegetative and minimally conscious states (VS and MCS). The exact composition of EEG oscillations was assessed by the probability-classification analysis of short-term EEG spectral patterns.

Results: The probability of delta, theta and slow-alpha oscillations occurrence was smaller for patients in MCS than for VS. Additionally, only patients in MCS demonstrated fast-alpha oscillation occurrence. Depending on the type and composition of EEG oscillations, the probability of their occurrence was either aetiology dependent or independent. The probability of EEG oscillations occurrence differentiated brain injuries with different aetiologies.

Conclusions: Spontaneous EEG oscillations have a potential value in distinguishing patients in VS and MCS.

Significance: This work may have implications for clinical care, rehabilitative programs and medical–legal decisions in patients with impaired consciousness states following coma due to acute brain injuries.

Keywords: electroencephalogram (EEG); disorder of consciousness; EEG oscillations; patients in vegetative and minimally conscious states (VS, MCS).

1. Introduction

Severe brain injuries constitute an epidemic public health problem affecting, for example, more than 100000 Americans annually (Winslade, 1998; NIH Consensus Development Panel, 1999). Severe brain injuries are caused mainly by either trauma, or by vascular or anoxic events and lead to disorders of consciousness such as vegetative state (VS) or minimally conscious state (MCS) following coma. Vegetative state (VS) is “a clinical condition of unawareness of self and environment in which the patient breathes spontaneously, has a stable circulation, and shows cycles of eye closure and opening which may simulate sleep and waking” (Monti et al., 2010). The minimally conscious state (MCS) is “a condition of severely altered consciousness in which minimal but definite behavioural evidence of self or environmental awareness is demonstrated. In MCS, cognitively mediated behaviour occurs inconsistently, but is reproducible or sustained long enough to be differentiated from reflexive behaviour” (Giacino et al., 2002).

Studies indicated that 10-17 years ago the MCS caseload in the USA was estimated at 112,000–280,000 (Strauss et al., 2000) and a VS caseload was estimated at 10,000–25,000 adults and 4,000–10,000 children (The Multi-Society Task Force on PVS, 1994). Thanks to advances in critical care, VS and MCS incidence and prevalence are progressively increasing (Beaumont and Kenealy, 2005).

In spite of significant progress in Neuroimaging and the introduction of clear-cut diagnostic criteria, patients with disorders of consciousness still represent an important clinical problem in terms of diagnosis, prognosis, treatment, everyday management and end-of-life decision-making. Indeed, the rate of misdiagnosis of VS/MCS has not substantially changed in the past 15 years (Schnakers et al., 2009).

Misdiagnoses of VS and MCS are common and have been shown to be as high as 37–43% (Tresch et al., 1991; Childs et al., 1993; Andrews et al., 1996; Schnakers et al., 2006). Such misdiagnoses may have a profound effect on end-of-life decision-making (Andrews et al., 1996; Andrews, 2004; Gill-Thwaites, 2006). Today, almost half of all deaths in critical care units follow a decision to withhold or withdraw therapy (Smedira et al., 1990).

Misdiagnosis of VS and MCS are due to the fact that the diagnosis of VS and MCS patients is based on clinical observation of subjectively interpreted behavioural responses mostly, while conscious experience often occurs without behavioural signs. Therefore, determining whether or not non-communicative or minimally communicative patients are phenomenally conscious is still a major clinical and ethical challenge. For this reason, additional objective measurement tools are needed for achieving more accurate diagnoses.

Electrophysiological (EEG) measures which permit bedside assessment could be particularly useful since EEG directly and objectively records spontaneous brain activity without requiring any behavioural response by the patient. It has been proposed that EEG oscillations act as communication networks with functional relationships to the integrative brain functions (Basar et al., 2001a). It is assumed that EEG oscillations are of fundamental importance for mediating and distributing “higher-level” processes in the human brain (Klimesch 1999; Basar et al., 2001b). Moreover it was repeatedly demonstrated that changes in EEG oscillations are associated with cognitive deficits, brain and mind pathologies (for the review and discussion see Basar and Güntekin, 2008; Basar 2010). Although EEG is a routine examination in patients with disorders of consciousness, there is a considerable lack of studies which investigate explicitly the value of EEG oscillations in distinguishing MCS and VS patients. To our best knowledge there is only one such study which used EEG bispectral index (BIS): see Schnakers et al. (2008). Even though, BIS seem to correlate empirically with consciousness (Myles et al., 2004) it has no clear theoretical foundation (Massimini et al., 2009).

Earlier Fingelkurts et al. (submitted) using automatic advanced analysis of EEG demonstrated that particular types of EEG oscillatory phenomena were associated with awareness (the probability of the occurrence of some EEG oscillations was in the order of $NORM > MCS > VS$) or unawareness (the probability of the occurrence of other EEG oscillations was in the order of $NORM < MCS < VS$). This study was theoretically motivated and it provided an empirical support that spontaneous EEG oscillatory states have a potential value in revealing neural constituents of consciousness. Hence, it is reasonable to assume that spontaneous EEG oscillations can be useful in distinguishing patients with disorders of consciousness with different degree of expression of consciousness.

Therefore, the aim of the present study was, to investigate the capacity of spontaneous EEG oscillations to distinguish VS and MCS patients considering different aetiologies of brain damage. In this study we will consider only those differences in EEG oscillations between VS and MCS patients which demonstrated association with awareness/unawareness in earlier study (Fingelkurts et al., submitted).

2. Methods

2.1. Subjects

The study was performed on 21 non- or minimally communicative patients with severe brain injuries suffering from different consciousness disorders (Table 1), admitted to the Neurorehabilitation Unit of Fondazione Istituto “San Raffaele - G. Giglio” to carry out an intensive neurorehabilitation program.

