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EEG Oscillatory States as Neuro-phenomenology of Consciousness as revealed from patients in vegetative and minimally conscious states

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Abstract

The value of resting electroencephalogram (EEG) in revealing neural constitutes of consciousness (NCC) was examined. We quantified the dynamic repertoire, duration and oscillatory type of EEG microstates in eyes-closed rest in relation to the degree of expression of clinical self-consciousness. For NCC a model was suggested that contrasted normal, severely disturbed state of consciousness and state without consciousness. Patients with disorders of consciousness were used. Results suggested that the repertoire, duration and oscillatory type of EEG microstates in resting condition quantitatively related to the level of consciousness expression in brain-damaged patients and healthy-conscious subjects. Specifically, results demonstrated that (a) decreased number of EEG microstate types was associated with altered states of consciousness, (b) unawareness was associated with the lack of diversity in EEG alpha-rhythmic microstates, and (c) the probability for the occurrence and duration of delta-, theta- and slow-alpha-rhythmic microstates were associated with unawareness, whereas the probability for the occurrence and duration of fast-alpha-rhythmic microstates were associated with consciousness. In conclusion, resting EEG has a potential value in revealing NCC. This work may have implications for clinical care and medical–legal decisions in patients with disorders of consciousness.

Key words: electroencephalogram (EEG); disorder of consciousness; EEG oscillations; brain microstates; awareness; minimally conscious state (MCS); vegetative state (VS); spectral patterns.

> *“The current state of the field of cognitive neuroscience*
> *allows us nowadays to tell with a reasonable amount*
> *of certainty what is going on in someone’s mind,*
> *based solely on inspection of his or her neural activity.”*
> *(John F. Stins, 2009)*

1. Introduction

1.1. Consciousness versus Vigilance

Consciousness is often conceptualized as (a) a phenomenon with two components: wakefulness and awareness (Laureys, 2005) and (b) a gradual phenomenon with increasing degree of consciousness from its absence to full-fledged consciousness (Laureys et al., 2002). Both of these propositions are related to the fact that dependently on the level of vigilance, consciousness presents itself to a third-person perspective in varying amounts. Nevertheless, from the first-person perspective one is discretely either fully aware of something or not. There is no additional degree of ‘consciousness’. What is varied it is the amount of the content (information) which is available for conscious awareness (Rusalova, 2006). The amount of content available for consciousness is in turn dependent on the level of vigilance (and physical integrity of the brain) which is characterized by a particular state of consciousness. As an example, consider a patient with left anterior cingulate stroke one month after the stroke, described by Antonio Damasio (1999):

“The patient was remarkably recovered. She had considerable insight into the acute period of the illness and was able to give precious testimony as to her experiences then. Asked if she had ever experienced anguish for being apparently unable to communicate she answered negatively. She did not talk because she had nothing to say. Her mind was empty. She apparently was able to follow our conversations even during the early period of the illness, but felt no will to reply to our questions.”

Rusalova (2006) also described a conscious state with very low content (information) which experimental healthy subjects described as “emptiness in the head” during decreased level of vigilance. During this state of cessation of mental activity “subjects were completely conscious and retained the ability to produce adequate assessments of their functional state, to contact the experimenter, and to communicate changes in the state of consciousness with movement responses” (Rusalova, 2006).

In both examples subjects were fully conscious about content which was very limited and perceived as “emptiness in the head.” In the first example the reduced content was caused by a stroke (physical integrity of the brain was disturbed); in the second case the reduced content was due to decreased level of vigilance.

Therefore, (a) wakefulness is not a component of consciousness but of vigilance and (b) consciousness is not a gradual but a discrete (all-or-none) phenomenon. In other words consciousness is not merely a quantitative matter of a degree but in fact is qualitative matter of absence or presence of a particular state (Plum et al., 1998). Hence, it is reasonable to assume that to be conscious is to be in a particular state which has projections onto mental/psychological, neurophysiological and cognitive/behavioural dimensions.

This suggestion is in line with a Russian psychophysiologist, Evgeniy Sokolov, who defined consciousness as a "specific state of the brain, the only one in which higher mental functions can occur [...] Consciousness is associated with a defined state of the brain and not with the content of informational processes" (Sokolov, 1990, p. 1049). Thus, the realization of a particular state of consciousness requires the corresponding functional state, level of vigilance and physical integrity of the brain. As any state, the state of consciousness is characterized by duration. It must be longer than the time it takes for a simplest cognitive act to be completed, which is of the order of several hundreds of milliseconds[1]. It seems that duration less than this threshold makes a state *un*-conscious (still mental domain) or *non*-conscious (non-mental neurophysiological domain) (for a discussion see Fingelkurts et al., 2010). Additionally, it has been suggested that there is a variety of separate states of consciousness (Edelman, 1989).

Therefore, consciousness can be conceptualized as a sequence of shifting states each of a particular duration (above the threshold) and with a particular degree of content (information) which is dependent on the level of vigilance and physical integrity of the brain. In this context, for consciousness to be realized it is necessary to have a sufficient number of accessible states each of sufficient duration. This view is in line with conceptualizations of Hans Flohr (1991) and Giulio Tononi (2004, 2008) according to whom the brain should be able to generate consciousness to the extent that it has a large repertoire of available states[2]. Moreover, the states should be organized hierarchically where elementary microstates would comprise more complex states which in turn would form macrostates (Fingelkurts et al., 2010). Additionally, there should be the number of ways that the microstates can rearrange themselves and still produce the same macrostate.

In order to reveal parameters of the dynamic repertoire of brain microstates associated with consciousness it is important to choose an appropriate level of neuroscientific description.

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[1] Consciousness of external events may take 120 (Lehmann et al., 1998) to 500 (Libet, 1982, 2004) msec to develop.

[2] See also earlier works of Charles Tart (1972, 1975) who conceptualized states of consciousness as discrete. For the recent development see Fingelkurts & Fingelkurts (2006).

1.2. Neuroscientific Level of Consciousness Description

We believe that the appropriate level should articulate the phenomenal level of brain organization, and in particular, of cognition and consciousness (Revonsuo, 2001). Recent work in different fields of cognitive neuroscience seems to support the idea that the "translation" from phenomenological/psychological constructs to brain activity should focus on the dynamic operations of large-scale cortical networks (see Edelman & Tononi, 2000; Bressler & Kelso, 2001; McIntosh et al., 2001; Revonsuo, 2001; Varela et al., 2001; John, 2002; Fingelkurts et al., 2010).

Electroencephalogram (EEG) is a suitable measure which is adequate for the purpose, because it provides a *direct* measure of the behaviour of large-scale neuronal networks with a *millisecond temporal resolution* and reflects *functional* properties and states of brain functioning and as well as being closely connected to information processing in neuronal assemblies (Corsi-Cabrera et al., 1989; Lehmann, 1990; Arieli et al., 1996; Nunez, 2000; Bressler & Kelso, 2001). On the one hand, EEG is remarkably correlated with behaviour, cognition, and mental phenomenology (Bodunov, 1988; Jansen & Cheng 1988; Lehmann, 1990; John et al., 1991; Nunez, 2000; John, 2001; Fingelkurts et al., 2003a,b; Freeman, 2003a; see also recent detailed review Fingelkurts & Fingelkurts, 2005). On the other hand, changes in behaviour, cognition, and mental phenomenology are reflected in the temporal structure of EEG (see reviews Fingelkurts & Fingelkurts, 2004, 2008; Kaplan et al., 2005).

This temporal or piecewise stationary structure of EEG is considered as a result of "gluing" of stationary casual processes with different probability characteristics (for the reviews see Fingelkurts & Fingelkurts, 2004, 2005, 2008; Kaplan et al., 2005). The abrupt transition from one segment to another in this sense reflects the change of the generator system state or changes in the activity of the two or more systems (Jansen & Cheng, 1988; Lehmann, 1990). There is growing neurophysiological evidence that brain activity involves the transient formation and disassembling of interconnecting cortical neuronal assemblies (John et al., 1997; Yufik, 1998; Rabinovich & Varona, 2011) which are understood to generate the EEG (Freeman, 1992). Each transient neuronal assembly is in a steady quasi-stationary state which signifies a functional cortical microstate (Lehmann, 1990). Therefore, a microstate is a steady, short-lived and self-organised operational unit. Activity within each microstate is stable (or quasi-stable) and is likely represent fingerprint of functionally distinct neuronal network mode, which emerges at the mesoscopic[3] level. Such a mode is dynamically regulated by interactions within a homeostatic system that are mediated by many different neurotransmitters in addition to functional tasks or various perceptual, cognitive and mental operations associated with a conscious state. In this context, microstates in specific neuronal networks, or cortex areas, contribute to information processing, and may be the essence of brain and mind functioning (Kelso, 1995; Friston, 2001; Thompson & Varela, 2001; Varela et al., 2001; Yufik, 2002; Fingelkurts & Fingelkurts, 2004). It has been proposed that these microstates represent the basic building blocks of human mentation, i.e. the basic elements of conscious thinking and information processing (Lehmann et al., 1998). Many different microstates correspond to any one particular macrostate. In such a way, the dynamics of brain activity within a given macrostate can be considered as a sequence of relatively stable brain microstates which are reflected in EEG as piecewise stationary segments (Fingelkurts & Fingelkurts, 2006). Consecutive macrostates in turn comprise a new sequence on another (different) time-scale (Allefeld et al., 2009). Such functional EEG structure comprises hierarchical multivariability which reflects the poly-operational structure of brain activity (Fingelkurts & Fingelkurts, 2004, 2005; Fingelkurts et al., 2010).

