Neuropsychological Trends

25
April 2019

Fronto-parietal network in response to pleasant and unpleasant somatic stimuli in DoC patients: a pilot study

Irene Venturella[1, 2] - Davide Crivelli[1, 2] - Marina Fossati[3] Francesca Fiorillo[3] - Michela Balconi[1, 2]

[1] *Research Unit in Affective and Social Neuroscience, Catholic University of the Sacred Heart, Milan, Italy*

[2] *Department of Psychology, Catholic University of the Sacred Heart, Milan, Italy*

[3] *Residential Care Facility "Foscolo", Gruppo La Villa spa, Guanzate, Como, Italy*

DOI: http://dx.doi.org/10.7358/neur-2019-025-vent irene.venturella@unicatt.it

ABSTRACT

The assessment of responsivity and preserved cognitive functioning in patients presenting a vegetative state (VS) is primarily based on the observation of overt response patterns, which is however often difficult to classify. This pilot study investigates the potential of EEG oscillations as covert measures to detect residual processing of pleasant/unpleasant somatic stimuli in VS patients. 22 VS patients received two somatic stimulations – a wrist grasp and the placement of an ice pack on their wrist – during EEG recording. Results showed that both pleasant and unpleasant stimulations elicited increased frontal and parietal delta power, with greater parietal responses during the unpleasant stimulations than the pleasant ones. Pleasant stimulations were associated to greater decrease of alpha activity in left frontal areas compared to the unpleasant ones. These activation patterns might mirror basic vigilance responses to external stimuli, supported by residual fronto-parietal interactions. Analysis of EEG profiles during somatic stimulations might point out informative patterns of oscillatory responses.

Keywords: Disorder of Consciousness; EEG; sensory stimulation; fronto-parietal network; vigilance

1. Introduction

Conventional assessment of the preserved cognitive functioning in patients presenting disorders of consciousness (DoC) after a brain injury is usually based on the observation of overt motor actions (Cruse & Owen, 2010). Subjective experiences such as somatosensory percepts and pain are then typically inferred by evaluating behavioural responses to external stimuli (de Tommaso et al., 2015). However, in DoC patients motor responses are often not-systematic and may then be difficult to classify. Because of that, such forms of assessment are deemed as a real challenge. In an attempt to overcome such limitations and to avoid misdiagnosis of patients' level of awareness, covert responses are drawing more and more attention (Balconi & Arangio, 2015; Michela Balconi, Arangio, & Guarnerio, 2013; Cruse & Owen, 2010). Anyway, the use of classical neuroimaging methods could become a real challenge with this kind of patients due to movement artifacts and may cause physical and psychological stress to them. A technique that stands out for being non-invasive is electroencephalography (EEG), that is unaltered by metallic implants and that can be brought at the bedside (Balconi, 2011; Cruse et al., 2011). As an example, Calabrò and colleagues (2017) used advanced source localization tools applied to EEG recordings even to investigate brain activations in response to painful stimulation. They observed that Unresponsive Wakefulness Syndrome (UWS) patients, in particular, presented pain-related responses, including grimacing and crying. Such observation suggest that UWS patients can process some aspects of nociceptive stimuli at an unaware level – probably thanks to preserved thalamic and limbic circuits (Boly et al., 2005, Boly et al., 2008; Laureys et al., 2002) – while they seem to lack in pain perception – probably because of cortical-thalamocortical connectivity breakdown (Demertzi, Soddu, & Laureys, 2013; Di Perri et al., 2016, 2013; Massimini, Boly, Casali, Rosanova, & Tononi, 2009; Pistoia, Mura, Govoni, Fini, & Sarà, 2010; Rosanova et al., 2012). The authors also suggested that the global impairment of pain processing might follow a failure of cortical connectivity within Frontal-Temporo-Parietal (FTP) networks. In fact, while somatosensory cortex supervises the sensory-discriminative coding of nociceptive inputs (Derbyshire, 2000; Price, 2002), FTP networks organize voluntary behaviour and representations of self- and external world (Groenewegen & Uylings, 2000; Gusnard & Raichle, 2001). UWS patients may then perceive pain, but only in its basic aspects at an unaware level.