Table 1. Basic demographic and clinical characteristics of the patients

EEG ID	Age	Gender	Type of consciousness disorder	Aetiology	CT/MRI findings (in the acute phase)	Time (in days) between acute event and EEG	Drugs	LCF at the EEG recording day
1	38	M	MCS	Trauma	subdural and epidural hematoma in the right hemisphere; right fronto-temporal intraparenchymal hemorrhage; right fronto-temporal cortical contusions	36	None	3
5	19	F	MCS	Trauma	subdural hematoma in the right hemisphere; bilateral frontal cortical contusions	72	None	3
9	64	F	MCS	Trauma	cortical contusions in the temporal lobes and in the right parietal lobe	58	VPA 1500	3
11	61	F	MCS	Vascular	intraparenchymal hemorrhage in the right parietal lobe	76	None	3
13	29	F	MCS	Vascular	fronto-temporo-parietal intraparenchymal hemorrhage in the right hemisphere	44	VPA 600	3
14	60	F	MCS	Vascular	subdural hematoma in the left hemisphere	66	CBZ 800, PB 100	3
16	70	M	MCS	Vascular	left temporo-parietal ischemia	44	None	3
Mean±st.d Summary	48.7±19.8			TBI: 43%, NTBI: 57%	Left: 29%, Right: 71%	56.6±14.4	N: 57%, D: 43%	3±0.0
2	36	M	VS	Trauma	left parieto-temporal intraparenchymal hemorrhage; several intraparenchymal micro-hemorrhages	36	PB 100	2
3	35	M	VS	Trauma	diffuse axonal injury; right temporal cortical contusion	42	None	1
4	28	M	VS	Trauma	subdural and epidural hematoma in the right hemisphere	46	None	2
6	55	M	VS	Trauma	cortical contusions in the frontal lobes and in the right temporal lobe; subdural hematoma; diffuse axonal injury	37	None	2
7	14	M	VS	Trauma	subdural hematoma in the left hemisphere; widespread intraparenchymal microhemorrhages	89	PB 100	2
8	19	M	VS	Trauma	intraparenchymal microhemorrhages in the right frontal, temporal and parietal lobes; diffuse axonal injury	14	None	2
10	35	M	VS	Vascular	left subarachnoid hemorrhage and left temporo-parieto-occipital ischemia (due to vasospasm)	32	None	2
12	41	M	VS	Vascular	fronto-temporo-parietal intraparenchymal hemorrhage in the left hemisphere	44	None	1
15	79	F	VS	Vascular	intraparenchymal hemorrhage in left parieto-occipital region	77	LTG 200, PB 100	2
17	50	M	VS	Vascular	hemorrhage in the right putamen	79	None	2
18	66	M	VS	Vascular	right fronto-temporo-parietal intraparenchymal and subarachnoid hemorrhage	72	PB 100	1
19	57	M	VS	Vascular	brainstem hemorrhage	87	PB 100	2
20	16	M	VS	Anoxia		92	None	2
21	68	M	VS	Anoxia		63	None	1
Mean±st.d Summary	42.9±20			TBI: 43%, NTBI: 57%	Left: 42%, Right: 50%	57.8±25	N: 64%, D: 36%	1.7±0.5

M - male, F - female, MCS - minimally conscious state, VS - vegetative state, TBI - traumatic brain injury aetiology, NTBI - non-traumatic brain injury aetiology, N - no drug, D - drugs, LCF - level of cognitive functioning scale, VPA - valproic acid, CBZ - carbamazepine, PB - phenobarbital, LTG - lamotrigine

On admission all patients underwent a thorough and comprehensive clinical neurological examination. The diagnosis of VS and MCS was made according to currently accepted diagnostic criteria (ANA Committee on Ethical Affairs, 1993; The Multi-Society Task Force on PVS, 1994; Royal College of Physicians, 2003). Additionally, the Levels of Cognitive Functioning (LCF) score (Gouvier et al., 1987) was assessed on the day of admission and three days later when the EEG was recorded. We chose to use the LCF scale instead of the Glasgow Outcome Scale (GOS) (Jennett and Bond, 1975), the Glasgow Coma Scale (Jennett et al., 1981) or the JFK Coma Recovery Scale (Giacino et al., 2004) because LCF evaluates not only behavioural patterns but also cognitive functions (which are closely related to consciousness then behavioural patterns), and LCF has been found better related with the presence of EEG abnormalities in patients with disorders of

consciousness in previous studies (Bagnato et al., 2010; Boccagni et al., submitted). The LCF scale has different grades ranging from 1 to 8 (1 – patient does not respond to external stimuli and/or command; 8 – patient is self-oriented and responds to the environment but abstract reasoning abilities decrease relative to pre-morbid levels). LCF score of 1-2 is indicative for VS and LCF score of 3-4 is indicative for MCS patients (Gouvier et al., 1987).

Based on the LCF score all patients were divided into two groups: 14 of the patients (mean age 42.9 ± 20 years) were classified as being in a vegetative state (VS) (LCF: 1–2) and the remaining 7 patients (mean age 48.7 ± 19.8 years) were classified as being in a minimally conscious state (MCS) (LCF: 3). In order to reduce the variability of clinical evaluation, LCF scores were assigned to all patients only if they were unchanged between the day of admission and the day of the EEG registration; otherwise, patients were excluded from the study. Other exclusion criteria were (a) any acute comorbidity or unstable vital signs; (b) obvious communicating or obstructive hydrocephalus; (c) a history of neurological disease before admission; and (d) severe spasticity (causing constant EMG artefacts). Inclusion criteria included (a) confirmation of diagnosis of VS or MCS according to the clinical definitions (ANA Committee on Ethical Affairs, 1993; The Multi-Society Task Force on PVS, 1994; Giacino et al., 2002); (b) LCF = 1–2 for VS and 3–4 for MCS patients; (c) less than 3 months after the acute brain event onset; and (d) first-ever acute brain event. None of the chosen patients were excluded because the scores for all the patients in the study remained unchanged from the day of admission to the day that the EEG was recorded.

The study was approved by the local institutional Ethics Committee, and complies with Good Medical Practice. Overt consent of subjects' legal representatives, in line with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and standards established by the Fondazione Istituto "San Raffaele - G. Giglio" Review Board were acquired. The use of the data was authorized by means of written informed consent of the caregivers for VS and MCS patients.

2.2. EEG recording

Spontaneous electrical brain activity was recorded with a 21-channel EEG data acquisition system (Neuropack electroencephalograph; Nihon Kohden, Tokyo, Japan). EEG data were collected (cephalic reference – mean of the signals from C3 and C4 electrodes; 0.5–70 Hz bandpass; 200 Hz sampling rate; around 30 min) in patients during a waking resting state (eyes-closed) from 19 electrodes positioned in accordance with the International 10–20 system (i.e. O₁, O₂, P₃, P₄, P_z, T₅, T₆, C₃, C₄, C_z, T₃, T₄, F₃, F₄, F_z, F₇, F₈, Fp₁, Fp₂). Recording the full, physiologically relevant range of frequencies does not have trade-offs that would favour any frequency band at the expense of

another. The impedance of recording electrodes was monitored for each subject and was always below 5 k Ω . To monitor eye movements, an electrooculogram (0.5–70 Hz bandpass) was also recorded.

