Coherence and Consciousness: Study of Fronto-Parietal Gamma Synchrony in Patients with Disorders of Consciousness

Marianna Cavinato · Clara Genna · Paolo Manganotti · Emanuela Formaggio · Silvia Francesca Storti · Stefania Campostrini · Chiara Arcaro · Emanuela Casanova · Valeria Petrone · Roberto Piperno · Francesco Piccione

Accepted: 7 July 2014

Abstract Evaluation of consciousness needs to be supported by the evidence of brain activation during external stimulation in patients with unresponsive wakefulness syndrome (UWS). Assessment of patients should include techniques that do not depend on overt motor responses and allow an objective investigation of the spontaneous patterns of brain activity. In particular, electroencephalography (EEG) coherence allows to easily measure functional relationships between pairs of neocortical regions and seems to be closely correlated with cognitive or behavioral measures. Here, we show the contribution of higher order associative cortices of patients with disorder of consciousness (N = 26) in response to simple sensory stimuli, such as visual, auditory and noxious stimulation. In all stimulus modalities an increase of short-range parietal and long-range fronto-parietal coherences in gamma frequencies were seen in the controls and minimally conscious patients. By contrast, UWS patients showed no significant modifications in the EEG patterns after stimulation. Our results suggest that UWS patients can not activate associative cortical networks, suggesting a lack of information integration. In fact, fronto-parietal circuits result to be connectively disrupted, conversely to patients that exhibit some form of consciousness. In the light of this, EEG coherence can be considered a powerful tool to quantify the involvement of cognitive processing giving information about the integrity of fronto-parietal network. This measure can represent a new neurophysiological marker of unconsciousness and help in determining an accurate diagnosis and rehabilitative intervention in each patient.

Keywords EEG coherence · Unresponsive wakefulness syndrome · Sensory stimulation · Fronto-parietal network

Introduction

In the last decades, medical advances have allowed more severely impaired patients to survive. Consequently, the number of patients with unresponsive wakefulness syndrome (UWS, previously known as vegetative state. Laureys et al. 2010) for prolonged periods has proportionally increased (Beaumont and Kenealy 2005). The UWS is a condition in which a person has full or partial preservation of sleep-wake cycles and autonomic functions, but shows no evidence of reproducible and purposeful behavioral responses to external environment (The Multi-Society Task Force on PVS 1994; Zeman 2001).

Currently, clinical practice primarily relies on behavioral assessments to detect conscious awareness, without considering possible confounding factors and mechanisms producing impaired brain function. However, there is a growing consensus that the assessment of patients with

M. Cavinato (✉) · C. Genna · P. Manganotti · E. Formaggio · S. Campostrini · C. Arcaro · F. Piccione
Neurophysiology Department, San Camillo Foundation, Institute of Care and Research, Via Alberoni, 70, 30126 Venice, Italy
e-mail: marianna.cavinato@ospedalesancamillo.net

C. Genna
Otto Bock HealthCare GmbH, Duderstadt, Germany

P. Manganotti · S. F. Storti
Department of Neurological and Movement Sciences, Clinical Neurophysiology and Functional Neuroimaging Unit, Section of Neurology, University of Verona, Verona, Italy

E. Casanova · V. Petrone · R. Piperno
Department of Physical Medicine and Rehabilitation, Maggiore Hospital, Bologna, Italy

impaired consciousness should include techniques that do not depend on overt motor responses and allow an objective bedside exploration of the spontaneous patterns of brain activity (Owen et al. 2006; Boly et al. 2009; Zeman 2009; Fingelkurts et al. 2013a).

Electroencephalogram (EEG) represents a suitable choice to measure the activities of large-scale cortical networks closely related to behavior and consciousness, it is easily available and can overcome small movement artefacts and the presence of surgical metallic clips that often hamper use of neuroimaging (Harrison and Connolly, 2013; Fingelkurts et al. 2012a). In addition, average processing of the EEG when a repeated stimulus is delivered can help in quantifying small brain changes induced by sensory and cognitive activity (Lehembre et al. 2012b). Of particular interest, the presence of event related potentials (ERPs) seems to represent a high prognostic value for recovery of patients with disorders of consciousness (DOS), reflecting the time course of information processing (Fischer et al. 2006; Kotchoubey, 2005; Cavinato et al. 2011).

Despite the known usefulness of EEG in predicting recovery from coma and other neurological disorders (Young 2000; Zandbergen et al. 1998), there is scarce evidence reporting its predictive value in UWS recovery. Then, evoked potentials are valuable markers of good prognosis, but their utility as a diagnostic tool is still object of controversy (Guérit, 2007). Reasonably, this could be due to the inadequate EEG classification produced with traditional qualitative studies and the imprecise analysis of data (Wallace et al. 2001).

An alternative approach is represented by quantitative EEG analysis that consists in computations of parameters from the EEG, such as power spectra (Piccione et al. 2010; Manganotti et al. 2013) and connectivity values. This approach offers higher reliability than qualitative visual inspection of recordings. Especially the coherence, that is a measure of degree of association or coupling of frequency spectra between different times series, can provide complementary information of diagnostic and prognostic value, measuring functional relationships between pairs of neocortical regions (Hallett 1999; Pereda et al. 2005). Indeed, EEG coherence appears closely correlated with cognitive or behavioral measures, providing an index of the integrity of inter-regional networks and communication between cortical areas, as well as with subcortical structures (e.g., thalamus and basal ganglia) that mediate this connectivity (Davey et al. 2000; Srinivasan et al. 2007; Van der Hiele et al. 2007). In this sense, a high coherence between EEG signals at different sites of the scalp hints at an increased functional interplay between the underlying neuronal networks.

