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Towards operational architectonics of consciousness: basic evidence from patients with severe cerebral injuries

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Abstract

Although several studies propose that the integrity of neuronal assemblies may underlie a phenomenon referred to as awareness, none of the known studies have explicitly investigated dynamics and functional interactions among neuronal assemblies as a function of consciousness expression. In order to address this question EEG operational architectonics analysis (Fingelkurts and Fingelkurts, 2001, 2008) was conducted in patients in minimally conscious (MCS) and vegetative states (VS) to study the dynamics of neuronal assemblies and operational synchrony among them as a function of consciousness expression. We found that in minimally conscious patients and especially in vegetative patients neuronal assemblies got smaller, their life-span shortened and they became highly unstable. Furthermore, we demonstrated that the extent/volume and strength of operational synchrony among neuronal assemblies was smallest or even absent in VS patients, intermediate in MCS patients and highest in healthy fully-conscious subjects. All findings were similarly observed in EEG alpha as well as beta1 and beta2 frequency oscillations. The presented results support the basic tenets of Operational Architectonics theory of brain-mind functioning and suggest that EEG operational architectonics analysis may provide an objective and accurate means of assessing signs of (un)consciousness in patients with severe brain injuries. Therefore this methodological approach may complement the existing "gold standard" of behavioral assessment of this population of challenging patients and inform the diagnostic and treatment decision-making processes.

Key words: EEG alpha and beta rhythms, brain operations, neuronal assemblies, minimally conscious state (MCS), vegetative state (VS), metastability, neurophysiological pattern, synchronization, functional connectivity, (un)consciousness.

1. Introduction

This study was conceived as an empirical evaluation of the basic tenets of Operational Architectonics (OA) theory of consciousness that has been developed during the last decade (Fingelkurts and Fingelkurts 2001, 2004, 2005, 2006, 2008, Fingelkurts et al. 2009, 2010). The main tenets of the OA theory are: The brain generates a highly structured and dynamic extracellular electric field in spatial and temporal domains (McFadden 2002) over a range of frequencies (Başar et al. 2001). This field exists within the brain's internal physical space-time (IPST) and is best captured by an electroencephalogram (EEG) measurement (Nunez 2000; Freeman 2003, 2007). The OA theory explores temporal structure of information flow and the inter-area interactions within a network of dynamical, transient, and functional neuronal assemblies (whose activity is "hidden" in the complex non-stationary segmental structure of the EEG signal; Fingelkurts et al. 2010) by examining topographic sharp transition processes (on the millisecond scale) in the EEG signal (Fingelkurts and Fingelkurts, 2008). Detailed analysis of the structure of EEG's complex hierarchical architecture reveals the specific operational space-time (OST) which literally resides within the IPST and is isomorphic to phenomenal space-time (PST) and, as it has been proposed, may serve as a potential neurophysiological constituent of the phenomenal consciousness' architecture (see Fig. 1; Fingelkurts et al. 2009, 2010). Therefore, to test the suggested statement that consciousness is an emergent phenomenon of coherent dynamic binding of operations performed by multiple neuronal assemblies organized within a hierarchical brain architecture, further work was needed to experimentally demonstrate that the attributes and operational synchrony of local EEG segments would change in circumstances when awareness expression is either weakened or lost completely. For that purpose we have used the methodological approach that was articulated by Baars (1988) as a contrastive analysis between being conscious, having reduced expression of consciousness and being unconscious.

The *OA theory predicts* that both *low* and *high* levels of operational synchrony among neuronal assemblies would result in a dramatic fading of consciousness (Fingelkurts et al. 2010). In the first case, consciousness is likely to vanish in the presence of many small, short-lived neuronal assemblies that perform their operations totally independently from one another (*functional disconnection*). Indeed, according to Tononi's computer simulations (Tononi 2004), major impairment of connectivity is expected to reduce the brain's ability to integrate information, and thus the level of consciousness expression. One example of such a condition is the loss of consciousness under general anaesthesia, which is characterized by loss of effective connectivity, functional uncoupling, and cognitive unbinding (Flohr 1995; Alkire et al. 2000; Mashour 2004; John and Prichep 2005; Hudetz 2010). In the second case, a state of *hypersynchrony* of operations of large, long-lived and stable neuronal assemblies would also lead to the vanishing of consciousness. This is so because excessively abundant brain connectivity, resulting in a loss of individual specificity of the brain's individual elements, would again lead to low values of information integration and consequently to the fading of consciousness expression (Tononi and Sporns 2003). Such a condition is present, for example, during generalized tonico-clonic seizures, which are characterized by a state of unconsciousness and increased brain functional connectivity (Blumenfeld 2008; Cavanna and Monaco 2009; Pockett and Holmes 2009).

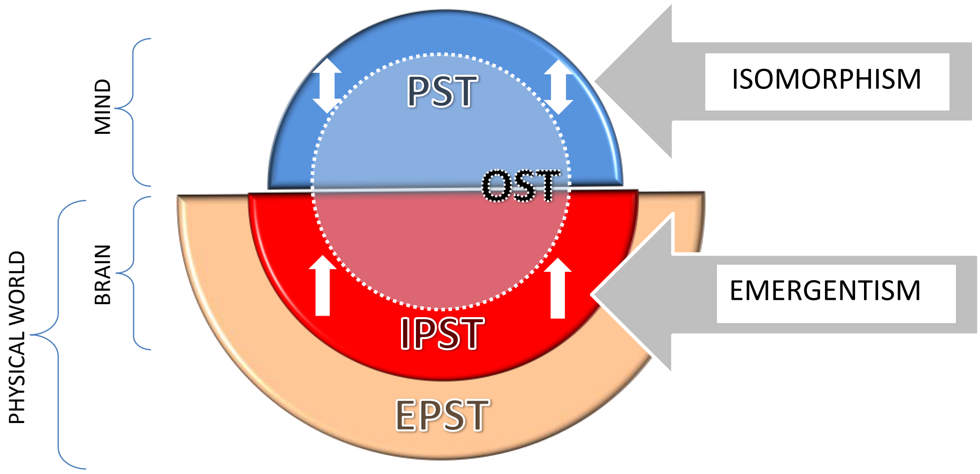

Figure 1. Relations between different levels of the brain–mind organization. EPST indicates the external physical world space–time (light brown colour); IPST indicates the internal physical space–time of the brain (red colour); OST indicates the operational space–time of the brain (indicated by white puncture line); PST indicates the phenomenal space–time of consciousness (blue colour). In this model the OST level represents a constitutive mechanism of phenomenal consciousness and ties the phenomenal (subjective) and neurophysiological (physical) levels together. Isomorphism might be taken to mean that there cannot be change in the arrangement of higher-order phenomena (phenomenal mind) without changing their underlying microphysical properties (brain operational architectonics). Emergentism on the other hand, usually allows for changes of higher-order phenomena (brain operational architectonics) that need not possess a one-on-one, direct linkage with changes at any underlying lower-order levels (internal physical space–time of the brain).

Therefore, it has been suggested that only a particular *dynamic balance* of integrated and segregated processes within the volumetric EEG field of the brain would be specific and sufficient to produce consciousness (Fingelkurts et al. 2010). Such a nonlinear coordinating dynamic of brain-mind functioning, when too little or too much coordination leads to cessation of efficient operation (an inverted U curve; see Fig. 2), is becoming increasingly recognized (Bressler and Kelso 2001; Bressler and Tognoli 2006; Kelso and Engstrøm 2006; Stam, 2006; Kelso and Tognoli 2007; van Leeuwen 2007; Fingelkurts et al. 2009).

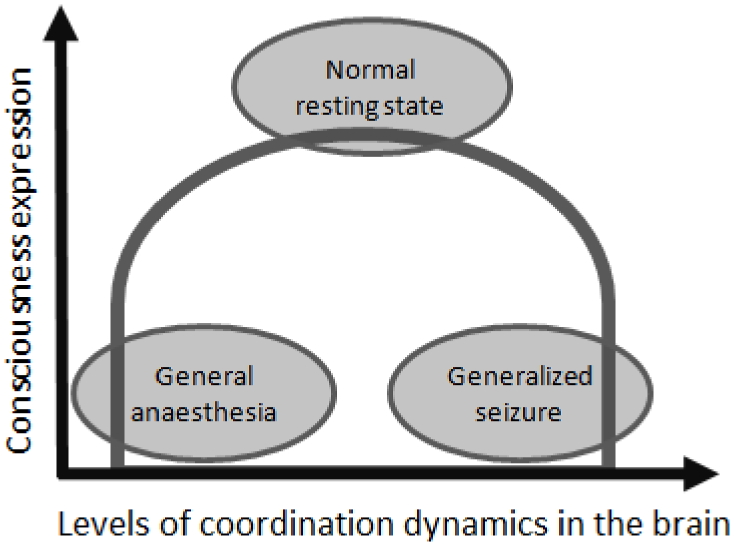

Figure 2. Illustration of nonlinear coordinating dynamic of the brain-mind functioning. When there are too few (functional segregation) or too many (functional integration) coordination processes in the brain, then its operation ceases to function efficiently and consciousness is lost.