In EEG literature, an ample research tradition explored the potential of Event-Related Potentials (ERPs) as markers of responsivity and integrity of residual ability to detect pain. For example, a negative-positive biphasic wave (N2–P2), peaking at around 200–350 ms, have been quite consistently

observed at the scalp vertex following the pain-inducing stimulation of a hand (de Tommaso et al., 2015; Garcia-Larrea, Frot, & Valeriani, 2003; Iannetti, Zambreanu, Cruccu, & Tracey, 2005). Again, spectral properties of EEG signals have also been used to assess the severity of DoC after brain injuries in various studies (Crivelli, Venturella, Fossati, Fiorillo, & Balconi, 2019; Gosseries et al., 2011; Varotto et al., 2014; Venturella, Crivelli, Fossati, Fiorillo & Balconi, 2019; Wu et al., 2011) because of the non-invasive nature of the tool, its ease-of-use, its availability in clinical settings, and its limited costs. Those pieces of evidence primarily ground on the analysis of connectivity patterns and focus on the so-called default mode network, showing specific patterns of deactivation that have been investigated as markers of lack of consciousness (Crone et al., 2011). Besides connectivity studies, researchers used cortical oscillations to detect activation or deactivation of distinct areas related to specific functions and to understand if similar-to-normal patterns of activity can be aroused in these patients even in the absence of awareness (Cruse et al., 2011). Higher-frequency power (beta band, 13-30 Hz), which is deemed as a marker of neural activation or general state of wakefulness, proved to be reduced in correspondence to damaged cortical areas (Balconi, Finocchiaro , & Canavesio, 2014; Davey, Victor, & Schiff, 2000). Moreover, DoC patients typically present a slower EEG trace, with greater low frequency power (delta band, 0.5-3.5 Hz; Davey et al. 2000). Moving to frequency-domain correlates of nociceptive stimulation, while evidence in DoC patients are still not consistent, a limited set of studies associated perception of pain and related motivational dimension in healthy people to the modulation of alpha and delta oscillatory responses (e.g. (Chang, Arendt-Nielsen, & Chen, 2002; Goudman et al., 2017; Shao, Shen, Yu, Wilder-Smith, & Li, 2012); but see also (Huber, Bartling, Pachur, Woikowsky-Biedau, & Lautenbacher, 2006).

Notwithstanding the potential of analysing covert responses to exogenous stimulation to refine the assessment of DoC patients' responsivity, the heterogeneity of cohorts of DoC patients that characterizes the vast majority of relevant literature is a diffused problem, which primarily affects judgements on potential markers for residual awareness and conscious processes. Moreover, the size of clinical cohorts is usually limited, with consequences on the discriminative power and reliability of statistical comparisons. Furthermore, moving to specific aspects of typical stimulation procedures, it is worth noting that the use of properly painful stimulation – such as high-intensity electrical stimulation of the median nerve (Laureys et al., 2002) – raises ethical issues concerning the actual nature and extent of pain-related experience in unresponsive patients even when they do not or cannot communicate whether and how much they are feeling such painful stimulations (Laureys et al., 2002; McQuillen, 1991). Finally, typical ERP detection methods need a remarkable

number of reiterated trials to get a reliable estimate of event-related deflections. Such requirement may stress and tire VS patients and lead to habituation and underestimation of patients' responses (Abbate, Trimarchi, Basile, Mazzucchi, & Devalle, 2014; Rankin et al., 2009).

The present pilot study aims at investigating the potential of EEG cortical oscillation profile as a covert measure to detect somatosensory and nociceptive processes in Vegetative State (VS) patients. We opted for the analyses of EEG oscillations in order to limit the number of reiterated stimulations and avoid straining patients. We also decided to use an unpleasant stimulus to induce responses related to nociception non-invasively and with no potential hazard to the patients instead of using traditional pain-inducing methods in order to overcome above-noted ethical issues. Actually we used the application of an ice pack and a wrist hold to stimulate peripheral somatic receptors and to induce somatosensory activation related to, respectively, unpleasant and pleasant stimulations. In particular, we expected: (i) to observe increased EEG responsivity during the exposure to somatic stimulations, with the peculiar modulation of dominant slower EEG band, especially following the unpleasant stimulation; (ii) different lateralization of EEG responses to pleasant and unpleasant stimulations, consistent with the dual systems model of neural signatures of affectively-connoted experiences (Balconi & Bortolotti, 2012; Balconi & Canavesio, 2014; Davidson, 1995), with greater activation of the left hemisphere during the pleasant stimulation compared to the unpleasant one.

