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Clinical study

EEG and autonomic responses to nociceptive stimulation in disorders of consciousness

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ABSTRACT

Since behavioral responses to external stimuli of patients presenting disorders of consciousness (DoC) are often difficult to qualify, covert physiological correlates of responsivity are deemed as potentially valuable tools to help assessment procedures. While noxious stimuli seem good candidates to explore DoC patients' responsivity, autonomic and electrophysiological correlates of pain detection in DoC patients are still debated. This research aims at investigating autonomic and cortical activation as covert measure of residual somatosensory and nociceptive processes in patients in vegetative state. Twenty-one patients received touch- and pain-related stimulations while autonomic and cortical measures were recorded, with minimal stress for them. Results showed an increased frontal and parietal activation in response to both touch and pain stimuli. Pain-related stimulation was however associated with greater delta parietal response, lower left frontal activation, and increased electrodermal and heart rate measures. Present findings suggest that both somatic stimulations could induce measurable central responses, which might mirror basic attention orientation and perceptual processes. Nonetheless, the nociceptive stimulation in particular seemed to induce a more consistent and informative pattern of covert response even if we used a mild pain-induction procedure.

1. Introduction

A novel research field that is beginning to draw the attention of the research and clinical communities tries to find an answer to the question of what 'it is like' to present a clinically-altered consciousness state [1]. Chronic disorders of consciousness (DoC) consequent to severe brain injury are indeed characterized by the dissociation between two fundamental dimensions of consciousness: arousal and subjective awareness [2]. In current clinical practice, decisions concerning patients' preserved level of consciousness are based principally on clinical observations [3]. Nonetheless, in DoC patients behavioral responses are often not-systematic and difficult to qualify. Consequently, such difficulties frequently lead to misdiagnosis and erroneous assessment of patients' state of consciousness. The use of covert measures is thus being deemed as an optimal solution to overcome the limitations of traditional behavioral methods. Besides the mostly-used neuroimaging (fMRI, PET), other techniques like the use of electrophysiological (EEG) tools (see: [1,4,5]) and the investigation of Autonomic Nervous System (ANS) functioning may also reveal their utility for the assessment of DoC due to the remarkable easiness and minimal invasivity of related physiological recordings.

The fact that patients can detect some aspects of painful stimuli, but only processing them at an unaware level, has been made even more clear thanks to covert measures, that allow us to detect the presence of stimuli elaboration even in the absence of behavioral evidences. Those pieces of evidence show that pain processing is here maybe due to the preservation of thalamic and limbic circuits [6–8]. Recent findings explain the apparent lack of pain perception with a breakdown of cortical-thalamocortical connectivity [9–14]. As hinted by Calabrò et al. [15] also Frontal-Temporo-Parietal (FTP) networks have a prominent role within the global impairment of pain processing, in fact they concur to arrange willing behavior and self- and external world images [16,17]. Somatosensory cortex, on the other hand, leads the sensory-discriminative component of pain regulation [18,19]. In sight of this, patients that present an Unresponsive Wakefulness Syndrome status, even if only unawarely, should be able to perceive primary pain aspects. To answer to the question whether DoC patients are able to feel pain, a wide

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EEG research tradition used Event-Related Potentials (ERPs) to detect residual pain processing ability. An interesting finding is the detection of a N2–P2 wave, with peak at around 200–350 ms, at the scalp vertex after painful hand stimulation [20–22]. Beside ERPs studies, spectral properties of EEG signals were used to perform connectivity studies [23–25] or to detect distinct areas' activation or deactivation. These studies allowed to consider if patterns of activity similar to the healthy ones, related to specific functions, can be evoked in these patients in spite of lack of awareness [26]. Focusing on studies about nociceptive perception in DoC patients, evidences regarding spectral and oscillatory components of EEG measures are however still not consistent. As a consequence we need to refer to studies on healthy populations, which show, within the main results, that pain perception and its motivational components are linked to alpha-delta bands modulation (e.g. [27–29] but see also [30]).