In this regard one practical approach that deserves special interest is to study patients who have disturbances of consciousness as a result of general anesthesia or brain damage. Patients under general anesthesia present only a limited model, because in such patients it is *not possible* to disentangle impairment in awareness from impairment in arousal (Laureys 2005). Patients with severe brain injuries however, offer a unique opportunity to study the neural basis of (un)consciousness due to the fact that impairment in awareness of self and environment is *dissociated* in such patients from preserved and stable wakefulness[1] (see Fig. 3). This is very important, because *wakefulness* is a behavioral indication of central nervous system arousal, whereas *consciousness* assumes subjective experience. Indeed, as noticed by Hudetz (2010) “a creature having only subliminal sensations of any kind may not be conscious, although it could be considered to be awake. Patients in a vegetative state become periodically awake, while in all likelihood they remain

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[1] One additional advantage of such a model is the fact that patients in a minimally conscious state and patients in a vegetative state (fully unconscious) have no significant pathological distinctions as it has been shown in histopathological studies (Jennett et al. 2001). This is important because possible differences in states could not be attributed to differences in pathophysiology. At the same time, even in patients with severe brain injuries, consciousness could not be efficiently dissociated from multiple cognitive functions which always “melt” with subjective experiences (Fig. 3). For example, it was shown that the more complex and elaborate forms of conscious awareness found in adult humans are also likely to be associated with greater cognitive capacities (Kinsbourne 2005). This is in fact a limitation of the model, since consciousness is thought to be independent of specific cognitive functions (for a discussion see Revonsuo 2006). For example, consciousness can be dissociated from episodic memory (in the case of amnesic patients, who lack memory encoding, but are still conscious of themselves and their environment) or from language (in aphasic patients, who retain a preserved perception of their environment), or even from the sensorimotor processing (during dreaming, where the subject has vivid experiences despite the absence of sensorimotor interactions with the external world) (for an overview, see Tononi and Laureys 2008).

unconscious at all times. Conversely, dreams represent subjective experience that implies awareness without wakefulness. In normal, healthy individuals, arousal enables the conscious state, but in other cases, such as subjects under the influence of hallucinogenic agents like ketamine, experience can occur with a limited degree of arousal".

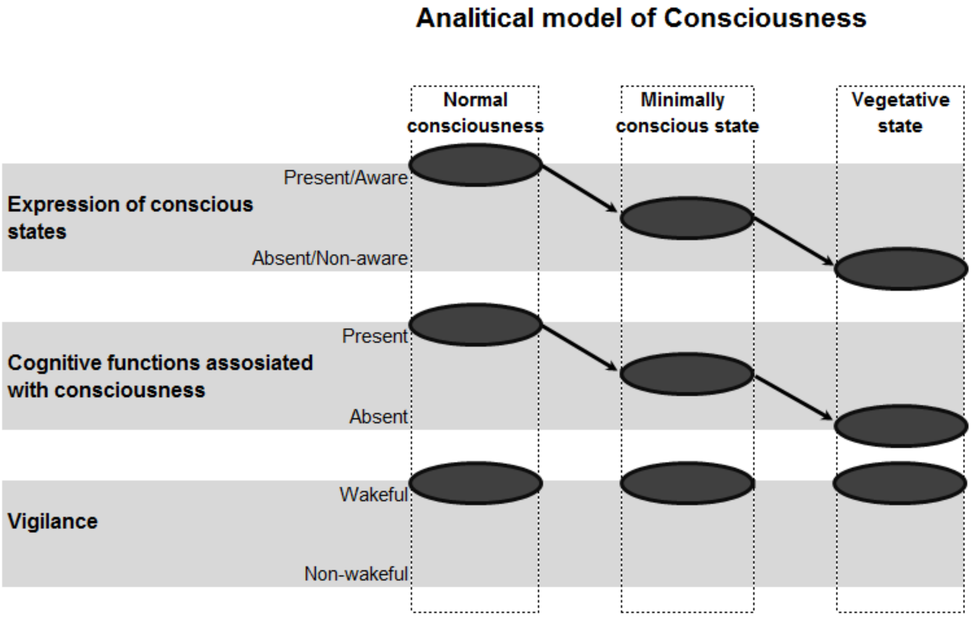

Figure 3. Schematic illustration of the analytical model of Consciousness. On the horizontal plane, conscious states and related with them cognitive functions, as well as vigilance states are plotted. On the vertical plane, normal conscious state, minimally conscious state and unconscious (vegetative) state conditions are presented. Arrows indicate a decrease in the expression of conscious states and related with them cognitive functions from normal, to minimal and to unconscious conditions. Vigilance is supposed to be nearly identical in all three conditions. Therefore, within this analytical model conscious expression could be reliably dissociated from vigilance. However, it is clear from the graph that the expression of consciousness and the related with it conscious cognitive functions/operations could not be disentangled; this is a limitation of the model.

Awareness is the hallmark of *phenomenal consciousness*, which refers to a higher level of organization in the brain (Revonsuo 2006); it captures all immediate and undeniable (from the first-person perspective) phenomena of subjective experiences (concerning self, hearing, seeing, touching, feeling, embodiment, moving, and thinking) that present to a person right here (subjective space) and right now (subjective present) (Fingelkurts et al. 2010). In this sense, when consciousness is separated from arousal/wakefulness, then it is more of a categorical (all-or-none) phenomenon than a continuous one (for experimental support see Sleigh et al. 2010). We discussed this issue in sufficient detail elsewhere (Fingelkurts et al. submitted), therefore here we shall mention only that it is the degree of vigilance (wakefulness) which conflate the expression of consciousness, resulting in an illusion of its continuous or graded[2] nature. Thus, consciousness is always complete (from the first-person perspective), but always about more or less of the available content (Rusalova 2006); and this "more or less" depends on the corresponding functional brain state architecture, level of vigilance and physical integrity of the brain (for example, in a minimally conscious state, patients are conscious of fewer things due to brain impairments).

1.1. Aim of the study, hypothesis and implications

The *specific aim* of the present study was to investigate (using EEG estimates) the attributes of neuronal assemblies and their integrated activity (synchrony) in a cohort of patients with disorders of consciousness, including *vegetative state* (VS) and *minimally conscious state* (MCS) patients, and compare them to analogous characteristics in healthy fully conscious subjects[3]. The 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). VS is, by definition, "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; see also Bernat 2006). Indeed, patients in MCS and VS represent unique cases of altered states of consciousness: from its complete abolishment in VS patients to reduced expression in MCS patients.

Keeping the discussed logic in mind and Baars's (1988) recommendation, the suggested analytic model for examining neural constitutes of consciousness offers the following rules (Fig. 3): the parameters of EEG operational architectonics which are associated with subjective awareness of self and environment should satisfy the rule: NORM $\geq$ MCS $>$ VS, whereas the features of EEG operational architectonics which are associated with subjective unawareness of self and environment should satisfy the opposite rule: NORM $\leq$ MCS $<$ VS.

Specifically we *hypothesized* that EEG segmental attributes and synchrony characteristics would be quantitatively related to the *degree of expression of consciousness* in non- or minimally communicative patients with severe brain injuries, as assessed by standardized Level of Cognitive Functioning (LCF) scale (Gouvier et al. 1987). If the operational architectonics of the brain EEG field

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[2] Curiously enough, the robustness of consciousness level gradation is accepted uncritically in clinical practice. As claimed by Hudetz (2010), although a continuum of states – from wakefulness through drowsiness to deep sleep or anesthesia – seems intuitive, such a one-dimensional model of states of consciousness is obviously an oversimplification.

[3] The strength of operational synchrony for the same groups of patients within default mode network (DMN) which has been related to self-consciousness is reported in another paper (Fingelkurts et al. submitted).

is a direct neural constituent of conscious awareness, it *has to reflect* the phenomenological difference in the integrity and expression of conscious mental states between patients with disorders of consciousness and healthy subjects.

If OA approach will provide an accurate means of assessing signs of (un)consciousness in patients with severe brain injuries, this would have *important clinical implications*: upon validation it could in future complement the existing "gold standard" of behavioral assessment of this population of challenging patients and inform the diagnostic and treatment decision-making processes.

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, admitted in Neurorehabilitation Unit at the Fondazione Istituto "San Raffaele - G. Giglio" to carry out an intensive neurorehabilitation program.

Upon admission all patients were submitted to 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 registered. We choose 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 cognitive functions also (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). 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 are decreased relative to pre-morbid levels).

Based on LCF score all patients were divided into two groups: 14 patients (mean age 42.9 ± 20 years) classified as vegetative state (VS) patients (LCF: 1–2) and 7 patients (mean age 48.7 ± 19.8 years) classified as minimally conscious state (MCS) patients (LCF: 3). In order to reduce the variability of clinical evaluation, LCF scores were assigned in all patients only if they were unchanged for the day of admission and the day of 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; (d) severe spasticity (causing constant EMG artifacts). Inclusion criteria for the patients 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; Royal College of Physicians, 2003); (b) LCF = 1–2 for VS and 3 for MCS patients; (c) less than 3 months after acute brain event onset; and (d) first-ever acute brain event.