The EEG recordings for all patients were performed during the late morning. EEG recordings in patients were started in all cases only if patients spontaneously had their eyes open, the eyelids were then closed by hand. At the end of the recordings all patients opened their eyes spontaneously. In order to keep a constant level of vigilance, an experimenter monitored patients EEG traces in real time, looking for signs of drowsiness and the onset of sleep (increase in “tonic” theta rhythms, K complexes and sleep spindles). The presence of an adequate EEG signal was determined by visual inspection of the raw signal on the computer screen. Even though it may be difficult to assess precisely the level of vigilance in patients in VS, preserved sleep patterns may be observed in the majority of patients in VS (for review see Colgan et al., 2010).

2.3. EEG-signal data processing

The presence of an adequate EEG signal was determined by visually checking each raw signal. Epochs containing artefacts due to eye movements, eyes opening, significant muscle activity, and movements on EEG channels were marked and then automatically removed from any further analysis.

Artefact-free EEG signals were filtered in the 1–30 Hz frequency range. This frequency range was chosen because approximately 98% of spectral power lies within these limits (Thatcher, 2001). Although it has recently been proposed that frequencies above 30 Hz (gamma band) may be functionally informative, there are a number of methodological issues which lead us to exclude frequencies above 30 Hz from the present analysis: (a) it was shown that volume conduction has little influence on the shape of the spectrum below about 25 Hz, however spatial filtering is significant for frequencies around 25 Hz (Robinson et al., 2001); (b) high-frequency spindles have a very low signal-to-noise ratio, which results in considerable noise contamination of the gamma band; (c) the dynamics of high-frequency effects may be a trivial by-product of power changes in lower frequencies (Pulvermuller et al., 1995); (d) increased power in the gamma range may be due to the harmonics of activity in lower frequency ranges, and/or due to the ringing of filters by EEG spikes recurring at theta rates (Freeman, 2003); (e) the gamma band may be an artefact of (un)conscious micro-constrictions of muscles of the organism and/or face muscles (Whitham et al., 2007; Yuval-Greenberg et al., 2008; Ball et al., 2008); (f) comprising just 2% of the spectral power (Thatcher, 2001), the contribution of high-frequency band to the spectrum cannot be significant; (g)

Bullock et al. (2003) demonstrated many “good” rhythms in the 2-25 Hz range which were mainly sinusoidal but did not find them in the 30-50 Hz band. In light of the above, there may be difficulties in carrying out a meaningful interpretation of effects at the high-frequency band regardless of how powerful or statistically significant they are.

DC drifts were removed using high pass filters (1 Hz cut-off).

For each patient a full EEG stream, free from any artefacts, was fragmented into consecutive one-minute epochs. Therefore “VS” group (patients in vegetative state) has 137 one-min EEGs and “MCS” group (patients in minimally conscious state) has 87 one-min EEGs. Within each group further data processing was performed for each separate one-minute portion of the signal. Due to the technical requirements of the tools used to process the data, EEGs were re-sampled to 128 Hz. This procedure should not have affected the results since 128 Hz sampling rate meets the Nyquist Criterion (Faulkner, 1969) of a sample rate greater than twice the maximum input frequency and is sufficient to avoid aliasing and preserve all the information about the input signal. This method was considered sufficient since the sampling rate of the source signals was significantly higher than required.

After re-sampling EEG oscillations were identified. This procedure was undertaken in three stages (Fig. 1). During the first stage of EEG analysis, the data series from each EEG channel were separately divided into overlapping windows in order to capture EEG changing dynamics. EEG oscillations were quantified by calculation of individual short-term EEG spectral patterns (SPs). Individual power spectra were calculated in the range of 1–30 Hz with 0.5-Hz resolution, using a Fast Fourier Transform with a 2-sec Hanning window shifted by 50 samples (0.39-sec) for each channel of one-minute EEG (Fig. 1). According to previous studies, these values have proved to be the most effective for revealing oscillatory patterns from the signal (Levy, 1987; Kaplan, 1998). A sliding spectral analysis with overlapping segments, previously applied to EEG signals (Keidel et al., 1987; Tirsch et al., 1988), (a) takes the non-stationarity of the time series into account, (b) compensates for the effects of windowing and (c) prevents loss of information due to residual activity. Additionally, using overlapping intervals (which just means a different aggregation scheme) cannot add any artefactual information (Muller, 1993).

After calculation of EEG short-term SPs, the total number of individual SPs for each one-min EEG channel was 149 (Fig. 1).

During the second stage, with the help of a probability-classification analysis of the short-term EEG SPs (see Fingelkurts et al., 2003 and Appendix in Fingelkurts and Fingelkurts, 2010a), each SP was labelled according to the class index it belonged to. Sequential single EEG SPs were adaptively classified in each one-minute EEG channel using a set of standard SPs which were