Each EEG microstate is characterized by multiple EEG oscillations where individual oscillations are mixed in different proportions depending on vigilance level, perceptual, cognitive, and mental operations associated with the state of consciousness. During transition from one microstate to another the proportion of these EEG oscillations may change in the following manner: (a) all EEG oscillations continue to exist, but in different proportions, (b) some EEG oscillations cease, while others continue to exist, (c) EEG oscillations continue to exist but with the new characteristic frequencies and (d) any combination of (a-c). It was demonstrated that short-term power spectra (spectral patterns; SPs) reliably describe such EEG oscillatory microstates (Bodenstein & Praetorious, 1977; Bodunov, 1988; Jansen et al., 1981; Jansen & Cheng, 1988; Fingelkurts et al., 2003a,b, 2006; for the review see Fingelkurts & Fingelkurts, 2010a).

Considering that a single EEG spectrum illustrates the particular integral dynamics of tens and hundreds of thousands of neurons in a given cortical area at a particular point in time (Dumermuth & Molinari, 1987), it can be suggested that the SPs within each class are generated by the same or similar neurodynamics with the same or similar driving force (Manuca & Savit,

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[3] *Mesoscopic scale* refers to the coordinate behavior of local neuronal assemblies as measured by local field potentials and EEG (Freeman, 1992). According to Freeman (1975, 1992), mesoscopic effects operate at spatial scale of ~1 cm and temporal scale of ~100 ms and, thus, mediate between the two extremes of cortex organization: single neurons and the major lobes of the forebrain.

1996). SPs from different classes, however, are expected to have different driving forces and therefore to be generated by different neurodynamics. Therefore, each perceptual, cognitive, or mental operation associated with a particular state of consciousness is thought to constitute a single distinguishable neurophysiological state with a distinct and reliable SP type (Gevins, 1984, 1986). In this case, the frequency of each SP type occurrence reflects the probability for the occurrence of particular neuronal dynamics, which altogether constitute a dynamic repertoire of brain activity in a particular state of consciousness. Therefore, neural constitutes of consciousness are likely to be at the level of dynamic repertoire of brain states' parameters rather than the structural level of specific circuits or classes of neurons (Tononi & Edelman, 1998).

1.3. Analytic Model for Examination of Neural Constitutes of Consciousness

Adequate analytic model for examination of neural constitutes of consciousness should contrast states with the full presence of consciousness, reduced expression of consciousness and absence of consciousness. Simultaneously, vigilance level should be comparable between these three states. This can be achieved by comparing parameters of dynamic repertoire of EEG microstates in awake healthy subjects (fully expressed consciousness) and awake patients with severe brain injuries in minimally conscious (reduced expression of consciousness) and vegetative (absence of consciousness) states.

Analitic model for neural constitutes of consciousness

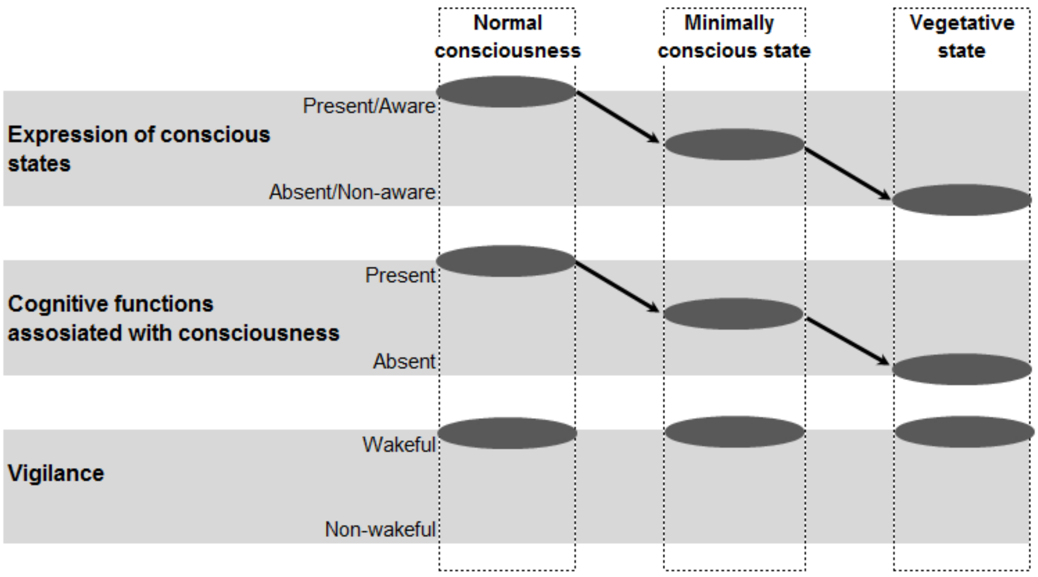


Figure 1. Schematic illustration of the analytic model for neural constitutes of consciousness. On the vertical plane, conscious states and their associated cognitive functions, as well as vigilance levels are plotted. On the horizontal plane, normal conscious state, minimally conscious state and unconscious (vegetative) state conditions are presented. Arrows indicate a decrease in the expression of conscious states and their associated cognitive functions from normal, to minimal and to unconscious conditions. Vigilance is supposed to be nearly identical in all three conditions. Therefore, within this analytic model conscious expression could be reliably dissociated from the vigilance. However, it is clear from the scheme that in this model the expression of consciousness could not be disentangled from its cognitive functions/operations.

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). Fluctuating (discrete) realizations of conscious in MCS patients may suggest that the number and duration of states of consciousness are considerably reduced in such patients and that only a few of the brain microstates reach necessary duration to permit consciousness to be expressed, rather than these patients are less conscious of themselves and environment. Also the amount of information which is accessible for consciousness in MCS patients is largely limited due to their physiological conditions and disturbed integrity of the brain.

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” (from Monti et al., 2010). One may assume that in this state none of the brain microstates reach necessary duration that permits consciousness to be expressed; therefore all of them stay either in unconscious cognitive or non-mental neurophysiological domains.

Indeed, patients in these states (MCS and VS) represent unique cases of altered states of consciousness (from its abolishment in VS patients to reduced expression in MCS patients) but, contrary to patients in coma or subjects under anaesthesia or in deep sleep, with preserved arousal (Fig. 1). Additionally, detailed histopathological studies have shown no pathological distinctions between VS and MCS patients (Jennett et al., 2001), what makes the comparison of these two groups legitimate.

Therefore, according to the model for neural constitutes of consciousness: the parameters of dynamic repertoire of EEG microstates which are associated with subjective awareness of self and environment should satisfy the following rule: NORM $\geq$ MCS > VS, whereas the features of EEG which are associated with subjective unawareness of self and environment should satisfy the opposite rule: NORM $\leq$ MCS < VS.

1.4. Hypothesis

It can be assumed that if a rich repertoire of EEG microstate types is dynamically present and covers all physiologic EEG oscillations, then a full conscious state is available. Deficiency or excess in one or more EEG microstate type would be associated with a state of limited expression of consciousness or with its total absence.

In order to check this assumption an analysis of EEG microstates was conducted in healthy subjects and patients with severe brain injuries (VS and MCS) to study the parameters of dynamic repertoire of EEG microstates as a function of consciousness expression.

Keeping in mind that during the phase of loss of consciousness (under anaesthesia) the number of EEG microstates is reduced (Flohr, 1991; Steyn-Ross et al., 2004) we hypothesize that the number of EEG microstates (indexed by SP types) will be reduced considerably in patients with disorders of consciousness (both, MCS and VS). Additionally, considering that in the literature different EEG oscillations were attributed to conscious awareness (for delta: Karakas et al., 2000; for theta: Klimesch et al., 2001; for alpha: Shaw, 2003; Rusalova, 2005; Babiloni et al., 2006; Knyazev, 2007, Başar & Güntekin, 2009; for beta: Sokolov, 1963; Rusalova, 2005; Lazarev, 2006) we aimed to reveal which of the EEG oscillations within a broad frequency range (1–30 Hz) are associated with consciousness or unawareness. We used the analytic model for neural constitutes of consciousness (see section 1.3.) to examine which EEG oscillations are associated with consciousness: contribute to EEG microstates in the order of NORM ≥ MCS > VS; and which EEG oscillations are associated with the biological needs of the organism, the orienting reflexes and/or unawareness: contribute to EEG microstates in the order of NORM ≤ MCS < VS.