Another face of the same coin can be showed by ANS investigations. Indeed, the assessment of electrodermal activity (EDA) and the analysis of heart rate allow to specifically investigate the functioning of both the sympathetic and parasympathetic branches of ANS [31]. Further, they can be used to measure automatic reactions to environmental modification and stimuli [32,33] – i.e. orienting response. The orienting response is differently affected by the nature and the intensity of a stimulus and it tends to extinguish with repeated stimulations [34,35]. Because of such properties, the physiological orienting response may be deemed as an informative marker for the investigation of many neuropsychological processes. In previous research, in fact, it has been interpreted to reflect attention to new or emotionally-connoted stimuli and information [34,36], as well as implicit memory [32,37]. Focusing on DoC patients' responses, electrodermal activity of people who had recovered from VS proved to differ from that of individuals who had remained in VS. Because of that, it has been suggested that electrodermal response could be used to predict potential for recovery from severe DoC states [32]. Again, many findings highlight the informativity of skin conductance responses (SCR) following auditory stimuli like white noise, music, relatives' voice, and patients' name (e.g. [38–40]). In addition, Keller, Hülsdunk and Müller [39], by comparing somatosensory (tactile) and auditory stimulations in medicated and non-medicated VS patients, reported a significant increment of SCRs in response to tactile stimulation. Notwithstanding the potential of such measures, literature on the use of such measures to specifically explore pain perception of DoC patients is not systematic.

As for cardiovascular metrics, literature on heart rate measures is way more limited. Most of published studies are related to circadian rhythms and sleep (e.g. [41]). In spite of its potential, in fact, only a limited number of studies have specifically addressed such valuable contribution [42]. One of the few findings concerning cardiovascular responses to somatosensory stimulations can be found in the above-cited study by Keller and colleagues [39], who also observed a significant increase of HR in response to tactile stimulation. To our best knowledge, no evidence on HR modulations associated to pain detection in DoC patients is available. Nonetheless, many studies with healthy participants have shown that painful stimulation induces the activation of the sympathetic system [43] with an increase in heart rate [44–46] and in skin conductance [47,48] indices.

Given the paucity of studies dedicated to testing EDA and HR potential for the assessment of pain detection in DoC patients and the related still lacking literature on oscillatory brain responses, the present research aims at investigating autonomic and cortical activation profile as covert measures of somatosensory and nociceptive information processing in VS patients. Moreover, using a multi-methods approach, we designed a paradigm employing the co-registration of the aforementioned autonomic measures and cortical activity measures. Thanks to brief single trial stimulations and the application of an ice pack instead of classical stimuli for pain induction (e.g. laser and electrical stimulation), we wanted to detect cortical and autonomic activation without stressing and tiring VS patients and to overcome ethical issues related to the actual experience of non-responsive people. In particular, we expected that pain-related stimulations, by inducing a basic stress response and by consequently activating the sympathetic branch of the ANS, would lead to an increase of skin conductance measures. Furthermore, we also expect that, in case stimulations will be able to activate touch-related and pain-related pathways and to induce a basic orienting response in enrolled patients, such response will be mirrored by a global increase of heart rate and skin conductance response, as well as by measurable markers of cortical activation (modulation of EEG oscillatory activity) in parietal somatosensory areas. Finally, given available literature on EEG frequency-domain correlates of pain perception, we expect that pain-related stimulation would induce a specific modulation of alpha and delta activity.

2. Methods

2.1. Sample

The clinical cohort was constituted by twenty-one patients (8 female; M_{age} = 59.12, SD_{age} = 9.08) presenting a vegetative state. Participants were enrolled at the Residential Care Facility "Foscolo" in Guanzate (Como, Italy – Gruppo La Villa S.p.A.). Inclusion criteria were: Coma/Near-Coma scale $\geq$2; Disability Rating Scale $\geq$22; clinical classification as patients in a vegetative state following Rappaport [49,50] guidelines; distance from the clinical event $\geq$12 months; no history of neurologic or psychiatric disorder prior to coma. Exclusion criteria were: absence of medical stability for 48 h prior to the assessment procedure; clinically relevant signs of hypothermia; clinically relevant signs of hyperidrosis; primary somatosensory deficits; spinal cord or brain injuries affecting transmission or processing of afferent somatosensory. Table 1 summarizes participants' primary demographics and clinical data.

The study has been designed following the principles of the Declaration of Helsinki. Procedures and methods 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.