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 according to 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). 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 collected.

The EEG recordings were performed late morning for all subjects. The control subjects 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 were spontaneously with open eyes, then the eyelids were 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 patient's

EEG traces in real time, looking for signs of drowsiness and sleep onset (increase of “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 precisely assess the level of vigilance in patients in VS, preserved sleep patterns may be observed in the majority of patients in VS (for review see Cologan et al., 2010).

2.3. EEG-signal data preprocessing

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 rejected from further analysis.

For each patient a full EEG stream, free from any artefacts, was fragmented into consecutive one-minute epochs. Therefore the “NORM” group (healthy subjects) has 18 one-min EEGs, “MCS” group (patients in minimally conscious state) has 87 one-min EEGs and “VS” group (patients in vegetative state) has 137 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 affect the results since 128 Hz sampling rate meets the Nyquist Criterion (Faulkner 1969) of a sample rate greater than twice the maximum input frequency for the alpha and beta activity and is sufficient to avoid aliasing and preserve all the information about alpha and beta activity in the input signal. This method was considered sufficient since the sampling rate of the source signals was significantly higher than required.

After re-sampling and prior to further processing procedures, each EEG signal was bandpass-filtered (Butterworth filter of the sixth order) in five frequency bands: delta (1-3 Hz), theta (4-6 Hz), alpha (7–13 Hz), beta1 (15–25 Hz) and beta2 (25–30 Hz) frequency bands. Phase shifts were eliminated by forward and backward filtering. Even though frequencies above 30 Hz (gamma band) have been recently proposed to be important for conscious processing, there are a number of methodological issues which lead us to exclude gamma band from the analysis of EEG in such challenging patients population (VS and MCS): (a) it was shown that 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, resulting in considerable noise contamination of the gamma band (Ryali et al. 2009); (c) dynamics of high-frequency effects may be a trivial by-product of power changes in lower frequencies (Pulvermüller et al. 1995) and/or due to ringing of filters by EEG spikes recurring at theta rates (Freeman 2003), (e) the gamma band may be an artifact 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). Keeping this in mind, there may be difficulties in meaningful interpretation of effects at the high-frequency band in MCS and VS patients regardless of how powerful or statistically significant they are.

2.4. First level of OA – Estimation of the local functional interrelations

According to the OA framework each homogeneous segment in the EEG signal corresponds to a temporary stable microstate – an *operation* executed by a neuronal assembly (Fingelkurts and Fingelkurts 2001, 2005). The transition from one segment to another then reflects the moment of *abrupt switching* from one neuronal assembly operation to another (see examples in Fingelkurts and Fingelkurts 2008). *Rapid transitional processes* (RTPs) occurring in the amplitude of a continuous EEG activity mark the boundaries between quasi-stationary segments for this activity. RTP is defined as an abrupt change in the analytical amplitude of the signal above a particular threshold established experimentally for each local EEG in modeling and empirical studies (see Fingelkurts and Fingelkurts 2008).

The general statistical principles of the *microstate segmentation* have been described extensively elsewhere (Fingelkurts and Fingelkurts 2001, 2005, 2008; Kaplan et al. 2005). Therefore, here we provide only a brief overview of this approach (see Fig. 4, upper part of the graph). The RTPseg toolkit (Fingelkurts and Fingelkurts 2008) was used for automatic segmentation of local EEG signals within the multichannel EEG record. This method is based on the automatic algorithm of moving double window screening. The ongoing amplitude values in the test window are compared with amplitude values averaged in the level window (test window << level window). If, in accord with the given level of probability of false alert, the value averaged in the level window is exceeded by the highest among the test window value, the time point with the highest amplitude is considered as a preliminary RTP. In order to exclude false alerts caused by anomalous peaks in amplitude, another condition must be fulfilled: the statistically significant difference must be detected between an amplitude value averaged across several time points (number depends on the frequency band) following the preliminary RTP and the amplitude value averaged across the level window. If these two criteria are met, the RTP is considered as actual. Thereafter, both windows are shifted from this RTP on one time-point, and the procedure is repeated. With this technique, at the *first phase*, the sequence of RTPs with statistically determined ($p < 0.05$, Student’s t-test) time coordinates has been determined for each EEG channel individually for each one-minute EEG epoch (see Fig. 4, upper part of the graph).

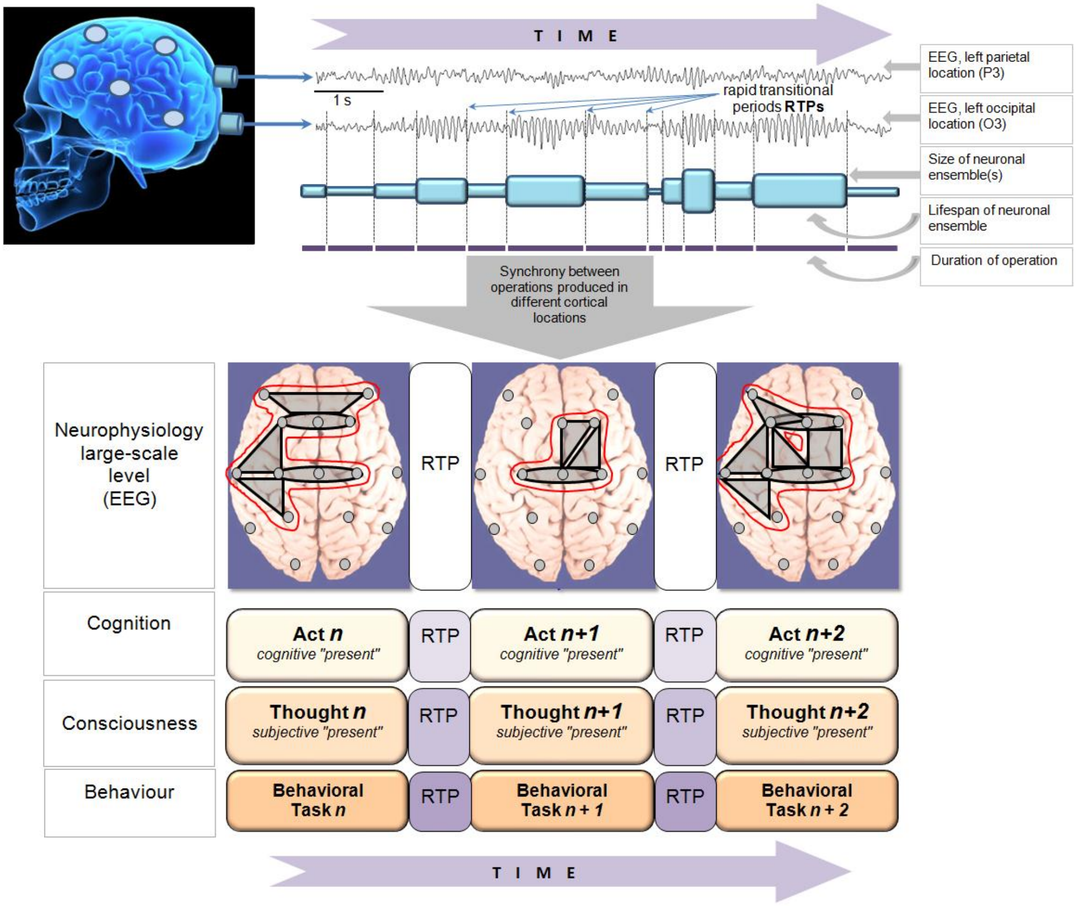

Figure 4. Schematic illustration of the dynamics of neuronal assemblies, their synchrony and relation to EEG parameters. As an example, two ongoing EEG channels with rapid transition periods (RTPs) are shown. EEG was registered in resting condition (closed eyes). Features of EEG segments corresponding to different attributes of neuronal assemblies are indicated (upper part of the Figure). Temporal synchronization of local fields/operations executed by multiple neuronal assemblies produces complex spatio-temporal patterns (indexed as operational modules, OMs) responsible for complex operations (lower part of the Figure). The simplest case is shown as an example: when cognitive, phenomenal and behavioural operations or acts coincide in time (in most cases these relations are more complex). Cognitive, phenomenological, and behavioural levels illustrate the ever-changing stream of cognitive / phenomenal / behavioural acts, where each momentarily stable pattern is a particular cognitive / phenomenal / behavioural macro-operation. Thus, the stream of cognitive / phenomenal / behavioural experience has a composite structure: it contains stable nuclei (or operations / thoughts / images / acts) and transitive fringes (or rapid transitional periods; RTPs). At the EEG level these processes are reflected in the chain of periods of short-term metastable states (or OMs) of the whole brain and its individual subsystems (grey shapes), when the numbers of degrees of freedom of the neuronal assemblies are maximally decreased due to synchronized operations. Grey shapes illustrate individual OMs. Red line illustrates complex OMs. Changes from one complex OM to another are achieved through RTPs.