Some authors have investigated connectivity in the unresponsive wakefulness syndrome. Laureys et al. (2000) identified functional disconnections between intralaminar thalamic nuclei and prefrontal and anterior cingulate cortices in patients suffering from DOC, demonstrating the importance of fronto-parietal network (FPN), but equally of cortico-thalamo-cortical circuits. Similarly, a case study on a UWS patient with severe asymmetric subcortical brain lesion showed a drop of coherence in the damaged hemisphere (Davey et al. 2000). The authors argued that the EEG coherence seems to be partially determined by subcortical structures and a damage of that circuitry can underlie the permanent state of unconsciousness. In fact, the activity of thalamo-cortical gating systems mediates neural mechanisms of perception (Schiff and Plum 2000). A decrease in coherence has also been observed in minimally conscious state (MCS) patients (Leon-Carrion et al. 2008). The authors stressed the importance of preservation of prefrontal-parietal networks that may account for the differences in the level of awareness of DOC patients. Further, using EEG operational synchrony measure (Fingelkurts et al. 2012b) demonstrated decrease in the cortex functional connectivity during unresponsive wakefulness state and, to a smaller extent, in a minimally conscious state, especially between areas involving in the default mode network (Fingelkurts et al. 2013b). Compatible findings have been reported by Lehembre et al. (2012a) and Boly et al. (2009).

In addition in order to measure resting cerebral connectivity, evaluation of awareness needs to be supported by the evidence of brain activation during external stimulation in patients with UWS. Indeed, research in animals suggests that an intense information flow links cortical and subcortical relays of the somatosensory system (Sherman 2005). As a consequence, distributed processing seems to allow an acceleration of the process needed to achieve complex behavioral domains, such as somatosensory perception (Jiang et al. 1991; Mesulam 1990; Waterhouse et al. 1993).

Multisensory stimulation has already been used as an intervention for the recovery of consciousness in patients in coma or with UWS. Although some encouraging results have been reported (Oh and Seo, 2003), no studies have demonstrated a reliable evidence to support the effectiveness of this technique and there is a consistent lack of assessment tools (Lombardi et al. 2002).

The present study examined neural responses to unstructured auditory, visual and noxious stimuli in a group of DOC patients and healthy controls in order to objectively assess cerebral processing during basic sensory activation. The use of EEG coherence could detect the possible persistence of remaining neural network activity allowing to assess the residual network properties that underlie the expression of fractional behaviors observed in UWS.

Methods

Patients

Twenty-six patients (9 women, 17 men; mean ± SD age, 53 ± 12) from 4 study centers across north Italy meeting the diagnostic criteria for unresponsive wakefulness syndrome or minimally conscious state and fifteen age-matched healthy controls (6 women, 9 men; mean ± SD age, 49 ± 18) were assessed for recruitment. Table 1 summarizes clinical and demographic features of the patients.

Alteration of consciousness was caused by ischemic or hemorrhagic stroke in twelve patients, anoxia in nine patients, and traumatic brain injury in five patients. Patients were admitted between 16 and 22 months after the injury.

Patients with unstable clinical conditions, such as heart and pulmonary failure, or a previous history of neurological, audiological or psychiatric disorders were excluded. No psychotropic drugs were being administered during the period of EEG recordings. All patients underwent a battery of neurophysiological tests to assess the integrity of afferent pathways. Normal or slightly delayed brain stem auditory evoked responses were seen in the participants. Somatosensory evoked potentials obtained by stimulation of the median nerve at wrist showed the presence of primary motor cortex responses (N20). Visual evoked responses generated from goggle-mounted flash stimulator could be recorded in all patients.

Assessment of consciousness was provided by three scales: the Disability Rating Scale (DRS), the Coma Recovery Scale Revised (CRS-R) and the Western Neuro Sensory Stimulation Profile (WNSSP) (Rappaport et al. 1982; Giacino et al. 2004; Ansell and Keenan 1989). We adopted three scales to have a more fine-grained assessment of the level of consciousness, recognizing that a behavior is not simply random or reflex, but contingent to a given stimulus. Only if the three scores were referable to the same level of consciousness patients were included in the study. Then, on the basis of the DRS score at admission, patients were classified into two groups. The first group consisted of 15 patients with a DRS scored ≥ 22 (vegetative and extremely vegetative states); they did not show any behavioural sign of awareness. The second group included 11 patients with a DRS lower than 22 who could be considered as in a MCS because some signs of purposeful behavior could be observed, even if highly inconsistent.

The present study was approved by the Research Ethics Committee (REC) of the Scientific Foundation "San Camillo" and was compliant with the declaration of Helsinki guidelines. All legal representatives gave written informed consent for the patients to participate. Each healthy volunteer signed his/her written consent documents.

Stimulation

The procedure was the same for either stimulation condition. Participants were seated upright in a chair located in a sound-attenuated laboratory. All participants had an eyes-closed baseline EEG recorded for 10 min at the beginning of the session. This baseline recording was analyzed to determine each subject's dominant activity. Participants were then provided visual, acoustic and electrical stimuli. For the acoustic stimulation, participants were stimulated via TDH-49 earphones with alternating polarity clicks. The estimation of auditory threshold was traced by the wave V detection which is clinically used as a robust indicator that the central nervous system detected an auditory stimulus (Kochhar et al. 2007). The participants exhibited large and reproducible waves V at an intensity of 90 dB. This threshold was chosen as the acoustic stimulus intensity and presented at a 10 Hz rate. During visual stimulation, each participant received unstructured intermittent photic stimulation with light flash at a frequency of 15 Hz and intensity of 18 ft Lamberts. Electrical stimulation was applied over the median nerve at wrist. Stimulus intensity was set to elicit sustained thumb twitching at a frequency of 3 Hz.

In order to avoid adaptation to stimuli, participants received stimulation in three sessions of 1 min each, with EEG recording occurring simultaneously. A post-session eyes-closed EEG was recorded for 1 min after every minute of stimulation. The same procedure was repeated for each type of stimulation. The order of stimuli presentation was counterbalanced between participants.

EEG Recordings and Analysis

Before and after each stimulation session, EEG was recorded from 21 electrodes in accordance with the International 10/20 System, with the common reference placed anterior to Fz and the ground behind Pz. The electrooculogram (EOG) was recorded bipolarly to detect both vertical and horizontal eyes movements.