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 and healthy subjects

Patients

	EEG ID	Age	Gender	Type of consciousness disorder	Aetiology	CT/MRI findings (in the acute phase)	Data of the acute event	Drugs	LCF at the EEG recording day
	1	38	M	MCS	Trauma	subdural and epidural hematoma in the rigth hemisphere; rigth fronto-temporal intraparenchymal hemorrhage; rigth fronto-temporal cortical contusions	18.09.08	None	3
	5	19	F	MCS	Trauma	subdural hematoma in the rigth hemisphere; bilateral frontal cortical contusions	06.07.08	None	3
	9	64	F	MCS	Trauma	cortical contusions in the temporal lobes and in the rigth parietal lobe	16.12.09	VPA 1500	3
	11	61	F	MCS	Vascular	intraparenchymal hemorrhage in the rigth parietal lobe	08.09.08	None	3
	13	29	F	MCS	Vascular	fronto-temporo-parietal intraparenchymal hemorrhage in the rigth hemisphere	14.12.07	VPA 600	3
	14	60	F	MCS	Vascular	subdural hematoma in the left hemisphere	20.08.07	CBZ 800, PB 100	3
	16	70	M	MCS	Vascular	left temporo-parietal ischemia	14.06.06	None	3
Mean±st.d Summary		48.7±19.8			T: 43%, NT: 57%	Left: 29%, Right: 71%		N: 57%, D: 43%	3±0.0
	2	36	M	VS	Trauma	left parieto-temporal intraparenchymal hemorrhage; several intraparenchymal micro-hemorrhages	17.03.09	PB 100	2
	3	35	M	VS	Trauma	diffuse axonal injury; rigth temporal cortical contusion	15.12.08	None	1
	4	28	M	VS	Trauma	subdural and epidural hematoma in the rigth hemisphere	23.08.08	None	2
	6	55	M	VS	Trauma	cortical contusions in the frontal lobes and in the rigth temporal lobe; subdural hematoma; diffuse axonal injury	11.08.08	None	2
	7	14	M	VS	Trauma	subdural hematoma in the left hemisphere; widespread intraparenchymal microhemorrhages	08.01.08	PB 100	2
	8	19	M	VS	Trauma	intraparenchymal microhemorrhages in the rigth frontal, temporal and parietal lobes; diffuse axonal injury	07.12.07	None	2
	10	35	M	VS	Vascular	left subarachnoid hemorrhage and left temporo-parieto-occipital ischemia (due to vasospasm)	05.09.09	None	2
	12	41	M	VS	Vascular	fronto-temporo-parietal intraparenchymal hemorrhage in the left hemisphere	24.05.08	None	1
	15	79	F	VS	Vascular	intraparenchymal hemorrhage in left parieto-occipital region	31.05.07	LTG 200, PB 100	2
	17	50	M	VS	Vascular	hemorrhage in the rigth putamen	05.05.07	None	2
	18	66	M	VS	Vascular	rigth fronto-temporo-parietal intraparenchymal and subarachnoid hemorrhage	16.05.06	PB 100	1
	19	57	M	VS	Vascular	brainstem hemorrhage	18.07.06	PB 100	2
	20	16	M	VS	Anoxia		26.08.07	None	2
	21	68	M	VS	Anoxia		16.04.07	None	1
Mean±st.d Summary		42.9±20			T: 43%, NT: 57%	Left: 42%, Right: 50%		N: 64%, D: 36%	1.7±0.5

M - male, F - female, MCS - minimaly conscious state, VS - vegetative state, T - traumatic aetiology, NT - non-traumatic aetiology, N - no drug, D - drugs, LCF - level of cognitiv functioning scale, VPA - valproic acid, CBZ - carbamazepine, PB - phenobarbital, LTG - lamotrigine

Healthy subjects (Norm)

	EEG ID	Age	Gender
	1	37	F
	2	27	M
	3	36	M
	4	28	M
	5	38	F
Mean±st.d		33.2±5.3	

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 & 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 rather than to 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., 2011). 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).

Based on the strict adherence to the aforesaid diagnostic criteria 14 of the patients (mean age 42.9 ± 20 years) were classified as being in a vegetative state (VS) and the remaining 7 patients (mean age 48.7 ± 19.8 years) were classified as being in a minimally conscious state (MCS). Patients in VS had a LCF score of 1 or 2 while patients in MCS had a LCF score of 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 (three days later); otherwise, patients were excluded from the study. Other exclusion criteria for the patients comprised: (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 for the patients included: (a) less than 3 months after the acute brain event onset; and (b) 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 control group was age matched and consisted of drug-free, healthy volunteers of both sexes (n = 5, mean age 33.2 ± 5.3 years). Before inclusion, the control subjects underwent a medical examination. Control subjects had no significant medical illnesses, were free from psychotropic medication, and none had a history of psychiatric and neurological disorders.

The study was approved by the local institutional Ethics Committee, and complies with Good Medical Practice. Informed and 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 subjects (controls) or caregivers (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 C_3 and C_4 electrodes; 0.5–70 Hz bandpass; 200 Hz sampling rate; around 30 min) in subjects during a waking resting state (eyes-closed) from 19 electrodes positioned in accordance with the International 10–20 system (i.e. O_1, O_2, P_3, P_4, P_z, T_5, T_6, C_3, C_4, C_z, T_3, T_4, F_3, F_4, F_z, F_7, F_8, Fp_1, Fp_2). 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 kΩ. To monitor eye movements, an electrooculogram (0.5–70 Hz bandpass) was also recorded.

The EEG recordings for all subjects were performed during the late morning. The control subjects and patients were requested to be relaxed and engaged in no specific mental activity during EEG recording. EEG recordings in patients were started in all cases only if patients spontaneously had their eyes open, the eyelids were then closed by hand. The eyes were closed by hand all the time until the end of EEG registration. At the end of the recordings all patients opened their eyes spontaneously thus suggesting that the level of vigilance (i.e. capability to open eyes) was unchanged compared to the onset of the EEG. In order to keep a constant level of vigilance, an experimenter monitored subjects' and 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; behaviour in control subjects). 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 there volume conduction has little influence on the shape of the spectrum below around 25 Hz, however spatial filtering is significant for frequencies above 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, 2003b); (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), 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 the 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 subject a full EEG stream free from any artefacts was fragmented into consecutive one-minute epochs. All one-min EEGs were split into three groups: "NORM" (for healthy subjects; 18 one-min EEGs), "VS" (137 one-min EEGs) and "MCS" (87 one-min EEGs) (for patients). 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 oscillatory microstates were identified. This procedure was undertaken in three stages (Fig. 2). 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 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. 2). 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.

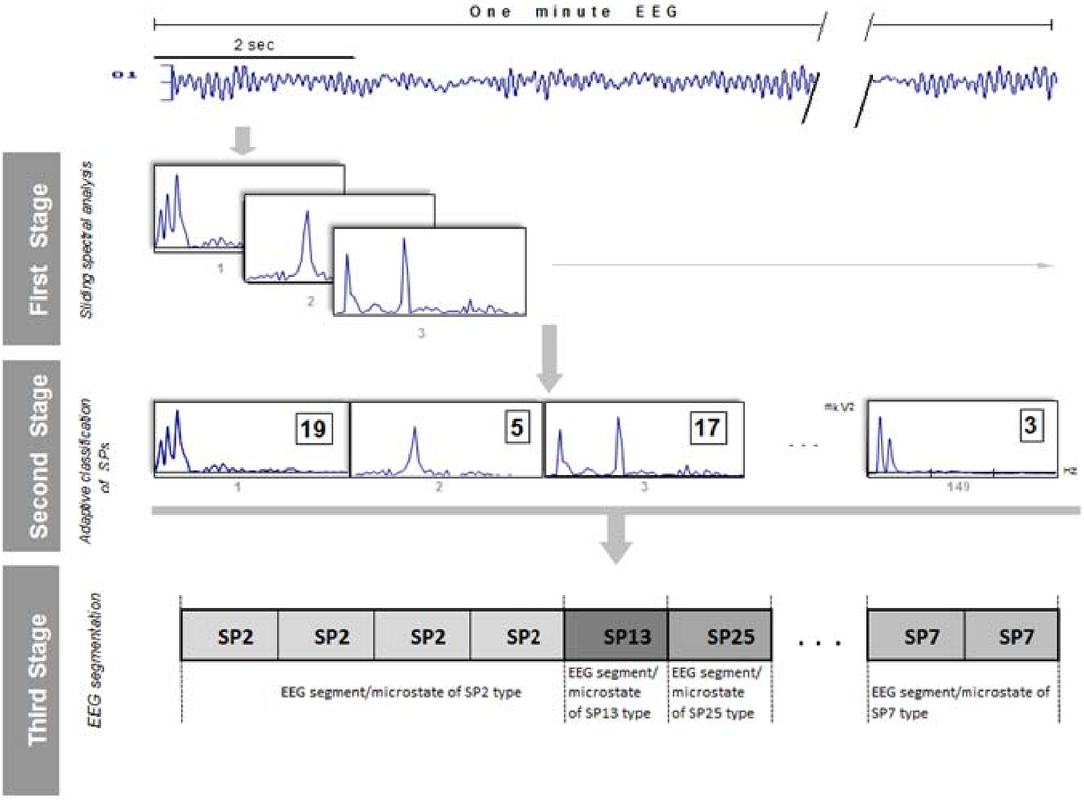


Figure 2. The scheme of data processing. *First stage*: A sliding spectral analysis was conducted separately for each subject and each one-min EEG channel. O1 = Left occipital EEG channel. *Second stage:* An adaptive classification of short-term spectral patterns (SP) was performed separately for each subject and each one-min EEG channel. The small gray numbers under each SP represent the running numbers from 1 to 149 for a one-min EEG. The number in the square represents the class to which a given SP was assigned during classification procedure. *Third stage*: Segmentation of EEG signal was performed based on SP type changes. The moment of change of SP-segment type marked a change in EEG oscillatory microstate.