At the *second phase*, after quasi-stationary segments (indexed by RTPs) were obtained for each EEG channel, several characteristics (attributes) of EEG segments (Kaplan and Borisov 2003) were calculated. These attributes are: (1) average amplitude within each segment (microvolts), – as generally agreed this index indicates mainly the volume or *size of neuronal assembly*, because the number of synchronized neurons recruited into assembly is reflected in the EEG amplitude (Nunez 2000; Klimesch et al. 2005). (2) Average length of segments (milliseconds) – illustrates the functional *life-span of neuronal assembly* or the *duration of operation* produced by this assembly. Because the transient neuronal assembly functions during a particular time interval, this period is reflected in EEG as a stabilized interval of quasi-stationary activity (Fingelkurts et al. 2004a; Fingelkurts and Fingelkurts 2008). (3) Coefficient of amplitude variability within segments (%) – shows the *stability of local neuronal synchronization* within neuronal assembly (Truccolo et al. 2002; Kaplan and Borisov 2003). (4) Average amplitude relation among adjacent segments (%) – indicates *neuronal assembly growth* (recruitment of new neurons) or *disassembling* (functional elimination of neurons) (Fingelkurts et al. 2004a; Fingelkurts and Fingelkurts 2008). (5) Average steepness among adjacent segments estimated in the close area of RTP (%) – shows the *speed of neuronal assembly growth or disassembling* (Fingelkurts et al. 2004a; Fingelkurts and Fingelkurts 2008). These attributes reflect different aspects of local processes in the cortex and thus permit assessing the *mesolevel* description of cortex interactions (interactions within *transient neuronal assemblies*) through large-scale EEG estimates (Fingelkurts et al. 2004a).

2.5. Second level of OA – Estimation of the remote operational (functional) connectivity

The synchronization of operations (i.e. *operational synchrony*) produced by different neuronal assemblies, which are located in different cortex regions, serve to *bind spatially* dispersed phenomenal features (bases of sensations) of a multimodal stimulus or objects into integrated and unified patterns of qualities and further into phenomenal objects or complex scenes (Fingelkurts et al. 2010; see also John et al. 1997; Feinberg 2000; Singer 2001). At the EEG level, operational synchrony phenomenon is expressed through *synchronization of the EEG quasi-stationary segments* (indexed by *Structural Synchrony*, ISS) obtained from different brain locations (Fig. 4, lower part of the graph; Fingelkurts and Fingelkurts 2001) and measured by means of RTPsyn toolkit (Fingelkurts and Fingelkurts 2008).

This measure reveals functional (operational) interrelations between cortical sites different from those measured by correlation, coherence and phase analysis (Fingelkurts and Fingelkurts 2008). The details of this technique are beyond the scope of this article therefore we will only concentrate on some essential aspects. In brief, each RTP in the reference EEG channel (the channel with the minimal number of RTPs from any pair of EEG channels) was surrounded by a short "window" (in milliseconds). Any RTP from another (test) channel was considered to coincide if it fell within this window. To arrive at a direct estimate at the 5% level of statistical significance ($p < 0.05$) of the ISS, computer simulation of RTPs synchronization is undertaken based on random shuffling of time segments marked by RTPs (500 independent trials). These share the properties of the experimental data (number of RTPs in each EEG channel of analyzed pair, number of segments, and number of windows of synchronization), but the time coordinates of RTPs were altered randomly in each trial so as to destroy the natural temporal structure of the data. The ISS tends toward zero where there is no synchronization between the EEG segments and has positive or negative values where such synchronization (or dis-synchronization) exists. Positive values indicate *"active" coupling* of EEG segments (synchronization of EEG segments is observed significantly more often than expected by chance; $p < 0.05$, random shuffling, computer simulation), whereas negative values mark *"active" decoupling* of segments (synchronization of EEG segments is observed significantly less than expected by chance; $p < 0.05$, random shuffling, computer simulation). From a qualitative perspective, coupling of EEG segments corresponds to the *synchronization of operations* executed by local neuronal assemblies or operational synchrony (OS) (Fingelkurts and Fingelkurts 2001, 2005, 2006).

Using pairwise analysis, ISS was identified in several channels (more than two). These are described as *operational modules* (OMs) (Fingelkurts and Fingelkurts 2004, 2005, 2008). OM means that the set of the cortical areas participated in the same functional act during the analyzed period (Fig. 4, lower part of the graph). The criterion for defining an OM is a sequence of the same synchrocomplexes (SC), where SC is a set of EEG channels in which each channel forms a paired combination with high values of ISS with all other EEG channels in the same SC; meaning that all pairs of channels in an SC have to have statistically significant ISS (see Fingelkurts and Fingelkurts 2008).

2.6. Statistics

For each analyzed condition (NORM, MCS, VS), group-EEG segment-attribute averages and respective standard deviations were calculated for the whole pull of correspondent one-minute EEGs. As in previous works, the comparison of the same segment attributes between different group conditions was performed using Wilcoxon *t*-test (Fingelkurts and Fingelkurts 2010a).

The number and strength of EEG operational synchrony was assessed using an ISS index (see previous subsection). The differences in number and strength of ISS patterns between different groups (NORM, MCS, and VS) were assessed using Wilcoxon *t*-test, which is used in the majority of functional connectivity studies (for an overview, see Weiss and Rappelsberger 2000). At first, all valid EEG functional connections were averaged within each analyzed condition (NORM, MCS, VS) for the whole pull of correspondent one-minute EEGs within nine categories of functional connectivity ($\text{short}_{\text{left/right}}$, $\text{short}_{\text{anterior/posterior}}$, $\text{long}_{\text{left/right}}$, $\text{long}_{\text{anterior/posterior}}$, and $\text{long}_{\text{interhemispheric}}$), separately for the number of functional connections and for the strength of these connections. Since the absolute number of possible functional connections within each category was different, their per-category percentage was calculated. During the final stage an average of all the categories was calculated. Thus only average values for all statistically valid functional connections for the whole cortex were used for further analysis.

Of course, these group-mean values do not allow analysis of the topological peculiarities of EEG segment attributes and synchrony characteristics, but it was our deliberate choice. The differences in brain injuries among chronically immobile, dependent patients with severe brain damage, resulting in distortions of neuroanatomy secondary to atrophy and loss of both grey and white matter structures (Sakatani et al. 2003), are very great and diverse. In such situations the comparison of topology presents a significant challenge. At the same time the use of averaged values for the whole cortex diminishes the contribution of a particular anatomical area (which could be either intact or destroyed in each particular patient) in the overall result of the study.

Since we compared several conditions at a time, a Bonferroni correction was made in order to control for repeated observations of the same measures. $P_{\text{corrected}}$ 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.

3. Results

3.1. Demographic 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 traumatic brain injuries (TBI) and non-TBI etiologies (43% TBI and 57% non-TBI in both groups), left- and right-side lesions (p = 0.62) and medicated *vs* non-medicated patients (p = 0.82).

3.2. EEG oscillations in relation to expression of consciousness

Even though all frequency bands of the human EEG may have some functional significance and could be linked with consciousness, among the five EEG frequency bands (delta, theta, alpha, beta1 and beta2) analyzed in this study, only alpha, beta1 and beta2 oscillations have shown behavior consistent with the analytical consciousness model (Fig. 3) for all studied attributes of EEG segments.

According to this model the features of EEG which are associated with the subjective (un)awareness of self and environment should satisfy one of the following rules: (a) NORM ≥ MCS > VS (for awareness) or (b) NORM ≤ MCS < VS (for unawareness). Therefore, in this paper we will limit further analysis only to the dynamics of alpha, beta1 and beta2 frequency bands.

3.3. Dynamics of neuronal assemblies (measured by EEG) as a function of (un)consciousness

Figure 5 presents the mean values of EEG segment attributes that characterize different features of neuronal assemblies for all EEG locations and subjects for each functional state/condition (NORM, MCS, VS). Corresponding data are presented separately for five features of neuronal assemblies (see Subsection 2.4). One can see that the size of neuronal assemblies and their life-span followed the proportion NORM ≥ MCS > VS ($p_{corrected} < 0.05$ – $p_{corrected} < 0.01$), while the instability of neuronal assemblies, recruitment of new neurons in the neuronal assemblies and the speed of such recruitment followed the opposite proportion NORM ≤ MCS < VS ($p_{corrected} < 0.05$ – $p_{corrected} < 0.01$). An exception was noticed only for the “speed” attribute for the alpha frequency band. Otherwise, similar differences were observed in all three (alpha, beta1 and beta2) frequency bands (Fig. 5).

3.4. Operational synchrony of neuronal assemblies (measured by EEG structural synchrony) as a function of (un)consciousness

Figure 6 presents mean values of the number and strength of functional connections for all EEG pair combinations that characterize remote functional connectivity between neuronal assemblies (see Subsection 2.5). Corresponding data are organized the same way as in Fig. 5 and are presented separately for different functional states/conditions (NORM, MCS, VS). We observed a significant decrease ($p_{corrected} < 0.05$) in the average number and strength of functional connectivity between neuronal assemblies in MCS patients and even stronger decrease ($p_{corrected} < 0.01$) in VS patients compared to healthy fully-conscious volunteers, thus following the proportion NORM > MCS > VS. Similar differences were observed in all three (alpha, beta1 and beta2) frequency bands (Fig. 6).