EEG signals were sampled at 256 Hz and pass-band filtered in the range of 0.5–50 Hz. The independent component analysis (ICA) was performed to detect, separate and remove activity in EEG records from ocular, muscular and cardiac sources to obtain artefact free EEG data. The data were subsequently divided in non over-lapping epochs of 2 s. All sweeps were inspected visually to detect further artefacts exceeding 75 μV which were removed manually. EEG segments free of artefacts were used in the analysis. Calculation of coherence, defined as the spectral cross-correlation between two signals normalised by their power spectra, was performed using Matlab platform (version 7.6) and was calculated according to the following equation:

Table 1 Clinical and structural imaging data of DOC patients

Patient No./ gender/ age(years)	DRS	CRS-R	WNSSP	Diagnosis	Cause	Months from trauma	MRI findings
1/M/28	24	4	8	UWS	vascular	20	Diffuse right hemisphere
2/F/46	21	6	16	MCS	anoxia	21	Diffuse anoxic-ischemic lesion
3/F/49	20	11	34	MCS	vascular	16	Diffuse left hemisphere. Parathalamic hematoma
4/F/32	22	7	14	UWS	trauma	18	Cortical contusions in the left temporo-parietal lobes
5/F/54	24	4	8	UWS	vascular	19	Right temporal, parietal and occipital lobes
6/M/42	20	9	52	MCS	vascular	20	Right frontal, temporal and parietal lobes
7/M/58	21	6	37	UWS	vascular	18	Bilateral temporal and parietal lobes
8/M/48	19	11	36	MCS	vascular	16	Diffuse left hemisphere/right temporal and parietal cortex
9/F/57	20	11	52	MCS	anoxia	20	Diffuse anoxic-ischemic lesion
10/M/45	23	4	11	UWS	vascular	21	Bilateral temporal, parietal and occipital lobes
11/M/72	22	6	9	UWS	vascular	18	Right frontal, temporal and parietal lobes
12/M/39	21	9	11	MCS	trauma	19	Bilateral frontal lobes
13/M/58	24	5	29	UWS	anoxia	20	Diffuse anoxic-ischemic lesion
14/M/66	21	9	16	MCS	vascular	18	Right frontal and temporal lobes Right thalamus
15/F/74	23	6	9	UWS	anoxia	18	Sovratentorial anoxic-ischemic lesions
16/F/66	21	9	12	MCS	anoxia	20	Diffuse anoxic-ischemic lesion
17/M/48	20	11	18	MCS	trauma	16	Bilateral temporal and occipital contusions
18/M/62	26	6	8	UWS	anoxia	16	Diffuse anoxic-ischemic lesion
19/M/57	24	6	9	UWS	anoxia	18	Diffuse anoxic-ischemic lesion
20/M/65	24	3	10	UWS	vascular	20	right temporal and parietal lobes. Corpus callosum, mesencephalus
21/F/59	21	14	34	MCS	anoxia	16	Diffuse anoxic-ischemic lesion
22/F/57	26	6	3	UWS	anoxia	21	Diffuse anoxic-ischemic lesion
23/M/65	18	14	61	MCS	vascular	18	Diffuse anoxic-ischemic lesion
24/M/30	21	11	31	MCS	trauma	21	Left temporal lobe. Left cerebral peduncle
25/M/41	22	9	9	MCS	trauma	22	Bilateral frontal lobes
26/M/51	20	9	52	MCS	vascular	19	Diffuse left hemisphere/right temporal and parietal cortex

DRS Disability Rating Scale, *CRS-R* Coma Recovery Scale Revised, *WNSSP* Western Neuro Sensory Stimulation Profile

$$Coh_{xy}^2(f) \;=\; \frac{|P_{xy}(f)|^2}{P_{xx}(f)P_{yy}(f)},$$

where Pxy(f) is the cross-power spectral density and Pxx(f) and Pyy(f) are the respective auto-power spectral densities of two signals. Coherence was computed over a frequency range of 0.5–50 Hz, with a resolution of 0.5 Hz. The mean values were estimated in the delta (0.5–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), beta (13–30 Hz), and gamma (30–50 Hz) ranges, in rest condition and after each stimulation. Coherence was computed for all possible pairwise combinations of the 19 leads, resulting in 171 combinations for each frequency band. Differences of coherence, with respect to EEG at rest, were computed in different frequency bands for the two groups, controls and DOC patients, for the three different stimulations: visual, acoustic and noxious.

Statistical Analysis

SPSS package was used for statistical analysis.

Fisher's Z transformation of coherence values in each derivation was implemented to normalize the distribution of coherence. The differences between the groups were assessed by ANOVA and included 'group' (UWS, MCS, and controls) as between-subjects factor and 'condition' (pre- vs. post-stimulation), 'electrode pair' (171 coherence values) and 'band' (delta, theta, alpha, beta, and gamma frequency bands) as within-subjects factors. Greenhouse–Geisser corrected values are reported. Post-hoc comparison between the two conditions was calculated by using paired sample *t* tests corrected for multiple comparisons with Bonferroni criterion.

Short-range connections of an anterior network with electrode positions Fp1, Fp2, F3, Fz and F4, a posterior network including electrodes P3, Pz, P4, O1 and O2 and long-range connections of a FPN with electrode sites F3, Fz, F4, P3, Pz and P4 were averaged to yield two short-range values (anterior and posterior) and one long-range value (fronto-parietal), in order to discriminate between short and long-range frontal and parietal connections. Thus, a second ANOVA with factors 'condition' (pre vs. post-stimulation), 'band' (delta, theta, alpha, beta, and gamma frequencies) and 'connection' (anterior short-range, posterior short-range, fronto-parietal long-range) was analysed and Greenhouse–Geisser corrected values are reported.

Pearson correlation was conducted to investigate the possible relations among clinical and neurophysiological data of coherence at rest and after stimulation in DOC patients.

Statistical significance was defined as $p < 0.05$.