2. Method

2.1 Sample

Twenty-two neurology patients (9 female; M_{age} = 60.18, SD_{age}=15.28) presenting a vegetative state and hosted at the Residential Care Facility "Foscolo" in Guanzate (Como, Italy - Gruppo La Villa S.p.A.) took part to the study. Inclusion criteria were: Coma/Near-Coma scale ≥ 2; Disability Rating Scale ≥ 22; clinical classification as patients in a vegetative state following Rappaport (1982; 2005) guidelines; chronic condition, i.e. distance from the clinical event ≥ 12 months; and no history of neurologic or psychiatric disorder prior to coma. Exclusion criteria were: absence of medical stability for 48 hours prior to the assessment procedure; clinically relevant signs of hypothermia; clinically relevant signs of hyperidrosis; primary sensory deficits, lesions to the spinal cord, or cortical lesions that would prevent afferent somatosensory information to be processed by subcortical-cortical structures. Table 1

summarizes primary demographics and clinical data of the patients included in the experimental cohort. Due to the high amount of artifacts affecting electrophysiological recordings, one participant has been excluded from subsequent data analysis.

The study and its procedures followed the principles of the Declaration of Helsinki and were approved by the Ethics Committee of the Department of Psychology of the Catholic University of the Sacred Heart. Written informed consent for the enrolment of patients included in the experimental cohort was obtained from their legal representatives.

Table 1. Synopsis of primary demographics and clinical data of patients included in the experimental cohort

ID	Sex	Age at event *(years)*	Age at assessment *(years)*	Distance from event *(months)*	Etiology	GCS	CNC	DRS
P01	M	50	51	14	TBI	9	2	23/30
P02	F	65	66	16	Stroke	9	3	23/30
P03	M	52	53	12	Anoxia	5	4	27/30
P04	M	53	57	57	Anoxia	6	4	26/30
P05	F	67	69	34	Stroke	8	3	24/30
P06	F	75	76	14	Stroke	8	3	24/30
P07	M	80	81	12	Anoxia	8	3	24/30
P08	M	51	52	22	TBI	5	4	27/30
P09	M	41	43	22	Anoxia	6	3	26/30
P10	F	56	60	49	TBI	3	4	28/30
P11	F	44	49	67	Stroke	5	3	27/30
P12	F	77	82	60	Stroke	8	3	24/30
P13	M	33	37	47	TBI	8	4	24/30
P14	F	67	70	40	Anoxia	8	3	24/30
P15	F	76	86	117	Anoxia	8	3	24/30
P16	M	43	51	85	TBI	6	4	26/30
P17	F	52	53	13	Stroke	9	3	23/30
P18	M	40	47	86	Anoxia	7	4	25/30
P19	M	28	29	15	TBI	6	4	26/30
P20	M	64	66	27	Stroke	6	3	26/30
P21	M	84	85	19	Stroke	8	4	24/30
P22	M	60	61	13	Stroke	8	3	24/30

M: male; F: female; TBI: Traumatic Brain Injury; GCS: Glasgow Coma Scale; CNC: Coma/Near-Coma scale; DRS: Disability Rating Scale

2.2 Procedure

Electrophysiological recordings and clinical observation of patients pattern of activity and responses was performed in a quiet room within the Residential Care facility. Patients were tested one at a time. During the preparation and recording of electrophysiological activity, the research staff was assisted by expert clinicians who monitored the state of the patient and observed his/her behaviour.

When patients were brought to the recording room, they were observed by the expert clinicians for a total of 10 minutes so to note behavioural patterns of activity and, in case of low activity or signs of lack of vigilance, to reschedule the recordings. After such clinical observation and after the placement of EEG sensors, resting-state data were collected so to obtain baseline physiological recordings (duration = 2 minutes). Then patients were presented with two kinds of somatic stimulation: a pleasant stimulation and an unpleasant stimulation. In the former case, a confederate gently grasped the wrist of patient's dominant hand. In the latter, a confederate placed an ice pack in correspondence to the wrist of patient's dominant hand. In both cases, the stimulation lasted for 10 seconds, with a 2-minute inter-stimulus interval. The order of stimulations was counterbalanced across participants**.**

2.3 EEG recording and analysis

Electrophysiological data have been recorded by means of a 16-channel V-Amp system and then processed offline via Vision Analyzer2 software (Brain Products GmbH, Gilching, Germany). EEG activity was recorded from 15 sintered Ag/AgCl electrodes (10-20 International System - Jasper, (1958); montage: F7, F3, Fz, F4, F8, C3, Cz, C4, P3, Pz, P4, T7, T8, O1, O2; reference to linked earlobes, see *Figure 1*). Electrodes impedance was kept under 5 kΩ and vEOG was recorded in order to keep track of ocular artifacts for subsequent rejection. Data were sampled at 500 Hz, with a 0.01-250 Hz bandpass and a 50 Hz notch input filter. Baseline and stimulation-related data have then been filtered offline (IIR 0.5-50 Hz bandpass filter, 48db/octave), segmented and visually inspected for ocular, muscle, and movement artifacts. Only artifact-free segments (rejected segments: 15%) have been used to compute baseline and condition-specific average power spectra by applying the Fast Fourier Transform (Hamming window, resolution: 0.5 Hz). Mean signal power for the main EEG frequency bands (delta - 0.5 - 3.5 Hz, theta - 4 - 7.5 Hz, alpha - 8 - 12.5 Hz, beta - 13 - 30 Hz, and gamma - 30.5 - 50 Hz) have finally been extracted and used to compute stimulation-specific modulation indices by weighting EEG activity during somatic stimulations over baseline EEG activity levels (Balconi & Bortolotti, 2012; Balconi & Pozzoli, 2005).