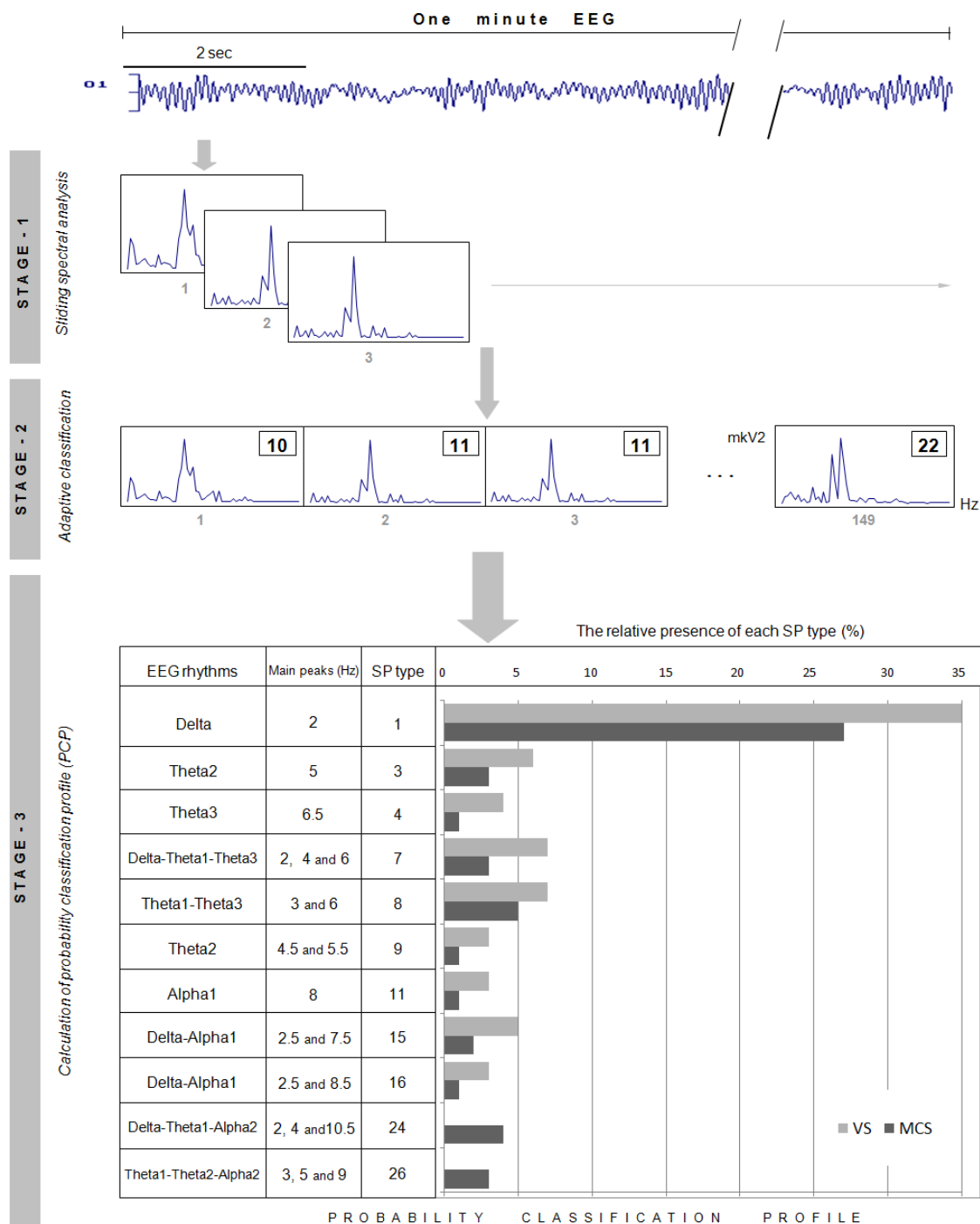


Figure 1. The scheme of data processing. First stage: Sliding spectral analysis was conducted separately for each patient and each one-minute EEG channel. O_1 = Left occipital EEG channel. Second stage: Adaptive classification of short-term spectral patterns (SP) was performed separately for each patient and each one-minute EEG channel. The small gray numbers under each SP represent the running numbers from 1 to 149 for one-minute EEG. The number in the square represents the class to which a given SP was assigned during classification procedure. Third stage: Probability-classification profile (PCP) separately for each patient and each one-minute EEG channel was calculated. Presented PCP illustrates an example of the composition and percent ratio of EEG oscillations in O_1 EEG channel for patients in minimally conscious state (MCS) and vegetative state (VS). “EEG rhythm(s)” - the brain oscillations which contribute the most into a particular SP. Column “Hz” represents the main dominant peak(s) in particular SP. “SP type” - represents the labels of spectral pattern types. Delta: 1-2.5 Hz; Theta₁: 3-4 Hz; Theta₂: 4.5-5.5 Hz; Theta₃: 6-7 Hz; Alpha₁: 7.5-8.5 Hz; Alpha₂: 9-13 Hz.

generated automatically from the EEG data itself (*first step*). The selection was not arbitrary: a pool of SPs ($n = 634\ 144$) was collated from all the SPs for all the EEG signals (all locations) for all patients. From this pool, all identical SPs with dominant power peaks (peaks that rise significantly above the general average) were counted automatically. The peak detection was based on normalising the SP to within-SP relative percentages of magnitude, where acceptance is achieved when the peak exceeds a given (60%) percent-magnitude (100% corresponds to the magnitude of the highest peak within the SP). According to the preliminary study, this value has proved to be the most effective for peak detection. The set of SPs with the highest count were the most probable candidates to form the “set of standard SPs.” Only those SPs with a minimum mutual correlation were selected. As a result, in this study the standard set included 32 SPs.

During the *second step*, the initial matrix of cross-correlations (Pearson’s correlation coefficients, CC) between standard and current individual SPs of analyzed EEG was calculated for each channel separately. The current SPs that their CC passed the acceptance criteria of $r \geq 0.71$ were attributed to their respective standard classes. Therefore, the same current SPs maybe included simultaneously into different standard classes. The CC acceptance criteria r was determined such as for $r \geq 0.71$ more than 50% of the SP variances were coupled/associated.

During the *third step*, the current SPs included in a particular class were averaged within this class. The same procedure was performed for all classes separately for each EEG channel. On the back of this, the standard spectra were reconstructed but this time taking into account the peculiarities of the spectral description of concrete channel of the particular EEG. In this way an “actualization” of the initial standard SP set was performed. In other words, standard SPs were converted into so-called actual spectral patterns. Notice that the main frequency peaks in the *actual* SP of every class stay the same as in the corresponding *standard* SP’s classes. However, overall shape of the power spectrum was automatically modulated in the direction to better represent the multitude of all SPs within each class in each given EEG channel.

An actual SP set was in turn used for the *fourth step*—the final classification of the current SPs: each of current SPs was attributed to only one actual SP class for which the CC was the *maximum* of the set of $r \geq 0.71$.

Thus, using a probability-classification procedure (Fingelkurts et al., 2003; Appendix in Fingelkurts and Fingelkurts, 2010a), each current SP was labelled according to the index of the class to which it belonged (Fig. 1). Hence, each one-minute EEG signal was reduced to a sequence of individually classified SPs. Notice that during the same time observation (2 sec) different EEG channels were characterised usually by different SP types.