Results

Resting State

As shown in Fig. 1, in resting condition UWS patients had significantly lower alpha coherence over the parietal regions than controls and minimally conscious state patients ($p = 0.03$ and $p = 0.04$, respectively). In addition, higher frontal and fronto-parietal theta coherences were seen in the unresponsive wakefulness syndrome participants ($p = 0.03$; $p = 0.02$).

Visual Stimulation

The first repeated measures analysis of variance revealed significant main effects for factors 'electrode pair' ($F_{44/1144} = 13.53$; $p < 0.001$) and 'band' ($F_{4/104} = 2.98$; $p = 0.02$). Significant interactions 'electrode pair' * 'group' ($F_{88/1144} = 8.10$; $p < 0.001$), 'electrode pair' * 'band' ($F_{176/4576} = 2.92$; $p = 0.001$) and 'electrode pair' * 'condition' ($F_{44/1144} = 7.84$; $p < 0.006$) were found. In addition, a four-way interaction between factors 'group', 'electrode pair', 'condition' and 'band' ($F_{352/4576} = 2.76$; $p = 0.02$) was also observed. This interaction indicates a higher gamma coherence, compared to rest, after visual stimulation in the frontal short-range and fronto-parietal long-range connections in the healthy controls compared to the patients, as seen in Fig. 2. In addition, a significant lower gamma activity was seen in the posterior short-range connectivity.

The second ANOVA showed significant main effects for factors 'band' ($F_{4/104} = 3.12$; $p = 0.05$), 'connection' ($F_{2/52} = 7.35$; $p = 0.008$) and significant interactions between 'connection' and 'group' ($F_{16/208} = 3.59$; $p = 0.03$) and 'condition' * 'group' ($F_{1/26} = 4.03$; $p = 0.02$) confirming a high fronto-parietal fast frequency coherence in the healthy controls after visual stimulation.

Acoustic Stimulation

The within-group analysis of the first ANOVA revealed that after acoustic stimulation, significant main effects for 'electrode pair' ($F_{44/1144} = 12.15$; $p < 0.001$) and 'band' ($F_{4/104} = 5.80$; $p = 0.006$) were seen. Interactions 'electrode pair'*'group' ($F_{88/1144} = 7.79$; $p < 0.001$) and 'electrode pair'*'band' ($F_{176/4576} = 2.67$; $p = 0.007$) were found. These effects are contained in a significant three-way interaction between factors 'band', 'condition' and 'electrode pair' ($F_{352/4576} = 11.67$; $p = 0.005$).

After acoustic stimulation, gamma showed an increase of coherence in a distributed fronto-parietal and intra-parietal network in the control group and minimally conscious state patients (Fig. 2).