4. Discussion

4.1. Demographic factors

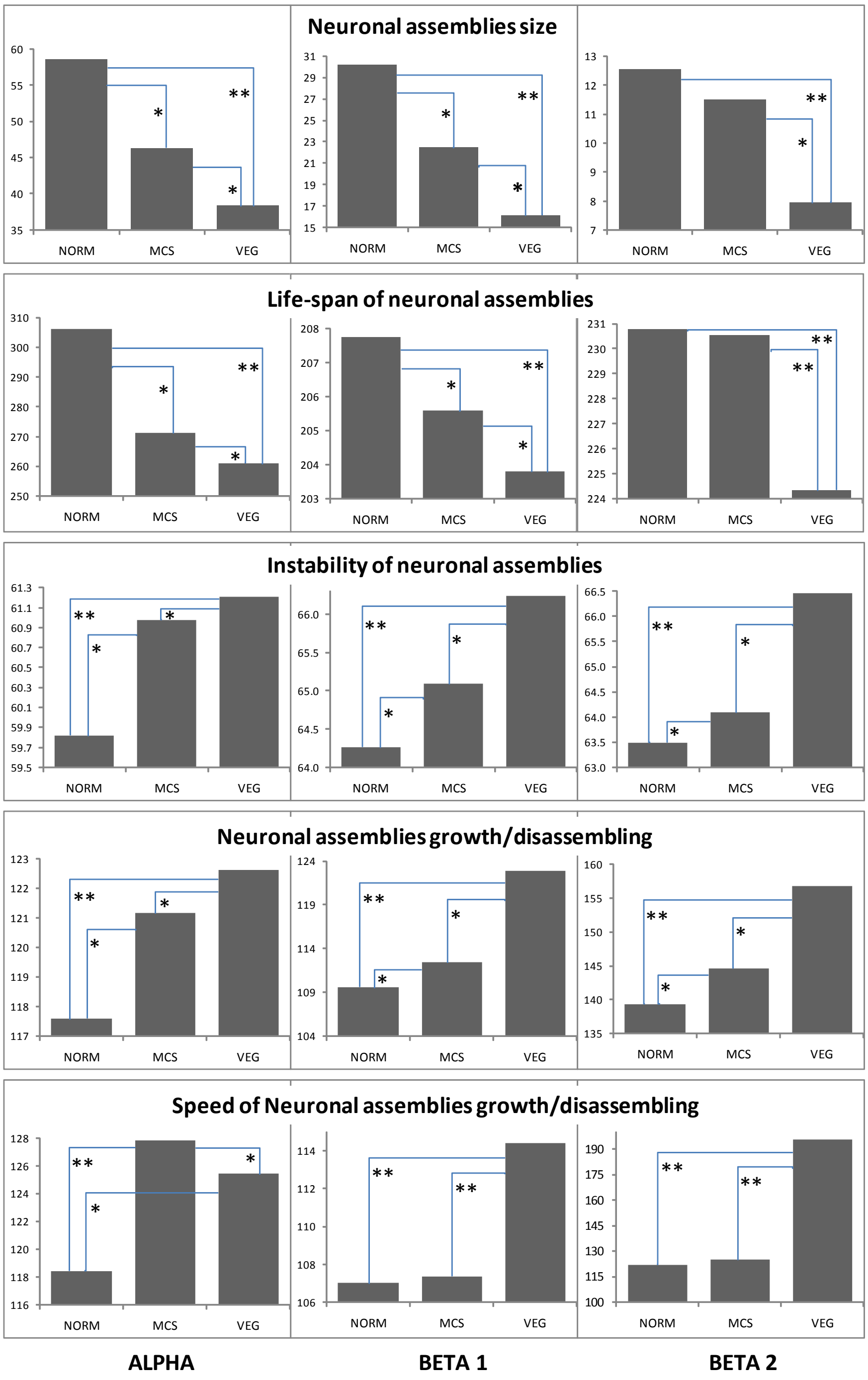

Figure 5. Dynamics of the features of neuronal assemblies (indexed by EEG segment attributes) as a function of consciousness expression. Data averaged across all EEG channels and all subjects within each state/condition (NORM, MCS, VS). The values of attributes of neuronal assemblies indicated by the *Y*-axis: size of neuronal assemblies — amplitude within each segment (microvolt); life-span of neuronal assemblies — length of segments (milliseconds); instability of neuronal assemblies — coefficient of amplitude variability within segments (%); growth/disassembling of neuronal assemblies — amplitude relation among adjacent segments (%); the growth/disassembling speed of neuronal assemblies — steepness among adjacent segments estimated in the close vicinity of the RTP (%). * – $p_{corrected} < 0.05$, ** – $p_{corrected} < 0.01$.

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 etiologies, 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 MCS and VS groups. The absence of significant difference in age between healthy (NORM) subjects and both (MCS and VS) patient groups indicates that age could not affect the observed differences between healthy subjects and patients.

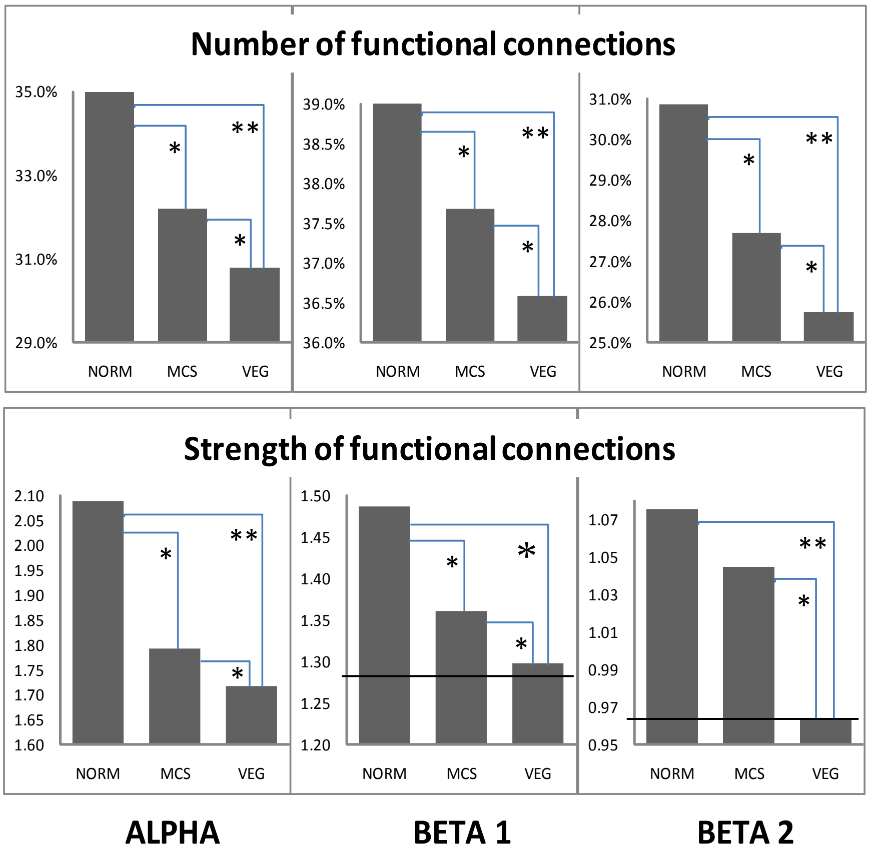

Figure 6. Operational connectivity among neuronal assemblies (indexed by EEG structural synchrony) as a function of consciousness expression. Data averaged across all pairs of EEG channels and all subjects within each state/condition (NORM, MCS, VS). The *Y*-axis presents values of either number or strength of functional connections. Horizontal line on beta1 and beta2 graph indicates the stochastic/random level of connectivity. Below this threshold any connectivity is random. * – $p_{corrected} < 0.05$, ** – $p_{corrected} < 0.01$.

4.2. Type of EEG oscillations in relation to the expression of consciousness

As it stands, the OA theory (Fingelkurts et al. 2010) does not predict any particular frequency bandwidth and thus any particular EEG oscillation as putative constituent mechanism of conscious states that could be experimentally verified. Nowadays a large body of knowledge has accumulated on functional significance of different EEG oscillations (for the overview see Fingelkurts and

Fingelkurts 2010b). This research has revealed that practically each frequency band could in principle correlate with some cognitive processes (Klimesch 1999; Steriade 2000; Başar et al. 2000, 2001; Buzsáki and Draguhn 2004; Knyazev 2007). At the same time, it is reasonable to suppose that only a few of such frequencies could constitute consciousness as a phenomenon. The main requirement for such EEG oscillations would be their partial independence from mechanisms serving other (biological) functions in the brain.