During the third stage, probability-classification profiles (PCPs) of SPs for each one-minute EEG channel in each patient were calculated. These PCPs were calculated by taking the relative number of cases of an SP type as a percentage of the total amount of all SPs within each EEG channel –, presented as the histogram of relative presence of each SP type. PCPs were averaged across 87 (for MCS patients) and 137 (for VS patients) 1-min EEG signals separately for each EEG channel. It was expected that these PCPs would make it possible to illustrate in detail (in SP description) the composition of EEG oscillations and their percent ratio for MCS and VS patients.

2.4. Statistics

The Wilcoxon *t*-test was used to reveal any statistically significant differences in the presence of each SP type in EEG between MCS and VS. Wilcoxon *t*-test was chosen because in contrast to parametric statistics such as a repeated measures ANOVA, Wilcoxon *t*-test is (a) distribution free, (b) suitable for statistics of small sample sizes and (c) not influenced by outliers (extremely high or low values). As the spectral patterns (SP) represent frequencies of events (the occurrence of a specific pattern during a time interval), they are likely not to follow normal distribution. Event frequencies may not be analyzed by parametric statistics. To control for repeated observations of the same measures a Bonferroni correction was made. *P_{corrected}* is the value required to keep the number of false positives at $p = 5\%$. Differences in the demographic data were assessed either by Wilcoxon *t*-test or by Chi-square test.

3. Results

3.1. Demographical data

There were no significant differences between the MCS and VS groups in terms of age ($p = 0.41$) and time post brain injury ($p = 1$), as well as distribution of traumatic brain injury (TBI) and non-TBI aetiologies (43% of TBI and 57% of non-TBI in both groups), left- and right-side lesions ($p = 0.62$) and medicated vs. non-medicated patients ($p = 0.82$).

3.2. General description of EEG for MCS and VS patients

To estimate which of EEG oscillations within a broad frequency range (1–30 Hz) are occurred more or less frequent for MCS and VS, we examined the probability of the occurrence of SP types (which characterise EEG oscillations and/or their mixture).

Analysis revealed that (a) EEGs in both MCS and VS were characterised by the same five EEG oscillations: delta (around 2 Hz), θ_{a1} (around 3 or 4 Hz), θ_{a2} (around 5 Hz), θ_{a3} (around 6 Hz), α_1 (around 7.5 or 8 or 8.5 Hz) and (b) only EEGs in MCS had in addition sixth EEG oscillation – α_2 (around 9 or 10.5 Hz). Each of these oscillations was present in EEG either alone or in combination with others in different EEG segments, thus exhibiting “mosaic” dynamics.

In general, MCS and VS patients differed from each other in all EEG channels: there was no a single EEG channel without statistically significant differences in the relative presence of at least 7% of SP types in PCPs between MCS and VS patients. At the same time, different cortical areas were characterized by different number of SP types which demonstrated statistically significant difference in their relative presence in PCPs, thus indicating the magnitude of that difference (Table 2). Thus, maximal magnitude of the difference between MCS and VS patients was observed in the posterior-central part of the cortex ($O_1, O_2, P_3, P_4, P_z, C_3, C_z$ EEG channels) ($p_{corrected} < 0.002$) – the number of SP types which demonstrated statistically significant difference in their relative presence in PCPs between MCS and VS patients reached in these areas up to 41% from all observed SP types. Medium magnitude of the difference between MCS and VS patients was in temporal lobes of the cortex ($T_4, T_5, T_6, C_4, F_7, F_8$ EEG channels) (up to 26%, $p_{corrected} < 0.002$). Minimum ($p_{corrected} < 0.002$) number of SP types (up to 11%) which demonstrated statistically significant difference in their relative presence in PCPs between MCS and VS patients was observed in anterior part of the cortex ($T_3, F_3, F_4, F_z, Fp_1, Fp_2$ EEG channels) (Table 2). At the same time, each from all observed SP types ($n = 14$) revealed statistically significant difference in its relative presence in PCPs between MCS and VS patients in at least 11% of EEG channels.

Table 2. EEG channel groups and the number (in %) of spectral pattern types which demonstrated statistically significant ($P_{corrected} < 0.05$ - $P_{corrected} < 0.000001$) difference in relative presence in probability-classification profiles between minimally conscious state (MCS) and vegetative state (VS). Data averaged across 87 EEGs for MCS and 137 EEGs for VS patients.

Brain regions	EEG channels	Range	Mean	St.d.	Stat. significance
Posterior-central	O1, O2, P3, P4, Pz, C3, Cz	36-50%	41%	1	$p_{corrected} < 0.002$ $p_{corrected} < 0.002$
Temporal	T4, T5, T6, C4, F7, F8	21-29%	26%	0.5	
Anterior	T3, F3, F4, Fz, Fp1, Fp2	7-14%	11%	0.5	

3.3. The probability of the occurrence of EEG oscillations (in terms of SP types) for MCS and VS patients

MCS and VS patients differed from each other according to the probability estimation of the occurrence of SP types in PCPs.

In the case of common EEG oscillations for both groups of patients, comparative analysis of the PCPs demonstrated that EEG during MCS was characterized by a smaller percentage of delta- [SP1 (main peak at 2 Hz)], delta–alpha₁- [SP15 (main peaks at 2.5 and 7.5 Hz), SP16 (2.5 and 8.5 Hz)], delta–theta₁–theta₃- [SP7 (2, 4 and 6 Hz)], theta₂- [SP3 (5 Hz), SP9 (4.5 and 5.5 Hz)], theta₃- [SP4 (6.5 Hz)], theta₁–theta₃- [SP8 (3 and 6 Hz)], and alpha₁- [SP11 (8 Hz)] rhythmic EEG segments when compared to VS ($p_{corrected} < 0.05$ – $p_{corrected} < 0.000001$ for different EEG channels and SPs) (Table 3).

Table 3. Spectral pattern types which demonstrated statistically significant ($P_{corrected} < 0.05$ – $P_{corrected} < 0.000001$) difference in relative presence in probability-classification profile between minimally conscious state (MCS) and vegetative state (VS), satisfying MCS<VS and/or MCS>VS. Data averaged across 87 EEGs for MCS and 137 EEGs for VS. Only SP types which demonstrated statistically significant differences in their presence between MCS and VS in more than 1 EEG channel from 19 are considered*.