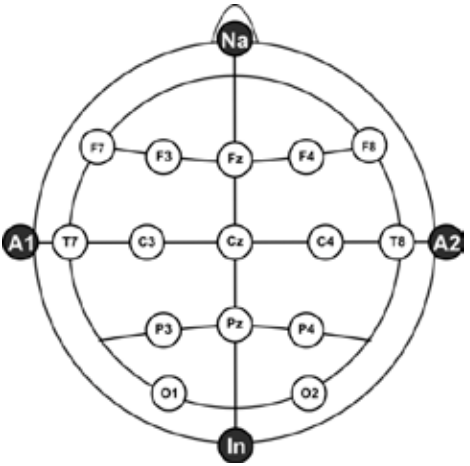

Figure 1. EEG Montage

3. Results

One set of analysis was performed with respect to EEG measures (for each frequency band). A repeated measure ANOVA with independent factor electrode and stimulation types (pleasant vs. unpleasant) was applied to dependent EEG measures. For all the ANOVA tests, the degrees of freedom have been corrected using Greenhouse-Geisser epsilon where appropriate. Post-hoc comparisons (contrast analyses) were applied to the data. Simple effects for significant interactions were further checked via pair-wise comparisons, and Bonferroni correction was used to reduce multiple comparisons potential biases. Furthermore, the normality of the data distribution was preliminary assessed by checking kurtosis and asymmetry indices.

As shown by ANOVA for delta band, interaction effect stimulation x electrode revealed significant results ($F[14, 20] = 7.09$, $p \leq .001$, $\eta^2 = .33$). Indeed post-hoc paired comparisons revealed increased frontal (Fz, F3, F4) and parietal (Pz, P3, P4) activation more than the other cortical sites in the case of both pleasant and unpleasant stimulation (all comparisons $p \leq .001$; see Figure 2). In addition, somatic stimulation revealed increased parietal (P3, P4) response in the case of unpleasant more than pleasant stimulation (respectively $F[1, 20] = 6.88$, $p \leq .001$, $\eta^2 = .30$; $F[1, 20] = 6.13$, $p \leq .001$, $\eta^2 = .30$).

About alpha band, stimulation x electrode showed significant results

(F[14, 20] = 7.55, $p \leq .001$, $\eta^2 = .33$). Indeed post-hoc paired comparisons revealed increased frontal (Fz, F3) activation (alpha decreasing) for pleasant stimulation more than the unpleasant one (respectively F[1, 20] = 6.55, $p \leq .001$, $\eta^2 = .29$; F[1, 20] = 6.68, $p \leq .001$, $\eta^2 = .30$; see Figure 3).
No other effect was statistically significant.

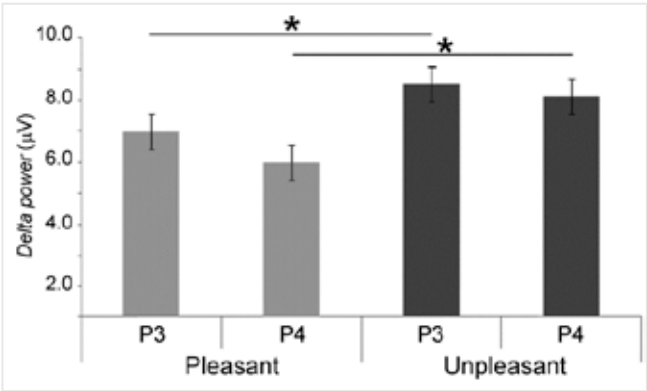

Figure 2. Delta band activity over parietal areas for both pleasant and unpleasant stimuli