After calculation of EEG short-term SPs, the total number of individual SPs for each one-min EEG channel was 149 (Fig. 2).

During the second stage, with the help of a probability-classification analysis of the short-term EEG SPs (see Fingelkurts et al., 2003a and Appendix in Fingelkurts & Fingelkurts, 2010b), each SP was labelled according to the class index it belongs to. Sequential single EEG SPs were adaptively classified in each one-min EEG channel using a set of standard SPs which were generated automatically from the EEG data itself (*first step*). The selection was not arbitrary: a pool of SPs (n = 685 102) was collated from all the SPs for all the EEG signals (all locations) for all subjects (healthy subjects and 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 normalizing 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., 2003a; Appendix in Fingelkurts & Fingelkurts, 2010b), each current SP was labelled according to the index of the class to which it belonged.

During the third stage, the EEG signal was segmented (Fig. 2) based on SP type changes. A single EEG spectrum illustrates the particular integral dynamics of tens and hundreds of thousands of neurons in a given cortical area at a particular point in time (Dumermuth & Molinari, 1987). Therefore, the absence of variance of a single SP type during several analyzed epochs proves that in a given cortical area the same macro-regimen of neuronal pool activity is maintained throughout that period. Thus, periods of several consecutive EEG epochs which are characterized by the same SP type comprise an SP-segment – EEG segment of quasi-stationary oscillatory activity or EEG oscillatory microstate. The moment of change of the type of SP-segment marks a transition in EEG oscillatory microstate (see argumentation given in section 1.2.). In such a way the sequence of EEG oscillatory states (indexed by SP types) through which the brain passes was obtained for each channel separately (Fig. 2). Notice that during the same time observation (2 sec) different EEG channels were characterised usually by different SP types.

In order to study the parameters of dynamic repertoire of EEG microstates as a function of consciousness expression, the analytic model for neural constitutes of consciousness (Fig. 1) was used. According to this model the parameters of dynamic repertoire of EEG microstates which are associated with subjective awareness of self and environment should satisfy the following rule: NORM ≥ MCS > VS, whereas the features of EEG which are associated with subjective unawareness of self and environment should satisfy the opposite rule: NORM ≤ MCS < VS.

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 NORM, MCS and VS. To control for repeated observations of the same measures a Bonferroni correction was made. $p_{\text{corrected}}$ 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.

Surrogate data were used to control for the neural origin of temporal dynamics of SPs, which is commonly applied as direct probing for a signal of a non-random temporal structure (Ivanov et al., 1996). Surrogate signals have identical parameters with original signals but do not have temporal correlations. Thus, each channel of the actual EEG was subjected to a randomized mixing of SPs. In such a way, the natural dynamics of the SP sequence within each EEG channel was completely destroyed, but the percentage ratio between different types of SPs was retained. This modified EEG was described as “random”.

3. Results

3.1. Demographical data

There were no significant differences between patients and healthy participants in terms of age ($p = 0.28$). 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 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) (Table 1).

3.2. The number of SPs types (EEG oscillatory microstates) in healthy subjects and patients with disorders of consciousness

Analysis revealed that the number of SP types in patients with disorders of consciousness was significantly reduced ($p_{\text{corrected}} < 0.00004$) in comparison with healthy subjects (Table 2). There was almost a 50% reduction in the number of EEG oscillatory microstates.

Table 2. The number of EEG microstates indexed by spectral pattern's types.

EEG channel	N	MCS	VS
O1	24	15	15
O2	19	15	15
P3	26	16	15
P4	19	15	14
Pz	24	15	15
T5	27	14	15
T6	23	13	15
C3	24	14	14
C4	24	12	14
Cz	24	14	14
T3	28	11	14
T4	24	12	14
F3	21	12	15
F4	25	12	15
Fz	25	10	14
F7	26	11	14
F8	27	11	14
Fp1	24	11	12
Fp2	23	10	13
Mean	24.1	12.8	14.3
St.Dev.	2.4	1.9	0.8

N = Norm (healthy subjects), MCS = minimally conscious state
VS = vegetative state, St.Dev. = standard deviation

3.3. Types of EEG oscillations associated with consciousness and unconsciousness

To reveal which of EEG oscillations within a broad frequency range (1–30 Hz) are associated with expression of consciousness, we examined the probability of the occurrence of SP types (EEG microstates) in the following order NORM ≥ MCS > VS (for consciousness) and NORM ≤ MCS < VS (for unconsciousness) according to the analytic model for neural constitutes of consciousness (see section 1.3.).

This analysis revealed that patients with disorders of consciousness (MCS and VS) were characterized by the lack of alpha-rhythmic SP types, whereas rich variety of alpha-rhythmic SP types was present in healthy subjects (NORM) (Table 3). Thus, the number of alpha-rhythmic SP types went from 100% (for NORM) to 37% (in MCS) and declined to 26% (in VS), thus the variety of alpha-rhythmic SP types followed the proportion NORM ≥ MCS > VS ($p_{\text{corrected}} < 0.00001$). Note that VS patients lost all SPs with fast-alpha components.

Table 3. Alpha-rhythmic SPs (sub-repertoire of SPs from total repertoire presented in Table 2)

SP type	Frequencies of the main peaks	Norm	MCS	VS
SP11	8Hz	+	+	+
SP12	9.5Hz	+	-	-
SP13	11Hz	+	-	-
SP14	12.5Hz	+	-	-
SP15	2.5 and 7.5 Hz	+	+	+
SP16	2.5 and 8.5Hz	+	+	+
SP17	3 and 10Hz	+	-	-
SP18	3 and 12Hz	+	-	-
SP19	4 and 8Hz	+	+	+
SP20	4.5 and 9Hz	+	-	-
SP21	7 and 12.5Hz	+	-	-
SP22	8 and 9Hz	+	+	+
SP23	8.5 and 11.5Hz	+	-	-
SP24	2, 4 and 10.5Hz	+	+	-
SP25	2, 5.5 and 10Hz	+	-	-
SP26	3, 5 and 9Hz	+	+	-
SP27	4, 9 and 10.5Hz	+	-	-
SP28	4.5, 7.5 and 11.5Hz	+	-	-
SP29	9, 10 and 19.5Hz	+	-	-
Sum of presented SP types		19	7	5

"+" - given SP type is present
"-" - given SP type is absent
Norm - healthy subjects
MCS - patients in minimally conscious state
VS - patients in vegetative state

Another finding was that the probability for the occurrence of delta-, theta-, delta–theta-, delta–slow-alpha, theta–slow-alpha- and slow-alpha- rhythmic SP types followed the proportion NORM $\leq$ MCS $<$ VS ($p_{\text{corrected}} < 0.05 - p_{\text{corrected}} < 0.000001$) and the probability for the occurrence of SPs with fast-alpha-rhythmic components followed the proportion NORM $\geq$ MCS $>$ VS ($p_{\text{corrected}} < 0.0001 - p_{\text{corrected}} < 0.000001$) (Table 4).

Table 4. Spectral pattern types which demonstrated statistically significant (*Pcorrected* < 0.05–*Pcorrected* < 0.000001) difference in relative presence in probability-classification profile between minimally conscious state (MCS), vegetative state (VS) and norm (N), satisfying "Consciousness Model": N≤MCS<VS and/or N≥MCS>VS. Data averaged across 87 EEGs for MCS, 137 EEGs for VS and across 18 EEGs for N. Only SP types which demonstrated statistically significant differences in their presence between MCS, VS and N in more than 1 EEG channel from 19 are considered*.

EEG rhythm(s)	Delta	Theta2	Theta3	Theta1_Theta3	Delta_Theta1_Theta3	Slow-Alpha	Delta_Slow-Alpha	Delta_Slow-Alpha	Delta_Theta1_Fast-Alpha	Theta1_Theta2_Fast-Alpha
Frequencies of the main peaks (Hz)	2	5	6.5	3 and 6	2, 4 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**	**SP7**	**SP11**	**SP15**	**SP16**	**SP24**	**SP26**
N ≤ MCS < VS	x	X	x	x	X	X	X	X		
N ≥ MCS > VS									X	X
EEG channels %	31.6	15.8	79	68.4	10.5	21	37	10.5	10.5	10.5

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; Slow-Alpha: 7.5-8.5 Hz; Fast-Alpha: 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 x 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 result 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 Section 5.2.

Table 5 gives the overall proportion of delta-, theta- and alpha-rhythmic SPs for anterior and posterior areas of the cortex. It can be seen that EEGs of healthy subjects (NORM) was dominated by alpha-rhythmic SPs types, whereas EEGs of patients with disorders of consciousness was dominated by delta- and theta-rhythmic SPs types (VS > MCS, Table 5).