EEG rhythm(s)	SP type	Frequencies of the main peaks (Hz)	Number of EEG channels	EEG channels affected	Effect globality **
MCS < VS					
Theta ₃	SP4	6.5	16 [79%]	all except Cz, T3, Fz, Fp1	Generalized
Theta ₁ -Theta ₃	SP8	3 and 6	13 [68.4%]	all except F3, F4, Fz, F7, Fp1, Fp2	Generalized
Delta	SP1	2	6 [31.6%]	T6, T4, F3, F7, Fp1, Fp2	Regional
Delta-Alpha ₁	SP15	2.5 and 7.5	8 [37%]	O1, O2, P4, Pz, C4, T3, F7	Regional
Alpha ₁	SP11	8	7 [21%]	P4, T6, Cz, T4	Regional
Theta ₂	SP3	5	3 [15.8%]	P4, Pz, F8	Local
Delta-Theta ₁ -Theta ₃	SP7	2, 4 and 6	2 [10.5%]	C3, Cz	Local
Delta-Alpha ₁	SP16	2.5 and 8.5	6 [10.5%]	O2, P4,	Local
MCS > VS					
Theta ₁ -Theta ₂ -Alpha ₂	SP26	3, 5 and 9	2 [10.5%]	Pz, Cz	Local
Delta-Theta ₁ -Alpha ₂	SP24	2, 4 and 10.5	2 [10.5%]	P3, P4	Local

SP - spectral pattern; "EEG rhythm(s)" column represents the brain oscillations which contribute the most into a particular SP. "SP type" column represents the labels of spectral pattern types; [%] - percent of EEG channels which demonstrated observed effect. Delta: 1-2.5 Hz; Theta₁: 3-4 Hz; Theta₂: 4.5-5.5 Hz; Theta₃: 6-7 Hz; Alpha₁: 7.5-8.5 Hz; Alpha₂: 9-13 Hz.

*This permits to arrive at a direct estimation of a 5% level of statistical significance ($P < 0.05$) of the observed effects: one can expect $19 \times 0.05 = 0.95$ false positives for 19 EEG channels analyzed under the null hypothesis (where 0.05 is the significance level). Based on these calculations, it is rather improbable that, a false-positive functional connection will emerge by chance simultaneously in 2 EEG channels. For the existence of statistical heterogeneity of the electromagnetic field in regard to neurodynamics within quasi-stable periods in regional EEGs see (Fingelkurts and Fingelkurts, 2010b; see also Kaplan et al., 2005 and Fingelkurts & Fingelkurts, 2008). **Generalized - observed effect is found in more than 68% of EEG channels; Regional - observed effect is found in 17-67% of EEG channels; Local - observed effect is found in less than 16% of EEG channels.

Additionally, the comparative analysis of PCPs for MCS and VS patients demonstrated that there were unique SP types associated only with MCS: SP24 (main peaks at 2, 4 and 10.5 Hz) and SP26 (3, 5 and 9 Hz) (Table 3). These SPs contain α_2 components.

It can be seen that differences in the probability of the occurrence of θ_1 and θ_3 oscillations between MCS and VS were generalised, meaning that they were observed mostly in the majority of EEG channels (up to 82%, Table 3). The differences in the probability of the occurrence of delta and α_1 oscillations between MCS and VS were mostly regional – they were observed mainly in 32-42% of EEG channels. The probability of the occurrence of θ_2 and α_2 oscillations differed between MCS and VS mainly locally – they were observed mainly in 10.5-16% of EEG channels (Table 3).

Both groups of patients were composed of patients with disorders of consciousness as a result of different aetiology: traumatic or vascular aetiology for MCS and traumatic, vascular or anoxic aetiologies for VS. Therefore it was interesting to check whether different aetiologies affect the probability of the occurrence of EEG oscillations differently. This will be examined in the next section.

3.4. The probability of the occurrence of EEG oscillations (in terms of SP types) and aetiology of MCS and VS

Comparative analysis of the PCPs *between* MCS and VS of different aetiologies demonstrated that the probability of the occurrence of SP4, SP8, SP15, SP24, and SP26 showed the same behaviour as for the combined groups (Table 4, A), thus being aetiology independent. Simultaneously, the probability of the occurrence of SP3 was trauma dependent, whereas the probability of the occurrence of SP1, SP11, and SP16 was vascular dependent (Table 4, A).

Analysis of the PCPs *within* MCS and VS of different aetiologies demonstrated that EEG in MCS of traumatic aetiology was characterised by less probability of the occurrence of SPs with mostly delta and/or θ_1 components and more probability of the occurrence of SPs with mostly θ_2 and/or θ_3 and/or $\alpha_{1/2}$ components when compared to MCS of vascular aetiology ($p_{corrected} < 0.05$ – $p_{corrected} < 0.000001$ for different EEG channels and SPs; Table 4, B). For EEG in VS, the probability of the occurrence of SPs with mostly delta and/or $\theta_{1/2/3}$ components was the greatest for VS of anoxic aetiology, lower for VS of vascular aetiology and the lowest for VS of traumatic aetiology ($p_{corrected} < 0.05$ – $p_{corrected} < 0.000001$ for different EEG channels and SPs; Table 4, B). Whereas the probability of the occurrence of SPs with θ_3 and/or α_1 components was the greatest for VS of traumatic aetiology, lower for VS of vascular aetiology and the lowest

for VS of anoxic aetiology ($p_{corrected} < 0.05$ – $p_{corrected} < 0.000001$ for different EEG channels and SPs; Table 4, B).

Table 4. Comparison of the relative presence of spectral pattern types for minimally conscious state (MCS) and vegetative state (VS) of different etiologies (T - trauma; V - vascular; A - anoxia).

Data averaged across 38 EEGs (traumatic etiology) and 49 EEGs (vascular etiology) for MCS and 70 EEGs (traumatic etiology), 56 EEGs (vascular etiology) and 11 EEGs (anoxia etiology) for VS. Only SP types which demonstrated statistically significant differences in their presence between MCS and VS in more than 1 EEG channel from 19 are considered*.

A. Spectral pattern types which demonstrated statistically significant ($P_{corrected} < 0.05$ – $P_{corrected} < 0.000001$) difference in relative presence in probability-classification profile between MCS and VS of different etiologies.