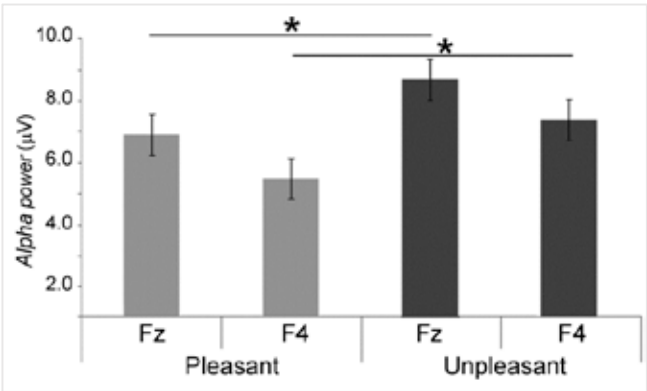

Figure 3. Alpha band activity over frontal areas for both pleasant and unpleasant stimuli

4. Discussion

The present pilot study aimed at exploring whether pleasant and unpleasant somatic stimulations were able to induce measurable patterns of activation in VS patients, with potential practical implications concerning the use of EEG oscillatory responses to detect somatosensory and nociceptive processes in such patients. The analysis of EEG profile in response to different somatic stimulations revealed partly different patterns of activations in the delta and alpha EEG bands. Namely, we observed that: (i) while both pleasant (a wrist hold) and unpleasant (the application of an ice pack) stimulations elicited an increase of delta band power in correspondence to frontal and parietal areas, parietal responses were greater during unpleasant stimulations than pleasant ones; and (ii) in correspondence to left frontal regions pleasant stimulation was associated to greater decrease of alpha activity with respect to the unpleasant one.

As for the first point, the increased responsivity of delta activity observed during the stimulations is in line with available literature and evidence on the functional role of event-relate or task-related delta oscillatory responses (Güntekin & Başar, 2016). Indeed, while it has been shown that a dominant delta rhythm in spontaneous wake EEG activity may be a marker of dysfunction and of inefficiency of information-processing, increased delta oscillatory responses following sensory or cognitive stimulation have been associated to cognitive processes related to perception and attention. Again, while task-related modulation of delta responses during cognitive load are usually observed at frontal and central sites, it has been shown that emotionally-connoted stimulations (e.g. facial expression of emotions, standardized visual stimuli conveying emotions) induce a notable modulation of delta activity even at posterior sites (Balconi, Brambilla, & Falbo, 2009; Balconi & Lucchiari, 2006). The observed increase of frontal-parietal responses in the delta band might then mirror basic vigilance responses to external stimuli, which might have activated elementary mechanisms for exogenous orientation of attention supported by residual interaction between frontal and parietal structures. The further connotation of somatic stimulations as pleasant-unpleasant experiences might have helped such mechanisms due to affective engagement, as suggested by consistent frontal and parietal responses. Chang, Arendt-Nielsen, and Chen (2002), for example, suggested that the modulation of delta oscillatory activity might be related to the motivational aspects of pain-related stimulations. The above-noted interpretation is also supported by the specific involvement of parietal areas during the unpleasant somatic stimulation devised to activate nociceptive pathways with no excessive stress for the patients. The modulation of delta oscillatory activity in parietal areas has indeed been recently proposed as a robust and stable correlate of induced

negative emotional experiences (Zheng, Zhu, & Lu, 2017). We nonetheless acknowledge that our empirical observations need further exploration and replication so to strengthen related interpretations, since available literature on specific frequency-domain correlates of somatic and nociceptive information processing and of related affective-motivational features even in non-pathological condition is limited, with a few studies reporting diffused modulation of alpha and delta bands (e.g. Chang et al., 2002; Shao et al., 2012; Goudman et al., 2017; but see also Huber et al., 2006).

As for the finding concerning the lateralization of frontal EEG responses to pleasant somatic stimulations, the observed suppression of alpha oscillatory activity in correspondence to medial and left-sided recording sites is in line with the wide literature supporting the dual systems model of neural signatures of affectively-connoted experiences (Balconi & Bortolotti, 2012; Balconi & Canavesio, 2014; Davidson, 1995). According to the dual model, positive emotional experiences and approach motivational drives are primarily mediated by a left-lateralized prefrontal neural system, whereas negative emotional experiences and avoidance motivational drives are primarily mediated by a right-lateralized prefrontal system. The activation of such systems is typically measured by quantifying the suppression of alpha oscillatory activity since the decrease of signal power in the alpha frequency range mirrors cortical activation and information-processing (Niedermeyer, 1997). The fact that pleasant somatic stimulations lead to a consistent modulation of left-sided frontal activity come down in favour of the informativity and validity of observed EEG responses. Nonetheless, we were not able to systematically observe a complementary increase of right-sided activation in response to unpleasant somatic stimulations. While such partial result might be explained by the peculiarity of the stimulation modality we chose (i.e. somatic stimulation instead of more traditional visual or acoustic ones), we acknowledge that the actual potential of affectively-connoted correlates of somatic stimulation for the investigation of responsivity of VS patients still need to be further tested.