2.2. Procedure

Participants have been tested one at a time in a quiet room within the Residential Care facility. Before patients were prepared for electrophysiological and psychophysiological recordings, they were observed by an expert clinician (duration = 10 min), who monitored their current behavioral patterns, noted any peculiar or atypical response, and decided whether to proceed with instrumental recording or to reschedule it if the participant did not present relevant signs of activity and vigilance.

Then, non-invasive sensors were placed (see Fig. 1) and, after a brief accommodation period, resting-state data were collected so to obtain baseline physiological recordings (duration = 2 min). Participants were thus presented with touch- and pain-related stimulations. The order of presentation was counterbalanced to prevent potential biases due to sequence effects. Stimulations lasted for 10 s and were followed by a 2-min inter-stimulus interval. During the touch-related stimulation, a confederate firmly grasped the wrist of participants' dominant hand. During the pain-related stimulation, a confederate placed a dry ice pack in correspondence to

Table 1
Primary demographics and clinical data of patients included in the experimental cohort. Saturation, heart rate and blood pressure data refer to monitoring sessions previous to experimental manipulations.

ID	Etiology	Sex	Age at event *(years)*	Age at assessment *(years)*	Distance from event *(months)*	GCS	CNC	DRS	Saturation *(%)*	Heart Rate *(bpm)*	Blood-Pressure *(systolic)*	Blood-Pressure *(diastolic)*
P01	TBI	M	50	51	14	9	2	23/30	97	65	120	80
P02	Stroke	F	65	66	16	9	3	23/30	96	94	120	80
P03	Anoxia	M	52	53	12	5	4	27/30	94	61	110	70
P04	Anoxia	M	53	57	57	6	4	26/30	96	84	110	70
P05	Stroke	F	67	69	34	8	3	24/30	95	76	110	80
P06	Stroke	F	75	76	14	8	3	24/30	94	76	120	70
P07	Anoxia	M	80	81	12	8	3	24/30	93	68	130	90
P08	TBI	M	51	52	22	5	4	27/30	96	74	100	60
P09	Anoxia	M	41	43	22	6	3	26/30	98	74	100	70
P10	TBI	F	56	60	49	3	4	28/30	97	65	110	75
P11	Stroke	F	44	49	67	5	3	27/30	97	72	130	80
P12	TBI	M	33	37	47	8	4	24/30	98	64	100	60
P13	Anoxia	F	67	70	40	8	3	24/30	97	74	100	60
P14	Anoxia	F	76	86	117	8	3	24/30	97	85	110	60
P15	TBI	M	43	51	85	6	4	26/30	96	60	100	60
P16	Stroke	F	52	53	13	9	3	23/30	98	60	140	75
P17	Anoxia	M	40	47	86	7	4	25/30	98	70	110	60
P18	TBI	M	28	29	15	6	4	26/30	99	75	100	70
P19	Stroke	M	64	66	27	6	3	26/30	99	77	100	70
P20	Stroke	M	84	85	19	8	4	24/30	93	60	100	70
P21	Stroke	M	60	61	13	8	3	24/30	99	66	100	60

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

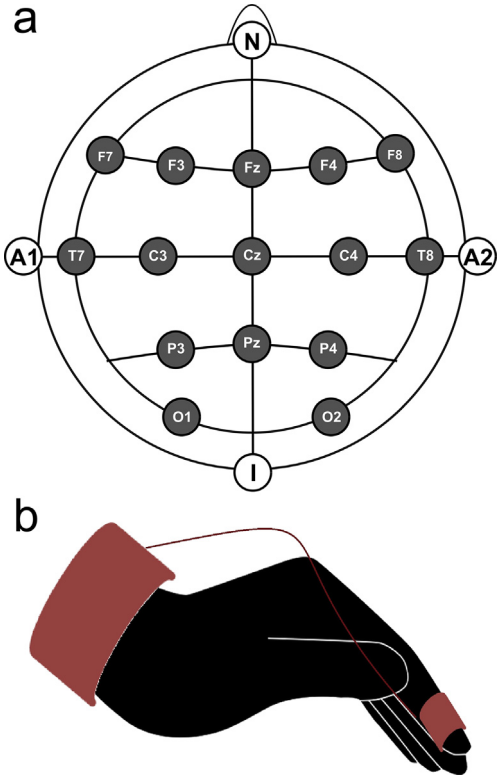

Fig. 1. (a) EEG montage according to the 10–20 International System. N: nasion; I: inion; A1–A2: left and right pre-auricular points. (b) Placement of the multipurpose sensor used to collect electrodermal and cardiovascular data with minimal invasivity.