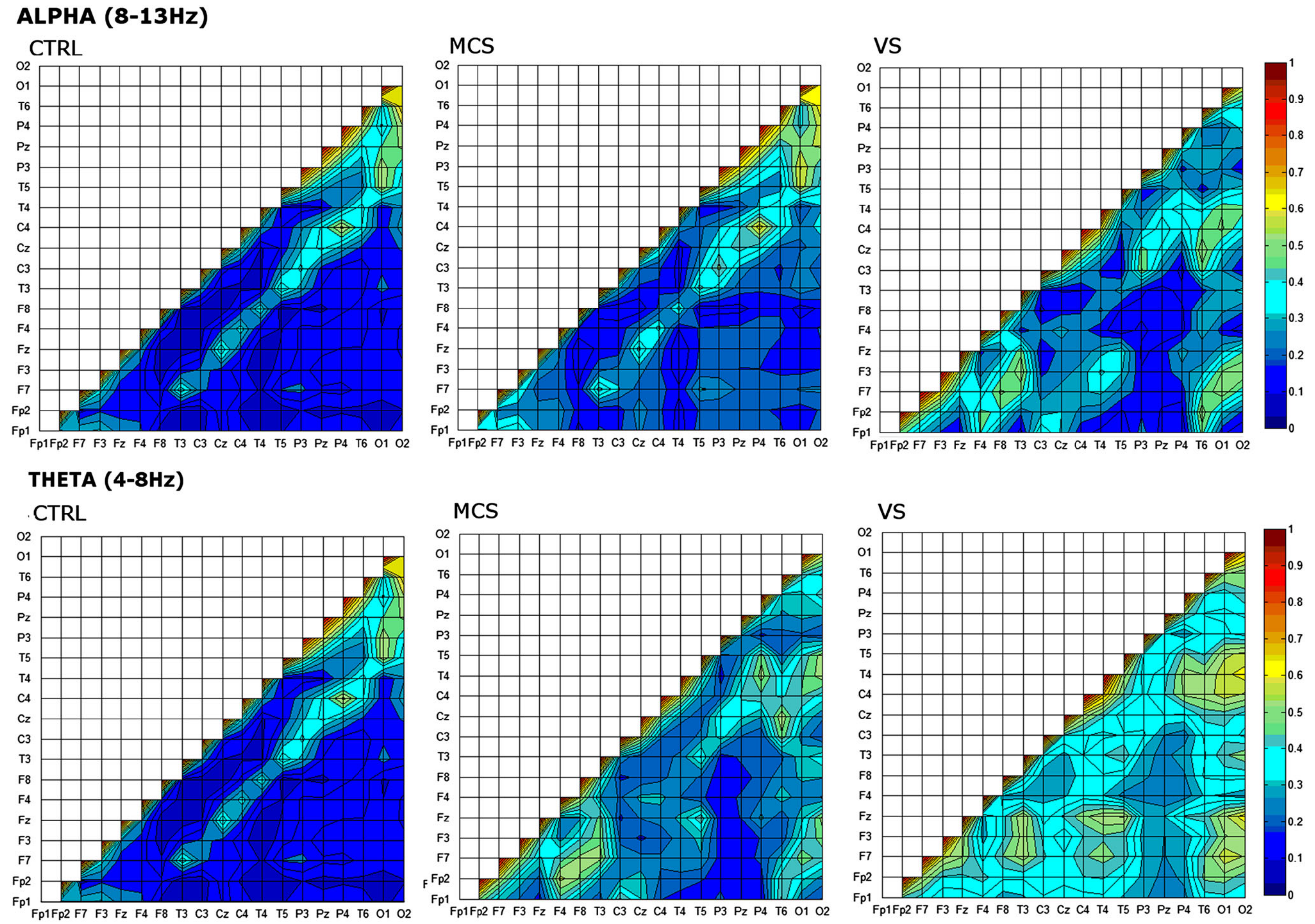

Fig. 1 Difference maps of Fisher-Z transformed coherence values at rest between groups for theta and alpha frequencies. Note the higher posterior alpha coherence in controls and minimally conscious state patients and the higher theta coherence in frontal and fronto-parietal regions in unresponsive wakefulness syndrome patients compared to other groups. *CTRL* controls, *MCS* minimally conscious state, *UWS* unresponsive wakefulness syndrome

For the second ANOVA, in addition to factors 'connection' ($F_{2/52} = 10.02$; $p = 0.002$) and 'band' ($F_{4/104} = 4.06$; $p = 0.02$), interactions between factors 'connection' and 'group' ($F_{4/52} = 4.03$; $p = 0.02$) and 'connection' and 'band' ($F_{8/208} = 8.62$; $p < 0.001$) reached significance. Most importantly a significant three-way interaction 'condition', 'band' and 'connection' ($F_{8/208} = 12.15$; $p < 0.001$) and a four-way interaction 'condition', 'band', connection', and 'group' ($F_{16/208} = 3.69$; $p = 0.003$) indicates that long-range and posterior short-range gamma connections are increased in the MCS and control groups rather than the UWS patients after auditory stimulation.

Electrical Stimulation

After peripheral electrical stimulation, there were significant main effects for 'electrode pair' ($F_{44/1144} = 15.80$; $p < 0.001$). In addition, significant interactions between 'electrode pair' and 'group' ($F_{88/1144} = 8.55$; $p < 0.001$), 'electrode pair' and 'band' ($F_{352/4576} = 3.34$; $p = 0.001$), and 'condition' and 'band' ($F_{4/104} = 4.29$; $p = 0.02$) were seen. These interactions were synthesised in a significant four-way interaction between 'band', 'condition', 'electrode pair', and 'group' ($F_{352/4576} = 1.68$; $p = 0.04$) indicating a significant increase of beta and gamma long-range coherence in the minimally conscious state patients and controls after peripheral electrical stimulation.

The second analysis of ANOVA revealed a significant main effect for factor 'connection' ($F_{2/52} = 10.37$; $p = 0.002$) and a two-way interaction involving 'connection' and 'group' ($F_{4/52} = 3.67$; $p = 0.03$). This indicates higher long-range fronto-parietal connections in the controls than unresponsive wakefulness syndrome patients.

Correlation Between Clinical and Electrophysiological Data

A significant inverse correlation between the DRS and the EEG coherence of the parietal short-range connections in beta and gamma bands at rest was found ($p = 0.008$),