To conclude, present findings suggest that the analyses of EEG profiles during somatic stimulations might point out informative and consistent patterns of oscillatory responses, and that the pleasant vs. unpleasant-nociceptive connotation of such stimulations lead to partly different modulations of alpha and delta activity. Given the non-invasivity, ease-of-use, and availability of EEG systems and the low-stressful and time-saving nature of block-based paradigms used to investigate modulations of EEG frequency-profile, present data hint at the potential of the stimulation paradigm we tested as a non-straining opportunity to test basic responsivity in DoC patients. This pilot study, however, also present a series of limitations. Firstly, even if the sample size is quite ample with respect to standards in literature, it is still

limited and should be improved in order to better account for typical inter-individual differences characterizing DoC patients. Further, future investigations should test patients' responsivity to pleasant/unpleasant sensory stimulations other than somatic ones, in order to sketch a complete picture of patients' responsivity. That would also allow for a more stringent comparison with available literature on neural signatures of positively vs. negatively connoted experiences. Finally, concurrent validity and clinical potential of EEG-based measures to assess responsivity to somatic stimulations in VS patients could be further tested by putting such measures in relation with widely-diffused psychometric diagnostic instruments and recovery scales.

Acknowledgements

The authors kindly thank all participants and their caregivers for their interest in taking part in the study.

References

Abbate, C., Trimarchi, P. D., Basile, I., Mazzucchi, A., & Devalle, G. (2014). Sensory stimulation for patients with disorders of consciousness: from stimulation to rehabilitation. *Frontiers in Human Neuroscience*, *8*(August), 1–5.

Balconi, M. (2011). State of consciousness and ERP (event-related potential) measure: diagnostic and prognostic value of electrophysiology for disorders of consciousness. *Neuropsychological Trends*, *10*, 43–54.

Balconi, M., & Arangio, R. (2015). The Relationship Between Coma Near Coma , Disability Ratings , and Event-Related Potentials in Patients with Disorders of Consciousness : A Semantic Association Task. *Applied Psychophysiology and Biofeedback*, *40*(4), 327–337.

Balconi, M., Arangio, R., & Guarnerio, C. (2013). Consciousness and N400 ERP Measures in Response to a Semantic Task. *Journal of Neuropsychiatry and Clinical Neuroscience*, *25*(3), 237–243.

Balconi, M., & Bortolotti, A. (2012). Detection of the facial expression of emotion and self-report measures in empathic situations are influenced by sensorimotor circuit inhibition by low-frequency rTMS. *Brain Stimulation*, *5*(3), 330–336.

Balconi, M., & Bortolotti, A. (2012). Resonance mechanism in empathic behavior. BEES, BIS/BAS and psychophysiological contribution. *Physiology and Behavior*, *105*(2), 298–304.

Balconi, M., Brambilla, E., & Falbo, L. (2009). BIS/BAS, cortical oscillations and coherence in response to emotional cues. *Brain Research Bulletin*, *80*(3), 151–157.

Balconi, M., & Canavesio, Y. (2014). High-frequency rTMS on DLPFC increases prosocial attitude in case of decision to support people High-frequency rTMS on DLPFC increases prosocial attitude in case of decision to support people. *Social Neuroscience*, *9*(1), 82–93.

Balconi, M., Finocchiaro, R., & Canavesio, Y. (2014). Reward-system effect (BAS rating), left hemispheric "unbalance" (alpha band oscillations) and decisional impairments in drug addiction. *Addictive Behaviors*, *39*(6), 1026–1032.

Balconi, M., & Lucchiari, C. (2006). EEG correlates (event-related desynchronization) of emotional face elaboration: A temporal analysis. *Neuroscience Letters*, *392*(1–2), 118–123.

Balconi, M., & Pozzoli, U. (2005). Morphed facial expressions elicited a N400 ERP effect: A domain-specific semantic module? *Scandinavian Journal of Psychology*, *46*(6), 467–474.

Boly, M., Faymonville, M. E., Peigneux, P., Lambermont, B., Damas, F., Luxen, A., … Laureys, S. (2005). Cerebral processing of auditory and noxious stimuli in severely brain injured patients: Differences between VS and MCS. *Neuropsychological Rehabilitation*, *15*(3–4), 283–289.