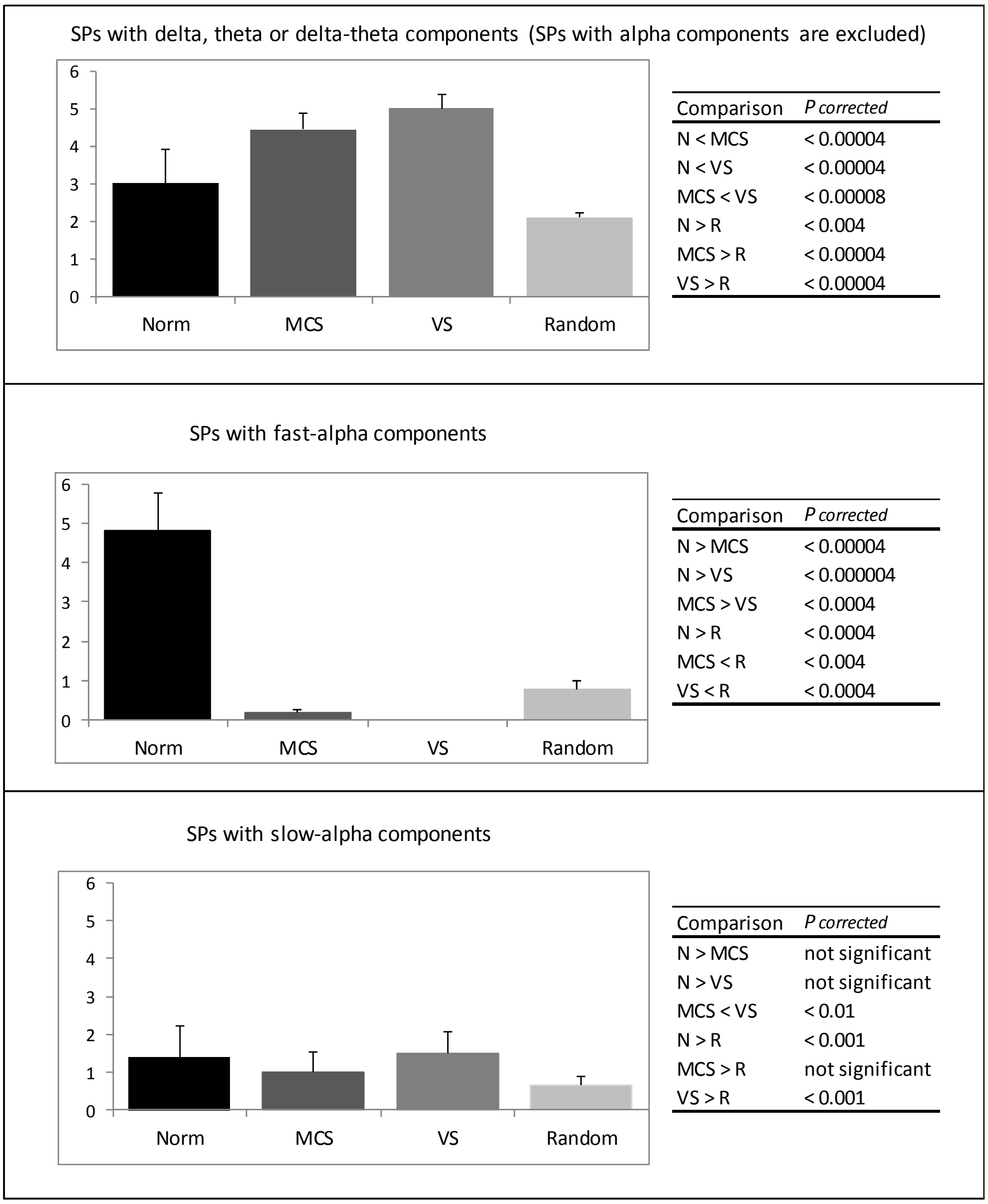
Table 5. Amount (in %) of one-min EEG which is characterised by delta-, theta- or alpha-rhythmic SPs for anterior and posterior areas. Data averaged across all subjects/patients within groups and across O1, O2, P3, P4, and Pz channels (for posterior areas) and across F3, F4, Fz, F7, F8, Fp1, and Fp2 channels (for anterior areas). Data presented as mean ± st.d.

	Posterior				Anterior			
	Delta %	Theta %	Slow Alpha %	Fast Alpha %	Delta %	Theta %	Slow Alpha %	Fast Alpha %
NORM	12.2 ± 3.5	9.4 ± 2.6	1.6 ± 1.5	79 ± 4.0	30.4 ± 6.8	18.9 ± 4.1	2.1 ± 0.8	49.4 ± 7.3
MCS	49.4 ± 1.0	42.8 ± 0.4	5 ± 0.6	2.4 ± 0.5	54.1 ± 1.1	44 ± 1.6	3.4 ± 2.9	0 ± 0.0
VS	53.4 ± 1.4	44 ± 2.8	6.6 ± 0.5	0 ± 0.0	54.2 ± 2.3	45.3 ± 2.3	4.3 ± 1.3	0 ± 0.0

Delta - a sum of the % of delta-rhythmic SPs and SPs with delta components (SPs with alpha components are excluded);
Theta - a sum of the % of theta-rhythmic SPs and SPs with theta components; (SPs with alpha components are excluded);
Slow alpha - a sum of the % of slow-alpha-rhythmic SPs and SPs with slow-alpha components;
Fast alpha - a sum of the % of fast-alpha-rhythmic SPs and SPs with fast-alpha components;
Norm - healthy subjects; MCS - patients in minimally conscious state; VS - patients in vegetative state

3.4. Maximum length of SPs temporal stabilization periods (maximum duration of EEG oscillatory microstates) in local EEGs

Maximum length of SPs temporal stabilization periods was evaluated by computing the maximum number (separately for each EEG channel) of successive *m* EEG epochs of the same SP type, where *m* ranges from 1 to 149, and was then described as a "block". In this case a particular block length reflects the specific period of temporal stabilization of brain oscillations – the EEG oscillatory microstate. The results of this analysis are summarized in Figure 3.



Comparison	*P corrected*
N < MCS	< 0.00004
N < VS	< 0.00004
MCS < VS	< 0.00008
N > R	< 0.004
MCS > R	< 0.00004
VS > R	< 0.00004

Comparison	*P corrected*
N > MCS	< 0.00004
N > VS	< 0.000004
MCS > VS	< 0.0004
N > R	< 0.0004
MCS < R	< 0.004
VS < R	< 0.0004

Comparison	*P corrected*
N > MCS	not significant
N > VS	not significant
MCS < VS	< 0.01
N > R	< 0.001
MCS > R	not significant
VS > R	< 0.001

Figure 3. Maximum length (in arbitrary units) of the period of temporal stabilization of SPs. Data averaged across all subjects, all EEG channels and different types of SPs. Arbitrary units are expressed in terms of block length – *m* EEG epochs follow in succession without SP type change, where *m* is the range from 1 to 149. SP = spectral patterns, Norm = healthy subjects, MCS = patients in minimally conscious

state, VS = patients in vegetative state, Random = EEG whose natural sequence of SP types has been completely removed by a randomized mixing of SPs in each individual channel, but the percentage ratio between different types of SPs remained unchanged.

It can be seen that the brain "maintains" longer stabilization periods of delta and/or theta neural activity for patients with disorders of consciousness when compared to healthy subjects following the order NORM ≤ MCS < VS ($p_{\text{corrected}} < 0.00008 - p_{\text{corrected}} < 0.00004$). At the same time, periods of temporal stabilization for fast-alpha-rhythmic SPs and SPs with fast-alpha components in healthy subjects were longer than in patients with disorders of consciousness following the order NORM ≥ MCS > VS ($p_{\text{corrected}} < 0.0004 - p_{\text{corrected}} < 0.000004$). Stabilization periods for SPs with slow-alpha components were not consistent with used analytical model (Fig. 3).

However, it is obvious that even in the absence of any correlation between the EEG SPs, there should be a temporary stochastic stabilization of the SPs, which may reflect merely occasional combinations of SP types. As control for the neural origin of temporal dynamics of SPs, "random" EEG (an EEG with a random mix of different SP types for each separate channel) was used. From Figure 3, it can be seen that temporal characteristics in the actual EEG data substantially differed from those of the "random EEG" ($p_{\text{corrected}} < 0.001 - p_{\text{corrected}} < 0.00004$). Note that periods of temporal stabilization for alpha-rhythmic SPs or SPs with alpha components in patients with disorders of consciousness were even shorter than those expected by chance.

4. Discussion

4.1. Demographic factors

Since there were no significant differences between the MCS and VS groups in terms of age and time following brain injury, distribution of TBI and non-TBI aetiologies, left- and right-side lesions, as well as the distribution of medicated *vs* non-medicated patients; all of these factors could not be responsible for the differences in EEG parameters found between MCS and VS groups. The absence of significant difference in age between healthy subjects (NORM) and both (MCS and VS) patient groups suggested that the observed differences between healthy subjects and patients could not be attributed to age.

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. Repertoire of EEG oscillatory microstates in relation to expression of consciousness

As it was predicted, patients with disorders of consciousness were characterized by considerably reduced repertoire of EEG oscillatory states (indexed by SP types) in comparison to healthy and fully conscious subjects. This may suggest that the unconscious state (as in VS patients) and altered states of consciousness (as in MCS patients) are more ordered and so are expected to have lower entropy with fewer microstates available to the cortex than in a fully conscious state (as in healthy subjects)[4]. This supposition is in line with the prediction of Tononi (Tononi & Edelman, 1998, Tononi & Laureys, 2008) according to which each conscious experience constitutes discrimination among a large repertoire of alternative states. Therefore, the fewer alternatives one can rule out, the less informative one’s conscious experience is. This prediction of a reduction in cortical entropy when minimally conscious or unconscious is consistent with our findings and the work of Flohr (1991) and Steyn-Ross et al. (2004) who demonstrated narrowing in the repertoire of EEG microstates during the phase of loss of consciousness in anaesthesia[5].