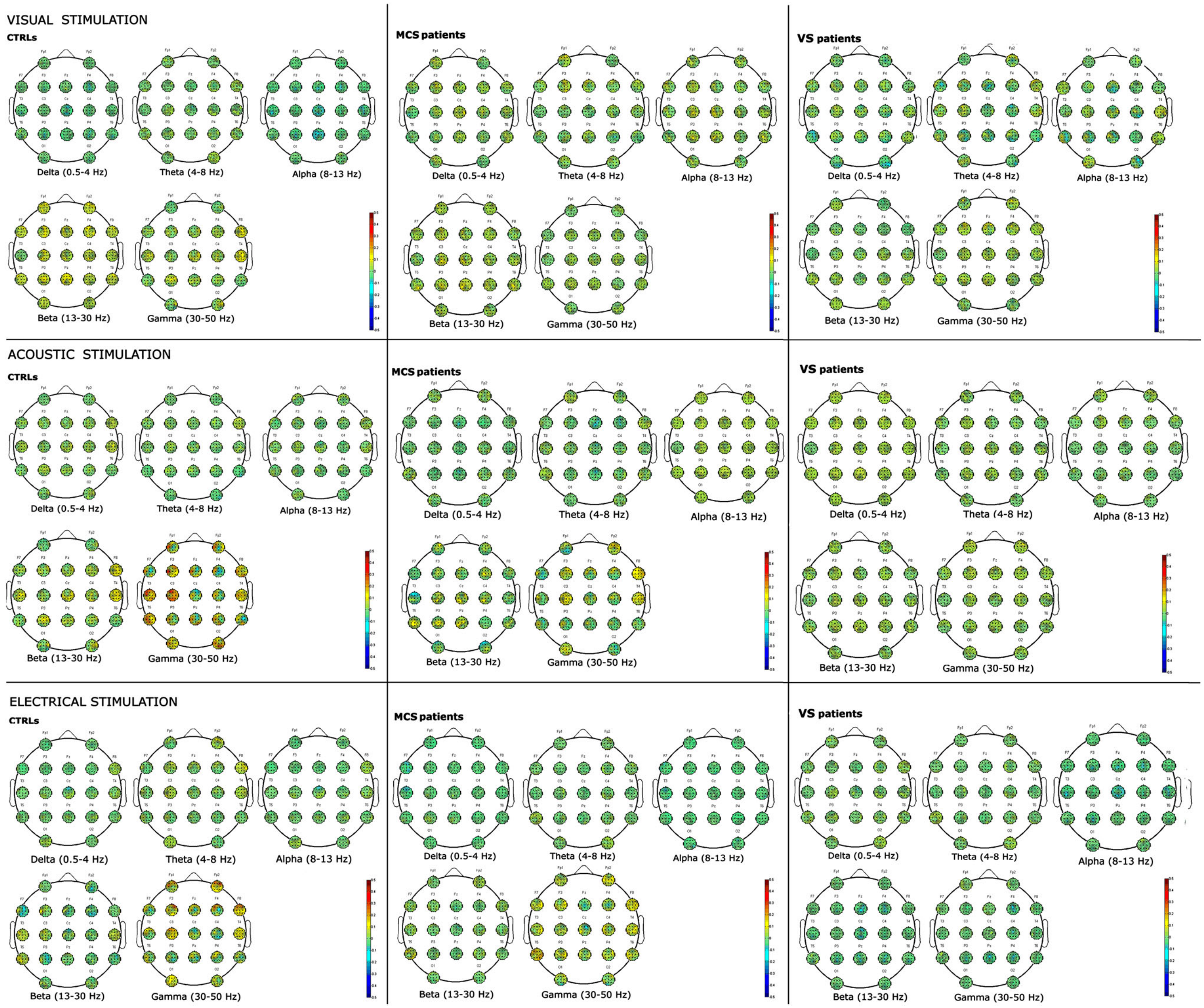

Fig. 2 Topography of the significant differences, with respect to EEG at rest, of the coherence in different frequency bands for the two groups, controls (*left panel*) and DOC patients (*right panel*), for the three different stimulations: visual, acoustic and noxious. The colour scale codes the degree of EEG coherence as compared to resting (*baseline*) condition with eyes closed. *Red* represents strong enhancement and *blue* reduction after stimulation

indicating that patients with higher disability had a lower coherence in the fast frequencies over the posterior areas.

Discussion

In the present study, we investigated whether different kinds of stimulation in the altered state of consciousness lead to specific patterns of physiological changes by means of quantitative EEG analysis.

Here, connectivity measurements at rest showed that the unresponsive wakefulness syndrome patients had a lower connected network in alpha frequency in the posterior cortical regions than controls and MCS patients, in addition to a higher and widespread theta coherence. Accordingly, previous studies have suggested a relation between excess of slow wave activity and reduced level of awareness in brain injury population (Leon-Carrion et al. 2008; Fingelkurts et al. 2012b). Thus, power in slow activity could be considered a good neurophysiological indicator of state of consciousness. However, since the spectrum of EEG in DOS is greatly variable, it appears to be difficult to quantify different EEG features and address their predictive value. To overcome this limitation, the sensory stimulation approach has most frequently been advocated for enhancing selective attention by regulating the environment in patients with limited capacity for information processing. As it still remains unclear whether sensory stimulation modifies the clinical condition of UWS patients, we investigated whether different kinds of stimulation could lead to specific neurophysiological response patterns.

In our study, quantitative EEG data revealed cortical electrophysiological changes restricted to healthy and minimally conscious state participants after sensory stimulation. These changes can be summarized in a modulation of cortical coherence in short-range parietal and long-range fronto-parietal areas within a gamma frequency range. By contrast, UWS patients showed no significant modifications in the EEG patterns after stimulation.

In a healthy brain, neurons can engage in synchronized oscillatory activity in the gamma-frequency range when responding to sensory stimuli and their oscillatory patterning can be enhanced with arousal and attention (Rodriguez et al. 2004). The effects of visual, auditory and peripheral electrical stimuli might have mechanisms in which the basal forebrain nucleus basalis of Meynert and the anterior cingulate cortex play a crucial role. The nucleus of Meynert is indeed the origin of the cortical cholinergic system and is essential for the level of cortical activity and cognitive processes, such as working memory (Shinotoh et al. 2003). At the same time, the anterior cingulate cortex can be activated by high-intensity electric stimulation of the median nerve at the wrist together with primary and secondary somatosensory cortices, bilateral insular and posterior parietal cortex (Laureys et al. 2002; Kwan et al. 2000).

External somatosensory stimulation could be considered as a type of enriched environment and promote cholinergic activity to the basal forebrain and its connections, in particular, the neocortex. Cognitive functions that depend on cholinergic activity and control such as the ability to focus attention and to retain stimulus features in short- and long-term memory are associated with increased synchronization of responses in the gamma frequency range (Mueller and Gruber 2000; Fries et al. 2001; Grueber et al. 2002). In fact, it has been demonstrated that neuronal gamma band is significantly increased in cortex activated by the presence of electrical, visual or auditory stimuli, and is enhanced among neurons activated by an attended stimulus (Sadaghiani et al. 2009; Brunet et al. 2013). Gamma frequency activity thus appears to be an attentionally modulated correlate of stimulus drive, diffused within and between different cortical areas, encompassing anterior cingulate, insular, prefrontal and posterior parietal cortices, and represents a likely target of top-down modulation (Laureys et al. 2002).

The increase of gamma connections in long-range fronto-parietal areas that we found in the MCS and healthy control groups could suggest that posterior sensory representations may be consistently activated by a frontally located control mechanism.

Our results suggest that the increase of gamma activity in the fronto-parietal interconnections in MCS patients and healthy controls may represent the engagement of brain in continuous information gathering and representation of self and the external environment (Fries 2009). State of consciousness could be associated with the activation of a network involving forebrain arousal functionally coupled with parts of frontal cortex and posterior sensory integration regions. In particular, the anterior cingulated cortex (ACC), a medial prefrontal area, has been proposed to play a critical role in consciousness by integrating cognitive-emotional processing with the state of arousal and the intent-to-act (Paus et al. 2001). The ACC is a key site of behavioral self-regulation and is closely connected with parietal cortex (Posner et al. 2007). Interactions between these areas can be reinforced by exposure to sensory stimulation as a method of environmental enrichment.

On the other hand, unresponsive wakefulness syndrome patients showed impaired functional connections between distant cortical areas and, in particular, of the fronto-parietal associative cortices. In fact, numerous studies have reported that sensory stimulation could activate partially preserved restricted sensory representations, but not higher-order multimodal areas from which they appear disconnected (Laureys et al. 2006).

Thus, the level of preservation of FPN may explain the different manifestations of awareness between minimally conscious and UWS patients, indicating the possible persistence of remaining cortical and cortico-subcortical network activity in the formers and a functional disconnection in the FPN circuit in the patients with UWS (Schiff et al. 2002).