Boly, M., Faymonville, M. E., Schnakers, C., Peigneux, P., Lambermont, B., Phillips, C., … Laureys, S. (2008). Perception of pain in the minimally conscious state with PET activation: an observational study. *The Lancet Neurology*, *7*(11), 1013–1020.

Calabrò, R. S., Naro, A., Manuli, A., Leo, A., De Luca, R., Lo Buono, V., … Bramanti, P. (2017). Pain perception in patients with chronic disorders of consciousness: What can limbic system tell us? *Clinical Neurophysiology*, *128*(3), 454–462.

Chang, P. F., Arendt-Nielsen, L., & Chen, A. C. N. (2002). Dynamic changes and spatial correlation of EEG activities during cold pressor test in man. *Brain Res Bull*, *57*(5), 667–675.

Crivelli, D., Venturella, I., Fossati, M., Fiorillo, F., & Balconi, M. (2019). EEG and ANS markers of attention response in Vegetative State: different

responses to own vs. other names. *Neuropsychological Rehabilitation*, Advance Online Publication.

Crone, J. S., Ladurner, G., Höller, Y., Golaszewski, S., Trinka, E., & Kronbichler, M. (2011). Deactivation of the default mode network as a marker of impaired consciousness: An fmri study. *PLoS ONE*, *6*(10).

Cruse, D., Chennu, S., Chatelle, C., Bekinschtein, T. A., Fernández-Espejo, D., Pickard, J. D., … Owen, A. M. (2011). Bedside detection of awareness in the vegetative state: A cohort study. *The Lancet*, *378*(9809), 2088–2094.

Cruse, D., & Owen, A. M. (2010). Consciousness revealed: New insights into the vegetative and minimally conscious states. *Current Opinion in Neurology*, *23*(6), 656–660.

Davey, M. P., Victor, J. D., & Schiff, N. D. (2000). Power spectra and coherence in the EEG of a vegetative patient with severe asymmetric brain damage. *Clinical Neurophysiology*, *111*(11), 1949–1954.

Davidson, R. J. (1995). Cerebral asymmetry, emotion and affective style. In R. J. & H. K. Davidson (Ed.), *Cerebral asymmetry* (pp. 361–387). Cambridge, MA: MITPress.

de Tommaso, M., Navarro, J., Lanzillotti, C., Ricci, K., Buonocunto, F., Livrea, P., & Lancioni, G. E. (2015). Response: Commentary: Cortical responses to salient nociceptive and not nociceptive stimuli in vegetative and minimal conscious state. *Frontiers in Human Neuroscience*, *10*, 1–14.

Demertzi, A., Soddu, A., & Laureys, S. (2013). Consciousness supporting networks. *Current Opinion in Neurobiology*, *23*(2), 1–6.

Derbyshire, S. W. (2000). Exploring the pain "neuromatrix". *Current Review of Pain*, *4*(6), 467–477.

Di Perri, C., Bahri, M. A., Amico, E., Thibaut, A., Heine, L., Antonopoulos, G., … Laureys, S. (2016). Neural correlates of consciousness in patients who have emerged from a minimally conscious state: A cross-sectional multimodal imaging study. *The Lancet Neurology*, *15*(8), 830–842.

Di Perri, C., Bastianello, S., Bartsch, A. J., Pistarini, C., Maggioni, G., Magrassi, L., … Di Salle, F. (2013). Limbic hyperconnectivity in the vegetative state. *Neurology*, *81*(16), 1417–1424.

Garcia-Larrea, L., Frot, M., & Valeriani, M. (2003). Brain generators of laser-evoked potentials: From dipoles to functional significance. *Neurophysiologie Clinique*, *33*(6), 279–292.

Gosseries, O., Schnakers, C., Ledoux, D., Vanhaudenhuyse, A., Bruno, M.-A., Demertzi, A., … Laureys, S. (2011). Automated EEG entropy

measurements in coma, vegetative state/unresponsive wakefulness syndrome and minimally conscious state. *Functional Neurology*, *26*(1), 25–30.

Goudman, L., Laton, J., Brouns, R., Nagels, G., Huysmans, E., Buyl, R., … Moens, M. (2017). Cortical mapping of painful electrical stimulation by quantitative electroencephalography: Unraveling the time-frequency-channel domain. *Journal of Pain Research*, *10*, 2675–2685.

Groenewegen, H. J., & Uylings, H. B. M. (2000). The prefrontal cortex and the integration of sensory, limbic and autonomic information. *Progress in Brain Research*, *126*(1), 3–28.