The oscillatory activity of neuronal pools, reflected in characteristic EEG rhythms, constitutes a mechanism by which the brain can regulate state changes in selected neuronal networks that lead to a qualitative transition between modes of information processing (Lopes Da Silva, 1996). Therefore, a reduced repertoire of EEG oscillatory states in patients with disorders of consciousness signifies a decrease in the number of information processing modes.

Observation that the reduction in the overall number of EEG oscillatory states did not follow the proportion NORM ≥ MCS > VS suggests that this index is sensitive to the alteration of consciousness but it is not proportional to the expression of consciousness. At the same time, the number of alpha-rhythmic oscillatory states or EEG oscillatory states with alpha-rhythmic components decreased (up to 74%) in the following proportion NORM ≥ MCS > VS suggesting

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[4] This form of explanation is consistent with functionalism as it does not attach itself to a specific neural process or location, but rather considers the overall dynamic or ‘‘functional” properties of such system as the brain.

[5] However, in their studies it was not possible to separate unconsciousness from a decreased level of vigilance.

that the sub-repertoire of EEG microstates (*fast-alpha-rhythmic oscillatory type*) is related in a quantitative manner to the level of consciousness expression.

4.3. Oscillatory type of EEG microstates in relation to expression of consciousness

Using the analytic model for neural constitutes of consciousness (see section 1.3.) and detailed analysis of the types of EEG oscillatory microstates (indexed by SP types) it was demonstrated that (a) only those EEG microstates which were characterized by *fast-alpha* oscillations were associated with consciousness: the probability of their occurrence followed a proportion of NORM ≥ MCS > VS, whereas (b) EEG microstates which were characterized mostly by *delta* and/or *theta* or *slow-alpha* oscillations were associated with unawareness: the probability of their occurrence was reversed NORM ≤ MCS < VS.

Such a distinction between alpha- and delta-theta- oscillatory types of EEG microstates in relation to the expression of consciousness is not surprising. Nowadays a large body of knowledge has accumulated on functional significance of EEG oscillations (for the review see Fingelkurts & Fingelkurts, 2010a; see also ref. list of this article). This field of cognitive neuroscience research is attempting to identify how EEG oscillations map onto mental states and/or behaviour states (Gazzaniga et al., 2002) and so far has revealed the following functional significance of EEG oscillations:

Delta oscillatory type of EEG microstates

The observed number of EEG delta-rhythmic microstates in this study was associated with unawareness: NORM (fully fledged consciousness) ≤ MCS (minimally expressed consciousness) < VS (unawareness). Generally, it was already demonstrated that a slowing of EEG background activity is associated with alterations of consciousness, stupor and coma (Brenner, 2005). Administration of different type of anaesthetics (Thiopental, Propofol, Etomidate, Sevoflurane, Ketamine) resulted in considerable increase in delta activity during the moment of loss of consciousness or shortly after it (Clark & Rosner, 1973; Engelhardt et al., 1994; Sleigh & Galletly, 1997; Gugino et al., 2001; Kuizenga et al., 2001).

Additionally, delta activity is expected to be sensitive to internal stimuli signalling danger to survival (such as hypoxia, hypoglycemia, fatigue, sustained pain), as well as to the stimuli signalling a need for sexual activity (e.g. the level of sex hormones) (Mosovich & Tallaferro, 1954; Heath, 1972; Tallroth et al., 1990; Hoffman & Polich, 1998). Thus, delta oscillations are associated with states oriented to the acquisition of *biologically* important goals such as physical maintenance, survival, dominance and mating (Knyazev, 2006, 2007). The organism does *not* need to have any awareness of these processes. Therefore it is not surprising that delta activity which is associated with these biological needs is dominating the EEG of VS patients and to a lesser extend of MCS patients.

Besides physiological functions, delta activity participates in mediation of *automatic* cognitive functions which may well be present in VS and MCS patients. On the one hand, it was demonstrated that delta activity is related to information detection (Başar-Eroglu et al., 1992). On the other hand, one- to two-thirds of patients in VS were capable of cortical differentiation of physical stimulus features and that at least 20% of these patients differentiated semantic stimuli (Kotchoubey et al., 2002). Studies generally showed that unconscious stimuli still evoke local feature activity in the sensory cortex (Baars, 2002). Some aspects of semantic processing may also occur without conscious awareness. Thus, imaging studies in healthy controls have shown that the semantic content of masked (unconscious) information can be primed to affect subsequent behaviour without explicit knowledge of the participant (Dehaene et al., 1998). These data suggest passive 'automatic' processing (which is occurring without conscious registration on the part of the subject) rather than demonstrating preserved awareness.

Theta oscillatory type of EEG microstates

As for EEG delta-rhythmic microstates, the number of EEG theta-rhythmic microstates was also associated with unawareness in this study: NORM (fully fledged consciousness) ≤ MCS (minimally expressed consciousness) < VS (unawareness). This is in line with the finding that with EEG slowing there is an associated decrease in mentation recall (Pivik & Foulkes, 1968). Additionally, administration of different type of anaesthetics (Thiopental, Propofol, Etomidate, Sevoflurane, Ketamine) demonstrated considerable increase in theta activity during the moment of loss of consciousness or shortly after it (Clark & Rosner, 1973; Engelhardt et al., 1994; Sleigh & Galletly, 1997; Gugino et al., 2001; Kuizenga et al., 2001).

Theta oscillations in resting conditions are expected to be associated with *emotional* regulation. Indeed, during emotional arousal, neurons in the amygdala produce theta activity (Pare & Collins, 2000; Aftanas et al., 2003; Sachs et al., 2004). The hippocampal theta in humans is involved in discrimination of emotional stimuli (Aftanas et al., 2001). Vinogradova (1995) suggested that theta activity may serve a gating function on the flow of information processing in limbic regions.

Additionally, synchronization at theta frequencies is suggested to represent activity in amygdalo-hippocampal pathways associated with consolidation of fear memory, which is supported by the cholinergic system (Pape et al., 2005). Gray (1982) and McNaughton and Gray (2000) considered the hippocampal theta as a manifestation of activity of the so-called Behavioural Inhibition System (BIS), which, according to Gray, underlies human anxiety.

However, emotional regulation does *not* need conscious awareness. Indeed, neuroscientific evidence indicates that raw emotional states (primary-process affects) can exist without any cognitive awareness (Panksepp et al., 2007). Therefore, one cannot deny the existence of unconscious emotional states in VS and MCS patients.

Alpha oscillatory type of EEG microstates

The observed association of EEG fast-alpha-rhythmic microstates with consciousness (NORM (fully fledged consciousness) ≥ MCS (minimally expressed consciousness) > VS (unawareness)) in this study is consistent with numerous diverse but complementary studies that reported significance of alpha activity for consciousness[6].

Indeed, it was demonstrated that alpha oscillations, which dominate the EEG of an adult human (Knyazev & Slobodskaya, 2003), are (a) involved in the organization of conscious interactions with the environment (Knyazev, 2007), (b) correlated with conscious awareness (Babiloni et al., 2006) and long-term semantic memory processes (Klimesch, 1996), and (c) highly correlated with mind wondering and spontaneous self-referential thoughts (Shaw, 2003). It seems that alpha activity (especially fast alpha) coordinates top-down control for cortical traces of discrete representations that are to be combined with associated semantic representations within the first-person perspective.

This supposition is supported by several lines of evidences:

(a) Rusalova (2006) demonstrated that decrease in thought process was accompanied by slowing and increasing irregularity of alpha rhythm. Thus, a state of increased spontaneous associations with thought having a logical nature was characterised by an increase in the power and regularity of the alpha rhythm. Whereas the state of thought process disintegration was characterised by slowing and irregularity of the alpha rhythm. Finally,

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[6] One may argue that there is such phenomenon as “alpha coma” (Austin et al., 1988), where alpha activity is present but consciousness is absent. At the first sight this fact does not support the supposition that alpha rhythm is important for consciousness. However, close inspection and comparison of the coma’s alpha characteristics to physiologic alpha rhythm revealed a number of significant differences: (a) the coma’s alpha differs in appearance from physiologic alpha rhythm (normal background activity) in its lack of reactivity and its spatial distribution (Westmoreland et al., 1975); (b) important differences were observed between the alpha activity in patient during the coma and alpha activity recorded before or after the coma in the same patient (Iragui & McCutchen, 1983); (c) “alpha coma” has also been reported in three children of 2, 22 and 30 months of age though a posterior dominant rhythm in the alpha range is non-existent in these age groups (Yamada et al., 1979; Collins & Chatrian, 1980; Homan & Jones, 1981); (d) alpha dimensionality in alpha coma differed from that of normal alpha (Kim et al., 1996). Thus, all these observations suggest that the alpha activity in comatose patients is an abnormally generated pattern different from the physiologic alpha rhythm.

the state of thought temporary ceasing (however with conscious awareness) was associated with minimum alpha activity (Rusalova, 2006).