In the light of this, the coherence between frontal and parietal areas could represent a new neurophysiological marker of unconsciousness and help in determining the diagnosis of unresponsive patients, together with behavioral evaluations. In fact, an accurate diagnosis is essential to plan the most suitable rehabilitative needs customized for each patient. Rehabilitation strategies for patients with DOS should provide medical and neurorehabilitative care in an attempt to facilitate where possible emergence from these compromised levels of neurologic function, as well as to minimize complications associated with them.

In the second place, the use of specific tools in the neurobehavioral assessment of DOC patients, such as the study of EEG coherence in the FPN, could be helpful to test the efficacy of new rehabilitative strategies based on programs of pharmacological, multisensory, cognitive or transcranial stimulation by correlates specifically oriented to the quantification of the neural functions related to consciousness. This could represent one of the key points to guarantee the better chance to recovery in each unresponsive patient.

Acknowledgment This work was partially supported by Myosens (FP7-PEOPLE-2011-IAPP-286208) project and by the Region of Veneto, current research funding (3984/08). We would like to thank Felice Silverio, and Paolo Fusaro for the skilled assistance in conducting the experiments.

References

AlA Fingelkurts, AnA Fingelkurts, Bagnato S, Boccagni C, Galardi G (2012) EEG oscillatory states as neuro-phenomenology of consciousness as revealed from patients in vegetative and minimally conscious states. Conscious Cogn 21:149–169

AnA Fingelkurts, AlA Fingelkurts, Bagnato S, Boccagni C, Galardi G (2013a) Prognostic value of resting-state electroencephalography structure in disentangling vegetative and minimally conscious states: a preliminary study. Neurorehabil Neural Repair 27:345–354

AnA Fingelkurts, AlA Fingelkurts, Bagnato S, Boccagni C, Galardi G (2013b) Dissociation of vegetative and minimally conscious patients based on brain operational architectonics: factor of etiology. Clin EEG Neurosci 44:209–220

Ansell BJ, Keenan JE (1989) The western neuro sensory stimulation profile: a tool for assessing slow-to-recover head-injured patients. Arch Phys Med Rehabil 70:104–108

Beaumont JG, Kenealy PM (2005) Incidence and prevalence of the vegetative and minimally conscious states. Neuropsychol Rehab 15:184–189

Boly M, Massimini M, Tononi G (2009) Theoretical approaches to the diagnosis of altered states of consciousness. Prog Brain Res 177:383–398

Brunet N, Bosman CA, Roberts M, Oostenveld R, Womelsdorf T, De Weerd P, Fries P (2013) visual cortical gamma-band activity during free viewing of natural images.Cereb Cortex Oct 9 (in press)

Cavinato M, Volpato C, Silvoni S, Sacchetto M, Merico A, Piccione F (2011) Event-related brain potential modulation in patients with severe brain damage. Clin Neurophysiol 122:719–724

Davey MP, Victor JD, Schiff ND (2000) Power spectra and coherence in the EEG of a vegetative patient with severe asymmetric brain damage. Clin Neurophysiol 111:1949–1954

Fingelkurts AA, Fingelkurts AA, Bagnato S, Boccagni C, Galardi G (2012) DMN operational synchrony relates to self-consciousness: evidence from patients in vegetative and minimally conscious states. Open Neuroimaging J 6:55–68

Fischer C, Luauté J, Némoz C, Morlet D, Kirkorian G, Mauguière F (2006) Improved prediction of awakening or non awakening from severe anoxic coma using tree-based classification analysis. Crit Care Med 34:1520–1524

Fries P (2009) Neuronal gamma-band synchronization as a fundamental process in cortical computation. Annu Rev Neurosci 32:209–224

Fries P, Reynolds JH, Rorie AE, Desimone R (2001) Modulation of oscillatory neuronal synchronization by selective visual attention. Science 291:1560–1563

Giacino JT, Kalmar K, Whyte J (2004) The JFK coma recovery scale—revised: measurement characteristics and diagnostic utility. Arch Phys Med Rehab 85:2020–2029

Gruber T, Muller MM, Keil A (2002) Modulation of induced gamma band responses in a perceptual learning task in the human EEG. J Cognit Neurosci 14:732–744

Guérit JM (2007) Electroencephalography: the worst traditionally recommended tool for brain death confirmation. Intensive Care Med 33:9–10

Hallett M (1999) EEG coherence: an introduction. J Clin Neurophysiol 16:499–500

Harrison AH, Connolly JF (2013) Finding a way in: a review and practical evaluation of fMRI and EEG for detection and assessment in disorders of consciousness. Neurosci Biobehav Rev 37:1403–1419

Jiang W, Chapman CE, Lamarre Y (1991) Modulation of the cutaneous responsiveness of neurones in the primary somatosensory cortex during conditioned arm movements in the monkey. Exp Brain Res 84:342–354

Kochhar A, Hildebrand MS, Smith RJ (2007) Clinical aspects of hereditary hearing loss. Genet Med 9:393–408

Kotchoubey B (2005) Event-related potential measures of consciousness: two equations with three unknowns. Prog Brain Res 150:427–444

Kwan CL, Crawley AP, Mikulis DJ, Davis KD (2000) An fMRI study of the anterior cingulate cortex and surrounding medial wall activations evoked by noxious cutaneous heat and cold stimuli. Pain 85:359–374

Laureys S, Faymonville ME, Degueldre C et al (2000) Auditory processing in the vegetative state. Brain 123:1589–1601

Laureys S, Faymonville ME, Peigneux P, Damas P, Lambermont B, Del Fiore G et al (2002) Cortical processing of noxious somatosensory stimuli in the persistent vegetative state. Neuroimage 17:732–741

Laureys S, Boly M, Maquet P (2006) Tracking the recovery of consciousness from coma. J Clin Invest 116:1823–1825