The results of the present study have clearly showed that changes only within alpha, beta1 and beta2 frequency bands (but not delta and theta), that characterize dynamics of neuronal assemblies and their operational synchrony, followed the rules proposed by the analytical model of (un)consciousness (Fig. 3): NORM ≥ MCS > VS (for consciousness) and/or NORM ≤ MCS < VS (for unconsciousness). This finding is not surprising considering the functional role of different EEG oscillations.

For example, *delta activity* is normally tuned to mostly internal stimuli signalling danger to survival (such as hypoxia, hypoglycaemia, fatigue, sustained pain), as well as to the stimuli signalling a need for sexual activity (e.g. the level of sex hormones) (Mosovich and Tallaferro 1954; Heath 1972; Tallroth et al. 1990; Hoffman and Polich 1998), which do not require (but could) accompany by conscious awareness (Knyazev 2006, 2007). *Theta oscillations* in resting conditions are expected to be associated with emotional regulation (Pare and Collins 2000; Aftanas et al. 2003; Sachs et al. 2004) that does not need conscious awareness either (Panksepp et al. 2007).

On the contrary *alpha activity* (a) is expected to play a leading part in organizing conscious interactions (specifically human – from the first point of view) with the environment (Knyazev 2007), (b) is correlated with conscious awareness (Babiloni et al. 2006) and (c) is highly correlated with mind wondering and spontaneous self-referential thoughts (Shaw 2003). *Beta activity*, on the other hand, plays a crucial role in "internal" attention (Mundy-Castle 1957; Ray and Cole 1985) and is (a) related to self sensory-motor processing, (b) strongly correlated with conscious mentation (as opposed to mental automation) (Sokolov 1963; Rusalova 2006; Lazarev 2006), and (c) particularly important for the maintenance of a conscious audio-visual image (Fingelkurts et al. 2007).

Taken together, these data show that consciousness alteration involves pronounced changes in *alpha* and *beta* oscillations (we will return to discussion of this issue later in the Subsection 4.5).

4.3. Dynamics of neuronal assemblies in relation to the expression of (un)consciousness

The results of this study enable us to choose between two alternatives predicted by the OA theory in relation to the specific case of (un)consciousness expression in minimally- and non-communicated patients with severe brain injuries (see Introduction). We found that the state of unconsciousness (in VS patients) was characterized by the smallest, shortest-lived and very unstable neuronal assemblies when compared to fully-conscious subjects, which exhibited the presence of near-to-normal (Fingelkurts and Fingelkurts 2010a) relatively large, long-lived and stable neuronal assemblies. The state of minimally expressed consciousness (in MCS patients) occupied an intermediate position, thus following the proportion NORM ≥ MCS > VS (Fig. 5). Generally, these findings suggest that an *unconscious brain* is subdivided into many small, causally independent and highly unstable processing units operating in all three alpha, beta1 and beta2 oscillations. This supposition is in line with the result of Tononi’s computer simulations (Tononi 2004): if a system (brain) is presented by a collection of many independent elements, while the elements by themselves could still be activated, such a system would malfunction as if its elements have been destroyed or permanently inactivated. All in all, the efficient integration of information is not possible in such conditions (Tononi and Sporns 2003; Tononi 2008).

A considerable body of empiric evidence, summarized by Velmans (1991) and Fingelkurts and Fingelkurts (2006), shows that for a consciousness to occur brain states must be longer than the time it takes for the simplest cognitive operation to be completed (which is of the order of several hundreds of milliseconds), while before that the brain is capable of a high degree of perceptual analysis, extraction of meaning, cognitive processing, and organization of action, all of which remains entirely unconscious (see also Libet 2003; Milner and Goodale 1995; Toates 1998; Treisman and Kanwisher 1998). The data of the present study suggest that the duration of operations lower than ~300 msec for alpha oscillations, ~207 msec for beta1 oscillations and ~230 msec for beta2 oscillations is associated with the diminished expression of consciousness, while the duration of operations as low as ~260 msec for alpha oscillations, ~203 msec for beta1 oscillations and ~225 msec for beta2 oscillations is associate with the state of unconsciousness (Fig 5). Thus, we could conclude that duration of operations produced by neuronal assemblies shorter than a certain threshold (individual for each temporal scale – frequency oscillation[4]) makes the brain state either *un*-conscious (still mental domain) or even *non*-conscious (non-mental neurophysiological domain) (for a discussion see Fingelkurts et al. 2010).

Besides being long enough, the elemental processing modules of the brain should be stable enough to guarantee that they will not decompose further into smaller or even singular elements, resulting in total loss of any integration, the particular level of which is considered important for the

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[4] Different EEG oscillations appear to be related to the timing of different neuronal assemblies (activated network parts), which are associated with different types of operations (von der Malsburg 1999; Varela 1995; Buzsáki 2004, 2006). The general assumption is that the functional interplay between units of the same assembly or between different assemblies is based on a coordinated timing that is enabled by oscillations (for a discussion see Fingelkurts et al. 2010).

emergence of consciousness (Tononi and Edelman 1998; Edelman and Tononi 2000; Tononi 2004; Stam 2006; Kelso and Engstrøm 2006; Bressler and McIntosh 2007; van Leeuwen 2007; Fingelkurts and Fingelkurts 2010a). This view is consistent with the results of the present study about highly unstable neuronal assemblies during unconscious state when compared to relatively normal level of instability for fully conscious state and intermediate position of minimally expressed conscious state (Fig. 5). Based on our previous research (Fingelkurts and Fingelkurts 2010a) we shall notice that the level of instability in VS patients (unconscious state) in the present study approached a stochastic/random level.

The second set of findings in this study complements previous results by providing evidence that the unconscious state (in VS patients) was characterized by functional recruitment of new neurons in the neuronal assemblies and that the speed of such recruitment was significantly higher than in minimally conscious state (in MCS patients) and even higher than in fully conscious state (healthy volunteers), thus following the proportion NORM < MCS ≤ VS (Fig. 5). These data indicate the tendency for growth of neuronal assemblies in the cortex during unconscious state, probably marking a compensating strategy of the brain which “tries” to reach more or less appropriate parameters of neuronal assemblies for its functioning.

Taken together these findings show that dynamics of neuronal assemblies could differentiate VS patients who completely lack consciousness from MCS patients who have partially preserved or incidentally organized appropriate (but transient) neuronal assemblies which are already capable of supporting minimal expression of consciousness. At the same time, the presence of disorganized activity of neuronal assemblies during VS may indicate insufficient (in contrast to MCS) levels of neuronal assemblies’ dynamics for supporting representational content in relation to awareness from the first-person perspective. Nevertheless, such a disabling state as VS could still be accompanied by isolated experiences associated with cognitive operations executed without self- or any other consciousness; the so-called returning to a rigid stimulus-response behavior of lower animal species (Kinsbourne 2005).

This supposition is consistent with results from EEG event-related potential studies (Neumann and Kotchoubey 2004; Kotchoubey 2005; Perrin et al. 2006) and fMRI/PET studies (Laureys et al. 2002; Boly et al. 2004), 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 and Schwall 1993; Schoenle and Witzke 2004), because experimentally unconscious stimuli could evoke similar local event-related potentials (Kihlstrom 1987; Brazdil et al. 2001; Yingling 2001; Baars 2002) or even demonstrate unconscious perception of word meaning (Naccache and Dehaene 2001). Therefore such neuronal responses in VS patients could represent only isolated cerebral functional modes (Kinney and Samuels 1994; Schiff and Plum 1999; Schiff et al. 2002), which are not associated with awareness (Kobylarz and Schiff 2004).

Thus we could propose that the brain of VS patients may be capable of processing, but not capable of conscious understanding of that processing. This is in line with the OA framework, which claims that simple processing operations could be responsible only for simple functions and/or phenomenal features; and that they are the building blocks of more complex operations responsible for complex/abstract functions and/or phenomenal objects or thoughts (Fingelkurts et al. 2010). For such complex operations to occur the synchronization of multiple and relevant simple operations produced by many neuronal assemblies is required (Fingelkurts and Fingelkurts 2005, 2006; Fingelkurts et al. 2010).

4.4. Operational synchrony of neuronal assemblies during the expression of (un)consciousness

According to the OA theory, individually each neuronal assembly presents only a partial aspect of the whole object/scene/concept (Fingelkurts et al. 2010), while the wholeness of the “perceived” or “imagined” is brought into existence by joint (*synchronized*) operations of many functional and transient neuronal assemblies in the brain (for extensive discussion see also Singer et al. 1997; Bressler and McIntosh 2007). The recombination of neuronal assemblies in new configurations makes it possible to present a practically infinite number of different qualities, patterns, objects, scenes and concepts (Fingelkurts and Fingelkurts 2004) – even those, with which we have never been acquainted before (Singer et al. 1997).