(b) Kondrat'eva (2004) found that the appearance of alpha activity in EEGs of VS patients undergoing benzodiazepine therapy was associated with transition of these patients to a minimally conscious state.

(c) Babiloni with co-workers (2009) reported that parietal and occipital source power of alpha rhythm was high in normal subjects, intermediate in MCS patients, and practically non-existent in VS patients.

Additionally, ontogenetic (individual) and phylogenetic (evolutionary) data offer indirect evidences on the significance of alpha activity for consciousness. Indeed, human children younger than 3 years are unable to produce higher cognitive processes and a full-fledged self-consciousness, they also do not show alpha activity (Başar & Güntekin, 2009, see also Praetorius, 2009). From an evolutionary perspective, the alpha band appeared only in primates (humans included), who are geared with a cortical mantle (Knyazev, 2007). The strongest expression of alpha activity is reached in humans who are at the same time carriers of a full-fledged consciousness of self and the environment (Knyazev & Slobodskaya, 2003). The brain of lower mammals produces predominantly theta oscillations (Klimesch, 1999), while the reptiles' brain activity is characterised by oscillations mostly in the delta range (Gaztelu et al., 1991). Neither one of these species can be assigned with phenomenal consciousness.

Considering that slow-alpha oscillations represent the activity in the thalamo-cortical network and fast-alpha oscillations reflect the activity in the cortical networks (Lopes da Silva et al., 1980; Klimesch, 1996), the present study's observation that the number and duration of exclusively *fast*-alpha-rhythmic microstates were associated with the expression of consciousness suggests that the activity in the cortical networks is necessary for consciousness expression. It seems that the thalamo-cortical network does not share the same significance (for the opposite view see Laureys et al., 2002). This supposition is supported by the fact that cortical electrical activity changes dramatically during loss of consciousness (using either propofol or sevoflurane), whereas changes in the thalamus activity were minimal (Boveroux et al., 2008), implying that for consciousness the activity in the cortical networks seems more important than the thalamic activity.

Additionally, experimental findings suggest that long-term (semantic) memory demands are associated with *fast*-alpha oscillations (Klimesch, 1996, 1997, 1999). Semantic memory processes make up a considerable part of the human consciousness (Knyazev & Slobodskaya, 2003).

Finally, it was demonstrated that administration of different type of anaesthetics (Thiopental, Propofol, Etomidate, Sevoflurane, Ketamine) resulted in a considerable decrease in mostly *fast*-alpha activity during the moment of loss of consciousness or shortly after it (Clark & Rosner, 1973; Engelhardt et al., 1994; Sleigh & Galletly, 1997; Gugino et al., 2001; Kuizenga et al., 2001). The emergence from unconsciousness was characterized by the opposite EEG effect.

One may wonder why VS and MCS patients have any alpha-rhythmic SPs at all and why some slow-alpha-rhythmic SPs followed the proportion NORM ≤ MCS < VS. First of all, alpha activity was not dominant (when compared with delta and theta oscillations) in VS and MCS patients in comparison to NORM. Indeed, alpha-rhythmic SPs taken together characterised from 80.6% ± 3 (in posterior areas) to 51.5% ± 4.1 (in anterior areas) of one-min EEG in NORM, whereas these values decreased considerably to an average of 7% ± 0.5 and 3.7% ± 1.1 respectively in patients with disorders of consciousness. Secondly, only three slow-alpha-rhythmic SPs (SP11, SP15, SP16) from 19 alpha-rhythmic SPs followed the proportion NORM ≤ MCS < VS and taken together these SPs characterised only 5.9% ± 1.6 (averaged across all EEG electrodes) of VS one-min EEGs, 3.1% ± 1.4 of MCS one-min EEGs, and 2.7% ± 2 of NORM one-min EEGs. It is clear that these variants of slow alpha activity are residual and probably represent different type of alpha activity – hippocampal – which is usually observed during unconscious states and reflects irritation of the limbic structures (Boldireva et al., 1995; Sharova et al., 1995).

To summarise, EEG *fast*-alpha-rhythmic microstates are *necessary* for a full fledged consciousness and may be considered a *minimally sufficient* neural condition for a consciousness to be expressed.

Based on this observation of the obtained results in light of reported functional significance of EEG oscillations, one may speculate that biological needs, passive 'automatic' processing, unconscious emotional regulation and fear memory consolidation decrease in the direction NORM ≤ MCS < VS. However, semantic memory processes and the expression of consciousness decrease in the opposite direction NORM ≥ MCS > VS; perhaps in proportion to the presence of delta, theta and fast-alpha EEG oscillations. In this sense VS and MCS differ from one another by varying amounts of delta, theta and fast-alpha oscillatory states which are combined temporally (and spatially) in a "mosaic" way. Thus VS is skewed towards functions which are invariant and necessary only for the acquisition of biologically important goals such as physical maintenance, survival, and unconscious emotional regulation (delta and theta oscillatory states). Whereas MCS already involves rare discrete states of conscious interactions with the environment (fast-alpha oscillatory states). This may explain clinically observed fluctuating (discrete) realizations of consciousness in MCS patients. However, more studies are needed to clarify the proposed relationship.

4.4. Duration of EEG oscillatory microstates in relation to the expression of consciousness

Duration of EEG oscillatory microstates (indexed by the maximum lifetime of each SP type) in relation to the expression of consciousness depended on the type of dominant frequency. Thus, duration of mostly fast-alpha-rhythmic microstates decreased significantly alongside a reduction in consciousness expression (NORM > MCS > VS), whereas duration of mostly delta- and/or theta-rhythmic microstates increased as the expression of consciousness decreased (NORM ≤ MCS < VS).

Such a distinction between fast-alpha-rhythmic and delta- and/or theta- rhythmic EEG microstates in relation to consciousness expression is consistent with the observations presented above. Thus, EEG fast-alpha-rhythmic microstates which were associated with consciousness tended to “live” longer in accordance with consciousness expression. Whereas unawareness was associated with longer EEG delta- and/or theta- rhythmic microstates.

Perhaps, differential increase in temporal stabilization periods of various EEG microstates indicates the brain’s capability to maintain either operations and processes which support consciousness, or operations and processes which underline *un*consciousness (mental domain which is not accessible to awareness) or *non*consciousness (physiological domain).

Therefore, it seems that having an appropriate EEG oscillatory type is not sufficient for the consciousness to be expressed. This type of EEG oscillatory activity should also be of appropriate *duration*, what supports the suggestion made in the Introduction (section 1.1.) (see also overview in Fingelkurts et al., 2010).

5. Concluding discussion, clinical significance and methodological limitations

5.1. Concluding discussion

In the present study we have found converging evidences for our hypothesis that the number and duration of particular oscillatory types of EEG microstates in non- and minimally communicative patients with severe brain injuries and in healthy subjects are proportional to the *degree of expression of clinical self-consciousness* measured by the LCF scale. Specifically, we demonstrated that (a) patients with disorders of consciousness were characterized by a considerably reduced repertoire of EEG oscillatory states (indexed by SP types) in comparison to healthy fully conscious subjects and (b) the number and duration of mostly fast-alpha-rhythmic microstates decreased significantly alongside a reduction in consciousness expression (NORM > MCS > VS), whereas the number and duration of mostly delta- and/or theta- rhythmic microstates increased significantly as the expression of consciousness decreased (NORM ≤ MCS < VS).

When taken together, the analysis of the different indices presented in this study show various (but converging) aspects of information content reduction in the EEG signal of patients with disorders of consciousness (MCS < VS). As the brain's ability to generate complex electrophysiologic activity is diminished, leading to a reduction in the entropy of EEG signals, the expression of consciousness is impaired.

Prevalence of mostly delta- and/or theta- rhythmic microstates which is observed in patients with disorders of consciousness (MCS < VS) may reflect disinhibition of evolutionary older systems which regulate behaviour based mostly on internal motivational and emotional drives (Knyazev & Slobodskaya, 2003). Whereas the dominance of diverse EEG alpha-rhythmic microstates (and especially fast-alpha-rhythmic) was associated with full fledged consciousness.

Integration of the results in the present study may suggest that a significant decrease in the number and duration of alpha-rhythmic states would result in a situation where the raw sensory stimulation coming from inside and outside of the organism would dominate without being properly integrated in context of a personally meaningful narrative. One would then be very much the victim of his/her environment; things would just happen to such a subject all the time, exactly as in the VS and, to a lesser degree, in the MCS brain-damaged patients.

At the same time VS patients may still have experiences associated with cognitive operations executed without self-consciousness; so-called returning to a rigid stimulus-response behaviour of lower animal species (Kinsbourne, 2005). This supposition is consistent with the results of EEG event-related potential (Neumann & Kotchoubey, 2004; Kotchoubey, 2005; Perrin et al., 2006) and fMRI/PET (Laureys et al., 2002; Boly et al., 2004) studies which indicated that external stimulation of VS patients still induced significant and consistent neuronal responses. It has been suggested that such simple responses are autonomic and unconscious (Schönle & Schwall, 1993; Schoenle & Witzke, 2004), because experimentally unconscious stimuli could evoke local event-related potentials (Kihlstrom, 1987; Brazdil et al., 2001; Yingling, 2001; Baars, 2002) or even demonstrate unconscious perception of word meaning (Naccache & Dehaene, 2001). Therefore such neuronal responses in VS patients could represent only isolated cerebral functional modes (Kinney & Samuels, 1994; Schiff & Plum, 1999; Schiff et al., 2002), which are not associated with awareness (Kobylarz & Schiff, 2004).