Güntekin, B., & Başar, E. (2016). Review of evoked and event-related delta responses in the human brain. *International Journal of Psychophysiology*, *103*, 43–52.

Gusnard, D. A., & Raichle, M. E. (2001). Searching for a Baseline Functional Imaging and the Resting Human Brain. *Nature Reviews Neuroscience*, *2*, 685–694.

Huber, M. T., Bartling, J., Pachur, D., Woikowsky-Biedau, S. V., & Lautenbacher, S. (2006). EEG responses to tonic heat pain. *Experimental Brain Research*, *173*(1), 14–24.

Iannetti, G. D., Zambreanu, L., Cruccu, G., & Tracey, I. (2005). Operculoinsular cortex encodes pain intensity at the earliest stages of cortical processing as indicated by amplitude of laser-evoked potentials in humans. *Neuroscience*, *131*(1), 199–208.

Jaspers, H. H. (1958). The ten-twenty electrode system of the International Federation. *Electroencephalography and Clinical Neurophysiology*, *10*, 370–375.

Laureys, S., Faymonville, M. E., Peigneux, P., Damas, P., Lambermont, B., Del Fiore, G., … Maquet, P. (2002). Cortical processing of noxious somatosensory stimuli in the persistent vegetative state. *NeuroImage*, *17*(2), 732–741.

Massimini, M., Boly, M., Casali, A., Rosanova, M., & Tononi, G. (2009). A perturbational approach for evaluating the brain's capacity for consciousness. *Progress in Brain Research*, *177*, 201–214.

McQuillen, M. P. (1991). Can People Who Are Unconscious or in the "Vegetative State" Perceive Pain. *Issues in Law & Medicine*, *6*(4), 373.

Niedermeyer, E. (1997). Alpha rhythms as physiological and abnormal phenomena. *International Journal of Psychophysiology*, *26*(1–3), 31–49.

Pistoia, F., Mura, E., Govoni, S., Fini, M., & Sarà, M. (2010). Awakenings and awareness recovery in disorders of consciousness: Is there a role for drugs? *CNS Drugs*, *24*(8), 625–638.

Price, D. D. (2002). Central Neural Mechanisms that Interrelate Sensory and Affective Dimensions of Pain. *Molecular Interventions*, *2*(6), 392–403.

Rankin, C. H., Abrams, T., Barry, R. J., Bhatnagar, S., Clayton, D. F., Colombo, J., … Thompson, R. F. (2009). Neurobiology of Learning and Memory Habituation revisited : An updated and revised description of the behavioral characteristics of habituation. *Neurobiology of Learning and Memory*, *92*(2), 135–138.

Rappaport, M. (2005). The Disability Rating and Coma/Near-Coma scales in evaluating severe head injury. *Neuropsychological Rehabilitation*, *15*(3–4), 442–453.

Rappaport, M., Hall, K. M., Hopkins, K., Belleza, T., & Cope, D. N. (1982). Disability Rating Scale for severe head trauma: coma to community. *Archives of Physical Medicine and Rehabilitation*, *63*(3), 118–123.

Rosanova, M., Gosseries, O., Casarotto, S., Boly, M., Casali, A. G., Bruno, M. A., … Massimini, M. (2012). Recovery of cortical effective connectivity and recovery of consciousness in vegetative patients. *Brain*, *135*(4), 1308–1320.

Shao, S., Shen, K., Yu, K., Wilder-Smith, E. P. V, & Li, X. (2012). Frequency-domain EEG source analysis for acute tonic cold pain perception. *Clinical Neurophysiology*, *123*(10), 2042–2049.

Varotto, G., Fazio, P., Rossi Sebastiano, D., Duran, D., D'Incerti, L., Parati, E., … Panzica, F. (2014). Altered resting state effective connectivity in long-standing vegetative state patients: An EEG study. *Clinical Neurophysiology*, *125*(1), 63–68.

Venturella, I., Crivelli, D., Fossati, M., Fiorillo, F., & Balconi, M. (2019). EEG and autonomic responses to nociceptive stimulation in disorders of consciousness. *Journal of Clinical Neuroscience*, *60*, 101–106.

Wu, D. yu, Cai, G., Yuan, Y., Liu, L., Li, G. qing, Song, W. qun, & Wang, M. bin. (2011). Application of nonlinear dynamics analysis in assessing unconsciousness: A preliminary study. *Clinical Neurophysiology*, *122*(3), 490–498.

Zheng, W.-L., Zhu, J.-Y., & Lu, B.-L. (2017). Identifying Stable Patterns over Time for Emotion Recognition from EEG. *IEEE Transactions on Affective Computing*, 1–15.