Results of this study on the operational synchrony among neuronal assemblies supported one of two alternative predictions made by the OA theory about the expression of (un)consciousness in patients with a severely injured brain (see Introduction). We have found that both the number of EEG functional connections and strength of EEG operational synchrony in all three alpha, beta1 and beta2 oscillations were highest in healthy fully-conscious subjects, lowest or even absent in VS patients, and intermediate in MCS patients[5], thus following the proportion NORM ≥ MCS > VS (Fig. 6). Since fully-conscious, healthy volunteers displayed a particular, relatively high level of operationally integrated EEG architecture (see also Fingelkurts and Fingelkurts 2010a), and considering the importance of an integrated network of neuronal assemblies during self- and environment awareness, as well as related cognitive functions (Aertsen et al. 1989; Varela 1995; Tononi and Edelman 1998;

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[5] As our data presented elsewhere (Fingelkurts et al. submitted) have shown, the strength of operational synchrony within DMN follows the same direction: NORM ≥ MCS > VS. It has been proposed recently that DMN is responsible for the self-consciousness awareness (for review see Fingelkurts and Fingelkurts 2011; Northoff et al. 2011).

Singer 1999; Engel and Singer 2001; Varela et al. 2001; Bressler 2002; Reijneveld et al. 2007), these results suggest that *the number* and *strength* of operational synchrony among neuronal assemblies could be the potential indicators of a patient's expression of (un)consciousness. Specifically our findings mark a very weak (or nonexistent) communication among neuronal assemblies located in different cortex areas during unconscious (VS) state. At the same time, during minimally expressed consciousness (MCS patients) the cortex was capable of supporting "fragile binding" states, when different neuronal assemblies exhibited a transient but strong enough engagement in functional communication with each other (Fig. 6). We propose that during such episodes MCS patients could experience moments of conscious awareness, which is clinically defined as "fluctuating" consciousness (Overgaard 2009). This finding stresses the importance of assessing residual operational architectures, which may support subjective awareness, in patients with disorders of consciousness, whose consciousness expression can be underestimated using traditional clinical bedside evaluation.

According to the OA framework (Fingelkurts and Fingelkurts 2001, 2005, 2006, 2008) there are multiple, simultaneously occurring interactions between different cognitive operations, which are subserved by the simultaneous presence of transient neuronal assemblies integrated within OMs (synchronized neuronal assemblies) of varying complexity (Fingelkurts et al. 2009, 2010). The integrated neuronal assemblies in healthy subjects are in a delicate metastable balance between local specialized processes and global integration (Fingelkurts and Fingelkurts 2004). Excess or lack of either process marks a deviation from this optimal state (Stam 2006; Kelso and Engstrøm 2006; Bressler and McIntosh 2007; Fingelkurts and Fingelkurts 2010a). Thus, diminished or absent (like in the beta1 and beta2 oscillations; Fig. 6) operational synchrony in patients with severe brain injuries suggests a disruption of integrated brain processes, responsible for conscious awareness, all the way down to its complete absence, as in the VS patients of this study.

These findings support the so-called "disconnection syndrome" proposed for the VS patients based on the PET/fMRI data (Laureys et al. 1999; Laureys et al. 2000). Even though presented in this paper results and the results of the cited studies point to the same disconnection syndrome, the metabolically/hemodynamically based methods (PET and MRI or fMRI) tell us nothing about fast, transient neuronal assemblies. On the contrary, EEG is a direct measure of electric current within masses of neuronal cell assemblies (Freeman 1975, 1992). Additionally, only the EEG (and magnetoencephalogram; MEG) provides a satisfactory temporal scale for accessing the dynamic evolution of brain activity associated with cognitive and conscious processes in healthy and diseased states (Livanov 1977; Nunez 2000; John 2001).

Taken together, our findings lead to the conclusion that the number and strength of operational connectivity between neuronal assemblies in resting state could be related in a quantitative manner to the expression of (un)consciousness in patients with severe brain injuries. This conclusion supports the OA theory tenet that for the *full expression of consciousness*, a parallel existence and interplay of many dynamic operationally synchronized spatio-temporal patterns (operational modules) is required (Fingelkurts and Fingelkurts 2001, 2005, 2006, 2008; Fingelkurts et al. 2009, 2010).

4.5. The functional role of alpha and beta oscillations in relation to the expression of consciousness

Our study has identified that dynamics of neuronal assemblies (indexed by different attributes of EEG quasi-stationary segments) and their operational integrity (indexed by EEG structural synchrony) behaved nearly identically in alpha, beta1 and beta2 frequency bands (Fig. 5 and 6). Such observations suggest that the temporal structure of EEG signals within alpha and both beta oscillations was approximately the same. This then could mean that neuronal assemblies located in different cortical sites synchronized their operations simultaneously in alpha and both beta oscillations. If so, we could then speculate further that neuronal assemblies also synchronized their operations among these different time-scales (EEG oscillations) – so-called cross-frequency synchrony (Palva et al. 2005). The possibility of operational synchronization between EEG oscillations at different frequencies has been previously demonstrated (Fingelkurts 1998; Fingelkurts et al., 2003b; see also Palva et al. 2005; Schack et al. 2005). Taken together, current and previously published data reflect a modern view of *inter-frequency consistency* as the main principle of integrative brain functioning (Nunez 1995; Başar et al. 2001; Varela et al. 2001; Le Van Quyen 2011). According to this principle, brain information processing takes place at multiple timescales and is mediated by dynamic binding between various EEG oscillations (see the review Palva et al. 2005; Başar 2006). This allows rapid information processing on both local and global scales simultaneously (Ingber 1995; Nunez 2000; Fingelkurts and Fingelkurts 2001, 2005, 2008; Le Van Quyen 2011).

Considering that among the five EEG oscillations (delta, theta, alpha, beta1 and beta2) only alpha, beta1 and beta2 rhythms have shown changes consistent with the analytical consciousness model (Fig. 3), a question arises about the specific functional contribution of these alpha and beta frequency oscillations in the emergence of consciousness. Usually adjacent frequency bands within the same neuronal network are associated with different functional brain states and compete with one another (Penttonen and Buzsáki 2003; Buzsáki and Draguhn 2004). At the same time several rhythms can coexist in the same cortical area and/or interact among each other or different cortical areas (Varela et al. 2001; Steriade 2001) if their individual functions are *complementary* in achieving the overall “*macro-function*” of the integrated networks (Fingelkurts and Fingelkurts 2001, 2005, 2008; Fingelkurts et al. 2010).

As we have mentioned in Subsection 4.2 of this paper, both alpha and beta frequency oscillations have functions that could be important for the expression of consciousness. Generally, *alpha* frequency oscillations allow for an integration of neuronal effects with longer delays and larger variability in delays and larger brain areas of involvement (Penttonen and Buzsáki 2003). Neural representations based on these oscillations are therefore *complex* and *abstract* (Varela et al. 2001), and mediate top-down processing (von Stein et al. 2000; Lamme 2006; Dehaene et al. 2006). In contrast, *beta* frequency oscillations allow for a more *precise* and spatially *limited* representation of information by incorporating synaptic events from closely located regions with short synaptic delays and limited variability (Penttonen and Buzsáki 2003). Neural representations based on these fast oscillations constitute the contents of each “snapshot” or “frame” of consciousness (Palva and Palva 2007).

These neurophysiological peculiarities of alpha and beta frequency oscillations are responsible for their specific functional roles. Thus, *alpha oscillations*, which dominate the adult human EEG[6] (Knyazev and Slobodskaya 2003), (a) are involved in organization of conscious interactions (specifically human – from first point of view) with the environment (Knyazev 2007), (b) are correlated with conscious awareness (Babiloni et al. 2006) and long-term semantic memory processes (Klimesch 1996) and (c) are highly correlated with mind wondering and spontaneous self-referential thoughts (Shaw 2003). *Beta frequency* bands[7], on the other hand, play a crucial role in “internal” focused attention (Mundy-Castle 1957; Ray and Cole 1985), relate to self sensory-motor processing and kinematic properties (Hari and Salmelin 1997; Pfurtscheller et al. 1998) and are strongly correlated with conscious mentation (as opposed to mental automation) (Sokolov 1963; Rusalova 2006; Lazarev 2006), as well as being particularly important for the maintenance of a conscious unified audio-visual image (Fingelkurts et al. 2007; Hipp et al. 2011).

The *beta1 frequency* band is specifically associated with semantic understanding and self-awareness (Williamson et al. 1986; Holzinger et al. 2006), as well as conscious sensory-motor processing (Kaiser and Sterman 1994). The *beta2 frequency* band is specifically tied to emotional and

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[6] Human children younger than 3 years are unable to produce higher cognitive processes, full-fledged consciousness, and do not show alpha activity (Başar and Güntekin 2009). At the same time, the brain in such children shows only sparse and weak connections (Thatcher et al. 1986, 1987).

[7] The beta band (along with the alpha band) evolutionary appeared only in primates (including humans), who are geared with a cortical mantle (Knyazev 2007). These frequency bands reach the strongest expressions in humans who are at the same time the carriers of a full-fledged consciousness of self and environment (Knyazev and Slobodskaya 2003). The theta oscillations predominate within the brain of a lower mammals (Klimesch 1999), while the reptile brain oscillates mostly in the delta range (Gaztelu et al. 1991). Neither of these species could be assigned with a phenomenal consciousness.

cognitive processes (Ray and Cole 1985) necessary for sensory-motor processing, as well as focused attention (Murthy and Fetz 1992) and semantic knowledge of motor end-postures (van Elk et al. 2010). Moreover, both beta frequency bands help to unite the processing resources of the two brain hemispheres needed for conscious integration (Knyazeva et al. 2006).