EEG rhythm(s)	Delta	Theta ₂	Theta ₃	Theta ₁ -Theta ₃	Alpha ₁	Delta-Alpha ₁	Delta-Alpha ₁	Delta-Theta ₁ -Alpha ₂	Theta ₁ -Theta ₂ -Alpha ₁
Frequencies of the main peaks (Hz)	2	5	6.5	3 and 6	8	2.5 and 7.5	2.5 and 8.5	2, 4 and 10.5	3, 5 and 9
SP TYPE	SP1	SP3	SP4	SP8	SP11	SP15	SP16	SP24	SP26
(MCS-T) < (VS-T)		X	X	X		X			
(MCS-V) < (VS-V)	X		X	X	X	X	X		
(MCS-T) > (VS-T)								X	X
(MCS-V) > (VS-V)								X	X

B. Spectral pattern types which demonstrated statistically significant ($P_{corrected} < 0.05$ – $P_{corrected} < 0.000001$) difference in relative presence in probability-classification profile within MCS and VS of different etiologies.

SPs with mostly delta and/or theta ₁ components	(MCS-T) < (MCS-V)
SPs with mostly theta ₂ and/or theta ₃ and/or alpha _{1/2} components	(MCS-T) > (MCS-V)
SPs with mostly delta and/or theta _{1/2/3} components	(VS-T) < (VS-V) < (VS-A)
SPs with mostly theta ₃ and/or alpha ₁ components	(VS-T) > (VS-V) > (VS-A)

SP - spectral pattern; "EEG rhythm(s)" - the brain oscillations which contribute the most into a particular SP. "SP type"- represents the labels of spectral pattern types; "EEG channels %" - percent of EEG channels which demonstrated observed effect. Delta: 1-2.5 Hz; Theta₁: 3-4 Hz; Theta₂: 4.5-5.5 Hz; Theta₃: 6-7 Hz; Alpha₁: 7.5-8.5 Hz; Alpha₂: 9-13 Hz.

*This permits to arrive at a direct estimation of a 5% level of statistical significance ($P < 0.05$) of the observed effects: one can expect $19 * 0.05 = 0.95$ false positives for 19 EEG channels analyzed under the null hypothesis (where 0.05 is the significance level). Based on these calculations, it is rather improbable that, a false-positive functional connection will emerge by chance simultaneously in 2 EEG channels.

4. Discussion

4.1. Demographic factors

Since there were no significant differences between the MCS and VS groups in terms of age and time post brain injury, distribution of TBI and non-TBI aetiologies, left- and right-side lesions, and distribution of medicated vs non-medicated patients, all these factors could not be responsible for the differences in EEG parameters found between the MCS and VS groups.

It could be argued that the effects of phenobarbital and valproic acid on the EEGs could give rise to the differences between MCS and VS groups. However, these drugs induce changes in the high frequency range mostly (Sannita et al., 1980; 1991; Drake et al., 1990), while our results were consistent with a differential value for delta, theta and alpha oscillations.

Patients with epidural or subdural hematomas may potentially affect EEG results due to the lower conductivities from brain to scalp. However, the time between brain injury and EEG recording was > 1 month for patients with epidural or subdural hematomas. We assume that sufficient time had lapsed for the hematoma to be reabsorbed.

4.2. Composition of multiple EEG oscillations for MCS and VS patients

The PCPs obtained for both MCS and VS patients revealed that all EEG channels were predominantly characterized by the same five EEG oscillations (indexed by 9 SP types) in multiple frequency bands, several of which were superimposed: delta, θ_1 , θ_2 , θ_3 , α_1 . In addition to these EEG oscillations, MCS was characterized by unique EEG oscillation: α_2 (indexed by 2 SP types). Additionally, MCS patients differed from VS patients according to the probability estimation of the occurrence of particular EEG oscillations and/or their compositions (indexed by relative presence of SP types in PCPs). Thus, delta, theta and α_1 oscillations were less probable, whereas α_2 oscillations were more probable for MCS than for VS patients. Differences in the brain activity between MCS and VS patients were observed in the whole cortex (various areas to different degrees). These findings combined suggest that different degree of consciousness expression (from its full absence in VS to its minimal expression in MCS) is reflected in the reorganization of the probability of the occurrence of several EEG oscillations and/or their composition.

Our results are in line with the observations that increase in the amount of slow EEG oscillations (mostly delta and theta) and decrease in the amount of fast-alpha oscillations are associated with stupor and alterations of consciousness (Brenner, 2005; Rusalova, 2006), decrease in mentation recall (Pivik and Foulkes, 1968), and loss of consciousness during general anaesthesia (Clark and Rosner, 1973; Engelhardt et al., 1994; Sleigh and Galletly, 1997; Gugino et al., 2001; Kuizenga et al., 2001). Additionally it was demonstrated that the amount of alpha oscillations correlated with conscious awareness (Babiloni et al., 2006) and is associated with transition of VS patients to a minimally conscious state (Kondrat'eva, 2004). Summary of functional significance of these EEG oscillations in relation to the degree of consciousness expression can be found in Fingelkurts et al., (submitted).

4.3. Composition of multiple EEG oscillations and aetiology of MCS and VS

Theta₃ (around 6.5 Hz) oscillation and compositions of such EEG oscillations as theta₁-theta₃ (around 3 and 6 Hz), delta-alpha₁ (around 2.5 and 7.5 Hz), delta-theta₁-alpha₂ (around 2, 4 and 10.5 Hz), and theta₁-theta₂-alpha₂ (around 3, 5 and 9 Hz) demonstrated independency from brain injury aetiology. This means that the probability of the occurrence of these multiple EEG oscillations differentiate MCS and VS independently on brain injury aetiology.

At the same time, several EEG oscillations were aetiology dependent. Thus, the probability of the occurrence of theta₂ (around 5 Hz) oscillation was trauma dependent, whereas the probability of the occurrence of delta (around 2 Hz) oscillation, alpha₁ (around 8 Hz) oscillation and composition of such EEG oscillations as delta-alpha₁ (around 2.5 and 8.5 Hz) was vascular dependent. These results may be due to the different brain damage neuropathology in traumatic and non-traumatic brain injuries (Bagnato et al., 2010).