In summary, our results suggest that the number, duration and the oscillatory type of EEG microstates in resting condition with closed eyes could be related in a quantitative manner to the level of consciousness expression in severely brain-damaged patients and healthy conscious subjects. Therefore we may conclude that EEG oscillatory microstates constitute a neuro-phenomenology of consciousness.

5.2. Clinical significance

From the *clinical point of view,* one potential importance of such EEG study concerns the fact that *resting state* EEG enables clinicians to assess directly and objectively spontaneous brain activity at each level of vigilance and in any state of consciousness without requiring the collaboration from the patients' part. This fact is particularly important in non- and minimally communicative patients with severe brain injuries (Vanhaudenhuyse et al., 2010). Additionally, resting state EEG is especially suitable for examining states of consciousness due to (a) neurological evidence which suggested independence of consciousness from specialized cognitive processes like episodic memory, language, introspection or reflection, sense of space, sense of body, sense of self, or sensorimotor processing, or attention (Tononi & Laureys, 2008; Boly et al., 2009), and (b) observation that spontaneous activity characteristic for resting state seems more self-relevant than standard cognitive tasks, which typically activate a number of cognitive processes and drive subjects to direct their attention away from their personal concerns (Baars et al., 2003).

The present study suggests that disentangling normal states of consciousness from altered states and from states without consciousness based solely on EEG recording is possible on a group level. This means that particular EEG measures can now identify some signs of awareness which are inaccessible to those using a clinical examination and may lead to a better understanding of the mechanisms of human consciousness as well as improving care of MCS and VS patients. However, until this experimental analysis is implemented in clinical practice much more work has to be done.

To our knowledge this is the first study demonstrating that EEG oscillatory microstates may be useful in quantifying the expression of consciousness in MCS and VS patients. Even though some studies have shown that EEG could be useful in defining different states of altered consciousness, none have utilized microstate EEG analysis. Generally routine EEG analysis does not produce consistent and reproducible results when trying to distinguish VS and MCS patients (Royal College of Physicians, 2003; Wijdicks & Cranford, 2005, just to mention a few). We believe that this, in part, is due to methodological limitations of standard methods used in EEG analysis (for a detailed methodological discussion see Fingelkurts & Fingelkurts, 2010a); such limitations are overcome in EEG oscillatory microstate analysis used in the present study.

fMRI or PET techniques widely used to study patients with severe brain injuries present a significant challenge since complex brain injuries result in distortions of normal neuroanatomy secondary to atrophy and loss of both grey and white matter structures (Sakatani et al., 2003). As a result, the brains of such patients often cannot be mapped accurately onto available reference atlases (Brett et al., 2001). On the contrary, EEG studies are less problematic in this respect, because local EEGs represent so-called 'functional sources', which are defined as part or parts of the brain that contribute to the activity recorded at a single sensor and are neutral with respect to the problems of localization of primary source and volume conduction (Stam, 2005; Wackermann & Allefeld, 2007). Furthermore, if the influence of volume conduction on the SP predominated, then one should expect the same type of SP occurring over the whole cortex (or its bigger parts) during the same observation time. However, analysis of the composition of EEG short-term SPs in different EEG channels demonstrated that each EEG channel or small group of channels has its own SP set (see also Fingelkurts et al., 2003a). Additionally, analysis of EEG short-term SP types in different EEG channels (during one minute) within the same observation (2 sec) revealed that the same type of SP can be observed simultaneously in two EEG channels in 70% of observations (notice that in the majority of cases these were homologous EEG channels: for example O1-O2) (Fingelkurts & Fingelkurts, 2010a). The simultaneous appearance of an identical SP type in three EEG channels was observed only in 36% of observations. For four EEG channels this value dropped significantly to 16%. For five, six and seven EEG channels the value was very small: all below 5%. The situation where eight EEG channels were characterized by the same type of SP was not observed at all. These results had very high within-subject test-retest (1-2 week intervals) reliability (R = 0.98-0.99, Spearman rank correlations test) (Fingelkurts & Fingelkurts, 2010a). Therefore, local EEG short-term SPs are mainly determined by an underlying neurodynamic and similarity of SPs reflects morpho-functional organization of the cortex rather than the effect of volume conduction (for a detailed discussion on volume conduction see Fingelkurts & Fingelkurts, 2010a). Considering the aforementioned findings one may suggest the existence of statistical heterogeneity in the electromagnetic field when looking at neurodynamics within quasi-stable periods in regional EEGs (see also Kaplan et al., 2005; Fingelkurts & Fingelkurts, 2008).

A further *advantages of EEG screening* in comparison to fMRI or PET studies are the following: (a) EEG equipment is inexpensive, readily available in each clinic (or could be easy installed if needed); (b) EEG can be recorded noninvasively at the patient's bedside or even at home (whereas invasive PET measurement in patients unable to communicate poses the ethical problems; Kotchoubey et al., 2002); (c) patients do not need to be transported with artificial ventilation and other life support equipment to a laboratory for EEG registration; (d) in contrast to EEG, the fMRI and PET procedures are related to a high stress due to loud noise and other circumstances, which can considerably interfere with a patient's brain functional state and (e) being *indirect* measures of brain activity PET and fMRI are methodologically complex with many problems of analysis and interpretation (Nunez & Silberstien, 2000; Mandeville & Rosen, 2002; Freeman et al., 2009; Siegel & Donner, 2010; just to mention a few).

5.3. Methodological limitations

One of the limitations is a relatively small experimental group sample (*n* = 21, 14 VS patients and 7 MCS patients). The season for that is the difficulty in finding non- and minimally communicative patients with severe brain injuries that would fulfill all inclusion criteria and have comparable brain lesions. In order to limit the effects from this constraint, we adopted a nonparametric statistics analyzing the obtained results. Notice also that the number of patients in the present study was substantially larger than in many other published studies on the patients with severe brain injuries which ranged from 1-3 patients (de Jong et al., 1997; Plum et al., 1998; Davey et al., 2000; Moritz et al., 2001; Goldfine et al., 2005; Schiff et al., 2005; Faran et al., 2006; Owen et al., 2006; Coleman et al., 2007; Cauda et al., 2009) to 4-5 patients (Laureys et al., 1999; Schiff et al., 2002; Juengling et al., 2005; Vanhaudenhuyse et al., 2010; just to mention a few). Nevertheless, future studies with a larger group of patients are required to confirm the results presented in this paper.

Another potential limitation is a healthy control group. It has been suggested that only other patients, who have similar brain lesions but differ from the main/experimental group in terms of intact consciousness, should be considered as a control for the patients with disorders of consciousness (Kotchoubey & Lang, 2011). It is assumed that differences between chronically immobile, dependent patients with severe brain injuries and the healthy population are so great and diverse that any comparison between such groups would be meaningless. However there is some evidence indicating that this putative limitation could be irrelevant. It has been reported that a patient who emerged from MCS had similar amounts of cortex functional connectivity (measured by coherence) compared to a healthy control subject; and this was in spite of the severe brain injury with massive white matter loss that the patient sustained (Goldfine et al., 2005). The next example presents a diametrically opposite phenomenon – the absence seizure, where the brain structures are intact, but consciousness is lost. Unlike syncope or pharmacologic anaesthesia, during the absence seizure arousal is preserved demonstrating the selective loss of integrative functions with this event (Schiff & Plum, 1999). Thus, taken together these studies indicate that loss of consciousness could be related with the overall dynamic or "functional" properties of the brain, rather than with particular brain lesions or amount of brain damage. In the present study we focused on residing functional properties of the brain such as dynamic repertoire, duration and oscillatory type of EEG microstates. In this context the use of a healthy control group can be justified. However, to confirm the presented results, future studies that include a control group of brain-damaged but fully conscious patients are required.

Cephalic EEG reference (mean of the signals from C3 and C4 electrodes) indicates another potential limitation of the present study. Even though no agreement on a preferred solution to the reference issue is established at present (Hagemann et al., 2001), the cephalic reference may result in an under- or over-estimation of the potentials at "target" sites, which in turn could lead to power distribution distortions (Lehmann, 1984). This limitation is irrelevant for the present study since we did not study the topography of potentials. At the same time it has been shown that amplitude in the delta, theta, alpha, and beta bands did not vary significantly as a function of reference (Ferree et al., 2001). Therefore our results are unlikely to be affected by the EEG reference used. However, given the possibility for distortion, the verification of presented results will require the use of more common EEG reference montage (linked ears) in future studies.

One more limitation should be mentioned, - in this study each EEG channel was analysed separately (see section 2.3.). However it was suggested that consciousness is most likely the consequence of a coherent activity involving structures distributed throughout the brain (Dehaene & Naccache, 2001) and therefore throughout different EEG channels (Fingelkurts et al., 2010). *Integrated* brain activity in relation to different levels of consciousness expression study, using patients with disorders of consciousness and healthy fully conscious subjects has been reported in another study (Fingelkurts et al., 2011).

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Conflict of Interest Statement:

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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