Laureys S, Celesia GG, Cohadon F, Lavrijsen J, León-Carrión J, Sannita WG, Sazbon L, Schmutzhard E, von Wild KR, Zeman A, Dolce G (2010) European task force on disorders of consciousness. Unresponsive wakefulness syndrome: a new name for the vegetative state or apallic syndrome. BMC Med 8:68

Lehembre R, Bruno MA, Vanhaudenhuyse A, Chatelle C, Cologan V, Leclercq Y, Soddu A, Macq B, Laureys S, Noirhomme Q (2012a) Resting state EEG study of comatose patients: a connectivity and frequency analysis to find differences between vegetative and minimally conscious states. Funct Neurol 27:41–47

Lehembre R, Gosseries O, Lugo Z, Jedidi Z, Chatelle C, Sadzot B, Laureys S, Noirhomme Q (2012b) Electrophysiological investigations of brain function in coma, vegetative and minimally conscious patients. Arch Ital Biol 150:122–139

Leon-Carrion J, Martin-Rodriguez JF, Damas-Lopez J, Barroso y Martin JM, Dominguez-Morales MR (2008) Brain function in the minimally conscious state: a quantitative neurophysiological study. Clin Neurophysiol 119:1506–1514

Lombardi F, Taricco M, De Tanti A, Telaro E, Liberati A. (2002) Sensory stimulation for brain injured individuals in coma or vegetative state. Cochrane Database Syst Rev (2):CD001427

Manganotti P, Formaggio E, Storti SF, Fiaschi A, Battistin L, Tonin P, Piccione F, Cavinato M (2013) Effect of high-frequency repetitive transcranial magnetic stimulation on brain excitability in severely brain-injured patients in minimally conscious or vegetative state. Brain Stimul 6:913–921

Mesulam MM (1990) Large-scale neurocognitive networks and distributed processing for attention, language, and memory. Ann Neurol 28:597–613

Mueller MM, Gruber T, Keil A (2000) Modulation of induced gamma band activity in the human EEG by attention and visual information processing. Int J Psychophysiol 38:283–299

Oh H, Seo W (2003) Sensory stimulation programme to improve recovery incomatose patients. J Clin Nurs 12:394–404

Owen AM, Coleman MR, Boly M, Davis MH, Laureys S, Pickard JD (2006) Detecting awareness in the vegetative state. Science 313(5792):1402

Paus T, Castro-Alamancos MA, Petrides M (2001) Cortico-cortical connectivity of the human mid-dorsolateral frontal cortex and its modulation by repetitive transcranial magnetic stimulation. Eur J Neurosci 14:1405–1411

Pereda E, Quiroga RQ, Bhattacharya J (2005) Nonlinear multivariate analysis of neurophysiological signals. Progr. Neurobiol 77:1–37

Piccione F, Cavinato M, Manganotti P, Formaggio E, Storti S, Battistin L, Cagnin A, Tonin P, Dam M (2010) Behavioural and neurophysiological effects of repetitive transcranial magnetic stimulation (rTMS) on minimally conscious state: a case study. Neurorehabil Neural Repair 25:98–102

Posner MI, Rothbart MK, Sheese BE, Tang Y (2007) The anterior cingulate gyrus and the mechanism of self-regulation. Cogn Affect Behav Neurosci 7(4):391–395

Rappaport M, Hall KM, Hopkins K, Belleza T, Cope DN (1982) Disability rating scale for severe head trauma: coma to community. Arch Phys Med Rehabil 63:118–123

Rodriguez R, Kallenbach U, Singer W, Munk MHJ (2004) Short- and long-term effects of cholinergic modulation on gamma oscillations and response synchronization in the visual cortex. J Neurosci 24:10369–10378

Sadaghiani S, Hesselmann G, Kleinschmidt A (2009) Distributed and antagonistic contributions of ongoing activity fluctuations to auditory stimulus detection. J Neurosci 29:13410–13417

Schiff ND, Plum F (2000) The role of arousal and "gating" systems in the neurology of impaired consciousness. J Clin Neurophysiol 17:438–452

Schiff ND, Ribary U, Moreno DR et al (2002) Residual cerebral activity and behavioural fragments can remain in the persistently vegetative brain. Brain 125:1210–1234

Sherman SM (2005) Thalamic relays and cortical functioning. Prog Brain Res 149:107–126

Shinotoh H, Fukushi K, Nagatsuka S, Tanaka N, Aotsuka A, Ota T, Namba H, Tanada S, Irie T (2003) The amygdala and Alzheimer's disease: positron emission tomography study of the cholinergic system. Ann N Y Acad Sci 985:411–419

Srinivasan R, Winter WR, Ding J, Nunez PL (2007) EEG and MEG coherence: measures of functional connectivity at distinct spatial scales of neocortical dynamics. J Neurosci Methods 15(166):41–52

The Multi-Society Task Force on PVS (1994) Medical aspects of the persistent vegetative state–second of two parts. N Engl J Med 333:1572–1579

Van der Hiele K, Vein AA, Reijntjes RH et al (2007) EEG correlates in the spectrum of cognitive decline. Clin Neurophysiol 118:1931–1939

Wallace BE, Wagner AK, Wagner EP, McDeavitt JT (2001) A history and review of quantitative electroencephalography in traumatic brain injury. J Head Trauma Rehabil 16(2):165–190

Waterhouse BD, Border B, Wahl L, Mihailoff GA (1993) Topographic organization of rat locus coeruleus and dorsal raphe nuclei: distribution of cells projecting to visual system structures. J Comp Neurol 336:345–361

Young GB (2000) The EEG in coma. J Clin Neurophysiol 17:473–485

Zandbergen EG, de Haan RJ, Stoutenbeek CP, Koelman JH, Hijdra A (1998) Systematic review of early prediction of poor outcome in anoxic-ischaemic coma. Lancet 352:1808–1812

Zeman A (2001) Conscious Brain 124:1263–1289

Zeman A (2009) The problem of unreportable awareness. Prog Brain Res 177:1–9