This supposition is supported by the results of the comparative analysis of the probability of the occurrence of SP types within MCS and VS of different aetiologies. Thus, for MCS it was demonstrated that the probability of the occurrence of SPs with mostly delta and/or theta₁ components followed the order: traumatic < vascular aetiology, whereas the probability of the occurrence of SPs with mostly theta₂ and/or theta₃ and/or alpha_{1/2} components followed the reverse order: traumatic > vascular aetiology. Similarly, for VS the probability of the occurrence of SPs with mostly delta and/or theta_{1/2/3} components followed the order: traumatic < vascular < anoxic aetiology, whereas the probability of the occurrence of SPs with mostly theta₃ and/or alpha₁ components followed the reverse order: traumatic > vascular > anoxic aetiology. Considering clinical significance of different types of EEG oscillations (for the review see Fingelkurts and

Fingelkurts, 2010b), we may suggest that for both MCS and VS patients, the brain after the injury with traumatic aetiology is characterised by better functional state than with vascular aetiology: fast-theta and slow-alpha oscillations versus delta and slow-theta oscillations correspondently. At the same time for VS patients, brain after the injury with anoxic aetiology is characterised by worst functional state of the brain when compared to vascular and traumatic aetiologies. Indeed, it is well known that increase in the amount of delta and slow-theta activity in resting awake EEG is usually proportional to the degree of pathological processes and reflects encephalopathy and/or structural lesions (Donnelly and Blum, 2007), whereas the increase in alpha activity reflects normalisation in brain functional state (Niedermeyer, 1999).

Perhaps such differences in oscillatory descriptors of brain functional states for brain injuries of different aetiologies contribute to known differences in their outcome. According to Multi-Society Task Force (1994) patients with nontraumatic (primarily anoxic) brain injury have the higher mortality figures and the lower chances to recover consciousness and other functions than patients with traumatic brain injury. Note, that convincing signs of consciousness have so far never been reported in the post-anoxic VS (Noirhomme et al., 2008).

Summarising, our supposition is in line with previous studies which demonstrated that a pattern of unvarying activity with the major frequency component in the delta–slow-theta (1–3 Hz) band predicts poor prognosis (Bricolo et al., 1978), whereas a peak in the alpha or fast-theta frequency band indicates a good outcome from traumatic coma (Steudel and Kruger, 1979; Cant and Shaw, 1984; Kane et al., 1998). Additionally, examination of the clinical outcome (mortality after 6 months and recovery of function (indexed by LCF score increase) after 3 months) for the patients participated in the present study confirmed our supposition: the outcome after 3-6 months was worse for the patients with nontraumatic brain injury (being the worst for anoxic aetiology) than for the patients with traumatic brain injury (Table 5).

4.4. Differences in the composition of multiple EEG oscillations between MCS and VS patients and topography

Observed findings in this study demonstrated that the number of EEG oscillations which demonstrated statistically significant difference in their relative presence in EEG between MCS and VS patients were the largest in the posterior cortex of the brain. This may suggest the importance of the posterior cortex for at least partial consciousness.

Indeed, posterior cortex is one of the most active cerebral regions in conscious waking (Andreasen et al., 1995; Maquet et al, 1997; Gusnard and Raichle, 2001). Vogele and Fink (2003)

suggested that parietal cortex is involved in the first-person perspective, the viewpoint of the observing self (see also Vogt and Laureys, 2005). Additionally, parts of posterior cortex such as PCC and precuneus are (a) believed to be involved in self-processing events with a visuospatial (attentional) connotation (Cavanna and Trimble, 2006), (b) considered to be involved in self integration — that is linkage of self-referential stimuli to the personal context (Northoff and Bermpohl, 2004) and (c) considered relevant for neural conscious processes, since their activity is reduced in low or absent consciousness states, such as in physiological sleep, drug-induced anaesthesia or neuro-psychiatric conditions (epilepsy, schizophrenia, coma, VS and MCS) (Cavanna, 2007; Boly et al., 2008; Buckner et al., 2008).

Table 5. The outcome for patients in MCS and VS of different aetiologies. Data presented as the number (in %) of patients which died after 6 months or demonstrated some improvement (measured by LCF core) after 3 months*.

Condition	Mortality (in %) after 6 months	Recovery of function (in %) after 3 months
MCS-T	0	67
MCS-V	50	50
VS-T	17	50
VS-V	33	17
VS-A	50	0

MCS - patients in minimally conscious state, T - traumatic aetiology, V - vascular aetiology, A - anoxic aetiology.

* To give the “Recovery rate” for all patients we used 3 month – the time where all patients were alive.

5. Conclusions

Summarising, the present study demonstrated that the resting brain activity between VS and MCS patients differed in nearly the whole cortex, rather than in only the frontal and/or parietal areas. This was reflected in the considerable reorganization of the composition of EEG oscillations in multiple frequencies in a broad frequency range (1-30 Hz) in majority of EEG channels. At the same time, the magnitude of the difference between VS and MCS patients was maximal in the posterior cortex of the brain.

In particular, for MCS patients delta, theta and slow-alpha oscillations were less probable, whereas fast-alpha oscillations were more probable in EEG when compared to VS patients. Some of the compositions of these EEG oscillations were aetiology independent, whereas others were aetiology dependent. Types of EEG oscillations which were aetiology dependent differentiated traumatic, vascular and anoxic aetiologies of brain injury in terms of the probability of EEG oscillations occurrence.

Finally, the probability of occurrence of EEG oscillations perhaps contributes to known and observed differences in the outcome of patients with brain injuries of different aetiologies after 3-6 months. However to establish any clinical relationship between the outcome and the probability of EEG oscillations occurrence a relevant statistical analysis in larger groups of patients should be performed.

Taken together, results in the present study suggest that automatic advanced EEG analysis may be useful in distinguishing VS and MCS patients. Such advanced automatic analysis of EEG (the procedure, which is easy, simple and available in most neurorehabilitation departments) may improve clinical characterization of VS and MCS patients what may lead to a redefining of their diagnosis. This will contribute to better clinical care, resource allocation and treatment and to more objective diagnostic criteria for consciousness and end-of-life decision-making in patients with disorders of consciousness following coma caused by severe brain damages.

Future studies including larger groups of patients with brain injuries for each aetiology are warranted to confirm these results.

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