Dynamic operational synchrony among these three alpha, beta1 and beta2 oscillations is thus well posed to mediate the integration of many simple distributed operations into cognitive macro-operations (Palva et al. 2005) required to take place so that reflective awareness become possible (Fingelkurts et al. 2010). During this integration, *alpha* activity would determine a *coordinate top-down control* for cortical traces of discrete representations (supported by *beta* frequencies) to be combined with associated semantic representations within the first-person perspective. More precisely such synchronization between alpha and beta oscillations may mediate the contents-to-context binding of complex phenomenal representations when multiple representations must be kept active simultaneously (Palva et al. 2005).

Therefore we may speculate that any decrease of such dynamic interplay would result in the situation where raw sensory stimuli (coming from both the outside and within the organism) dominate; and in the case of significant decrease it would result in a situation where raw sensory stimuli could not be ever integrated in the context of a personally meaningful narrative. Under such condition a person would very much be the victim of his/her environment, just a *passive recipient*; things would just happen to such a subject all the time exactly as in the VS and to a lesser extent in MCS patients.

5. Conclusions, significance and limitations

5.1. Concluding discussion

Taking together the results of this study, we could conclude that it is *intact coordinated activity* among *relatively large*, *long-lived* and *stable neuronal assemblies* that is important for enabling routine representational processes to be integrated within a coherent phenomenal world from the first-person perspective (Metzinger 2003, 2007; Revonsuo 2006). Additionally, and as predicted by the OA theory, transient operational integrity of neuronal assemblies allows discrete moments of “phenomenal present” to be bundled in larger units, making it possible not only to experience one’s existence in the present moment, but also to conceive of that existence in the past and propagate its continuation into the future (Fingelkurts et al. 2010). Impairment in the characteristics (size, life-span, stability) of neuronal assemblies and in operational integrity among them may underlie the fading of consciousness until its complete absence, if such impairment reaches a critical level as in the patients in VS (Fig. 5, 6), who have complete unawareness of self and the environment.

The observed differences in measured EEG characteristics between healthy subjects and patients with disorders of consciousness were similar for alpha, beta1 and beta2 frequency oscillations. Keeping in mind the complementary functional roles of these frequency bands discussed earlier in the paper, we can infer that MCS and especially VS were characterized by impairment in both global (*abstract*) and specific (*motor-sensory*) processing, as well as in efficient integration of these processes. This conclusion is in line with the view that integration of information processed in the cerebral cortex might depend on the dynamic formation and disassembling of synchronized neuronal assemblies, characterized by various frequency bands (Engel and Singer 2001; Palva et al. 2005; Palva and Palva 2007; Babiloni et al. 2009).

In summary, our data on the dynamics of neuronal assemblies and operational synchrony among them in patients suffering from disorders of consciousness strengthen the hypothesis of cortical disconnection syndrome in non- and minimally communicative patients with severe brain injuries (Laureys 2005) and suggest that EEG operational architectonics profoundly *shapes* conscious perception and awareness.

5.2. Clinical significance

One potential importance of spontaneous brain activity studies from a *clinical point of view* concerns the fact that *resting state* studies (both, fMRI and EEG) enable clinicians to assess higher order brain cognitive networks, without requiring active participation from the patient. This fact is particularly important in non- and minimally communicative patients with severe brain injuries (Vanhaudenhuyse et al. 2010). At the same time, fMRI or PET studies of patients with severe brain injuries present a significant challenge for using standard techniques, due to complex brain injuries resulting 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). EEG studies are less problematic in this respect, because local EEGs represent so-called ‘functional sources’, which are defined as the part or parts of the brain that contribute to the activity recorded at a single sensor (Stam 2005; Wackermann and Allefeld 2007). A functional source is an operational concept that does not have to coincide precisely with a well defined anatomical part of the brain, and is neutral with respect to the problems of localization of primary source and volume conduction (Stam 2005; Wackermann and Allefeld 2007). Additionally the use of averaged values for the whole cortex while assessing different EEG parameters diminishes the contribution of a particular anatomical area in the overall result of the study.

Further, it has been documented that conscious cognitive operations reflect surprisingly small (less than 6%) local alterations in mean energy consumption evaluated by metabolic measures (Schölvinck et al. 2008). This may result in conscious operations failing to be detected by PET, BOLD, fMRI functional imaging; while there is a large body of research indicating that conscious cognitive operations are well reflected in the changes of EEG signals (for the review see Nunez 2000; Fingelkurts et al. 2010).

Yet another *advantage of EEG screening* in comparison to fMRI or PET studies is that EEG equipment is inexpensive, readily available in each clinic (or could be easy installed if needed); EEG can be recorded nonintrusively and noninvasively at the patient's bedside or even at home; patients do not need to be transported with artificial ventilation and other life support equipment to a laboratory (leaving aside the ethical problems of invasive PET measurement in patients unable to communicate; Kotchoubey et al. 2002). Moreover the fMRI or PET procedures are usually related to a high stress due to loud noise and other circumstances, which can considerably interfere with a patient's brain functional state.

Keeping these in mind, we could conclude: our results suggest that following further validation on the larger samples of patients with severe brain injuries, the current EEG operational architectonics methodology could potentially be translated into a routine clinical setting, allowing clinicians (a) to objectively assess the degree of conscious cognition expression in a patient during bedside assessment, (b) to refine clinical evaluation and redefine diagnosis of patients, (c) to evaluate the most probable prognosis/outcome, and (c) to plan a rational rehabilitation intervention.

As we pursue our research further, we can expect to provide clinicians with an *objective instrument for signs of (un)consciousness* of self and environment, which will help to reduce the current level of misdiagnosis of VS patients among patients with severe brain injuries which is as high as 37-43% (Childs et al. 1993; Andrews et al. 1996; Schnakers et al. 2006). This aim is especially urgent and important for a clinical practice since the mentioned rate of misdiagnosis has not substantially changed in the past 15 years (Schnakers et al. 2009) despite years of conducted research. Behavioral assessment still remains the so-called "gold standard" for detecting signs of (un)consciousness and, hence, determining final diagnosis (Majerus et al. 2005). The problem is that misdiagnosis can lead to very *serious consequences*, especially in regard to end-of-life decision-making (Andrews 2004), because such decisions are likely to be influenced by whether the patient is diagnosed with MCS or VS (Schnakers et al. 2009).

5.3. Methodological limitations

A relatively small experimental group sample (*N* = 21, 14 VS patients and 7 MCS patients) represents one limitation. This is mainly due to 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 resultant effects due to this constraint, we adopted a nonparametric statistics to analyze the obtained results. At the same time the number of patients in the present study was substantially larger than in many other studies on the patients with severe brain injuries (1 patient: de Jong et al. 1997; Davey et al. 2000; Moritz et al. 2001; Goldfine et al. 2005; Faran et al. 2006; Owen et al. 2006; Coleman et al. 2007; 2 patients: Schiff et al. 2005; 3 patients: Plum et al. 1998; Cauda et al. 2009; 4 patients: Laureys et al. 1999; Vanhaudenhuyse et al. 2010; 5 patients: Schiff et al. 2002; Juengling et al. 2005; just to mention a few). Nevertheless, to confirm the presented in this paper results, future studies that include a larger group of patients is warranted.

Cephalic EEG reference (mean of the signals from C_3 and C_4 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). 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 or measurement electrode impedance (Ferree et al. 2001). However, since there is some possibility of distortion of the potentials’ topography, to verify the presented in this paper results, future studies need to be organized with the most widely used and reliable EEG reference montage – linked ears.

A healthy control group represents yet another potential limitation. It has been suggested that for the patients with disorders of consciousness 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 (Kotchoubey and Lang 2011). This suggestion is based on an assumption 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. At the same time there is some evidence indicating that this putative limitation could be irrelevant. It has been documented that a patient who emerged from MCS had similar amounts of cortex functional connectivity (measured by coherence) compared to a normal subject; and this was in spite of the severe brain injury that the patient sustained, which resulted in massive white matter loss, as was evaluated on MRI (Goldfine et al. 2005). Another example presents a diametrically opposite situation, where the brain structures are intact, but consciousness is lost: absence seizures present brief episodes of unconsciousness without any evidence of structural injury. Unlike syncope or pharmacologic anesthesia, arousal is preserved during the absence seizure demonstrating the selective loss of integrative functions with these events (Schiff and Plum 1999). Recent neuroimaging studies have shown functional deactivations in fronto-parietal associative cortices during these absence seizures (Salek-Haddadi et al. 2003; Laufs et al. 2006). Thus, taken together these studies indicate that loss of consciousness could be related with functional alterations in cortical structures and impairment in relations between them, rather than with particular brain lesions and the amount of brain damage. In this context the use of a healthy control group could be justified. However, to verify/confirm the results, presented in this paper future studies that include a control group of brain-damaged but fully conscious patients is warranted.

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