the wrist of participants' dominant hand. We opted for such procedure to induce physiological responses related to nociception with limited hazard to the patients and non-invasively since the extent to which DoC patients might experience pain and suffer is still a matter of debate and thus the use of properly noxious stimulations (e.g. electrical stimulation of the median nerve) might raise ethical issues [51,52].

2.3. Recording and analysis of EEG activity

Data concerning EEG activity and responsivity were collected via a V-Amp system and processed via Analyzer2 software (Brain Products GmbH, Gilching, Germany). The montage included 15 electrodes (sintered Ag/AgCl sensors referenced to linked earlobes, placement according to the 10–20 International System, [53]). Electrodes impedance was monitored and kept under 5 kΩ. Ocular activity was recorded via vEOG to keep track of artifacts. Data were sampled at 500 Hz (input filters: 0.01–250 Hz bandpass and 50 Hz notch) and then filtered offline with a 0.5–50 Hz IIR bandpass filter (slope: 48 db/octave). Data were then segmented and visually inspected for ocular, muscle, and movement artifacts. Fast Fourier Transform (Hamming window, resolution: 0.5 Hz) was applied to artifact-free segments (rejected segments: 14%) to compute baseline and condition-specific average power spectra. Finally, average 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) was extracted and used to compute stimulation-specific modulation indices by weighting EEG activity during stimulations over baseline values.

2.4. Recording and analysis of autonomic activity

Data concerning autonomic activity and responsivity were collected via a wireless Biofeedback2000^{xpert} system (Schuhfried GmbH, Mödling, Austria). The multipurpose integrated sensor was placed in correspondence to the distal phalanx of the second finger of the non-dominant hand. Skin conductance (tonic – SCL, skin conductance level – and phasic – SCR, skin conductance response – activity) and cardiovascular (HR, heart rate) data were sampled at 40 Hz and inspected for the presence of artifacts. Cardiovascular activity was collected via photoplethysmography and heart rate data were computed starting from measures of peripheral blood volume. SCR data were directly computed by the recording software by applying a 0.05 Hz high-pass filter to SCL data. An online notch filter (50 Hz) was used to minimize electrical noise. After artifact rejection, autonomic activity collected at rest and during somatic stimulations was segmented and averaged to calculate mean condition-specific SCL, SCR and HR modulations via

an *ad hoc* automated VBA script designed to localize event-markers and calculate condition-specific metrics.

3. Results

Two sets of analysis was performed with respect to EEG measures (for each frequency band) and autonomic measures (SCL, SCR, and HR). A first set of repeated measure ANOVAs with independent factor Electrode (15 levels) and Stimulation (touch vs. pain) was applied to dependent EEG measures. 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. A second set of repeated measure ANOVAs with independent factor Stimulation (touch vs. pain) was applied to dependent autonomic measures. For all the ANOVA tests, the degrees of freedom have been corrected using Greenhouse-Geisser epsilon where appropriate. Furthermore, the normality of the data distribution was preliminary assessed by checking kurtosis and asymmetry indices. The size of statistically significant effects has been estimated by computing partial eta squared (η^2) indices.

3.1. EEG data

As shown by ANOVA for delta band, interaction effect Stimulation × Electrode revealed significant results ($F[14,19] = 8.09$, $p \leq 0.001$, $\eta^2 = 0.32$). 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 touch and pain stimulation (all comparisons $p \leq 0.001$). In addition, somatic stimulation revealed increased parietal (P3, P4) response in the case of pain-related more than touch-related stimulation (respectively $F[1,19] = 6.98$, $p \leq 0.001$, $\eta^2 = 0.29$; $F[1,19] = 6.77$, $p \leq 0.001$, $\eta^2 = 0.29$; Fig. 2*a*).

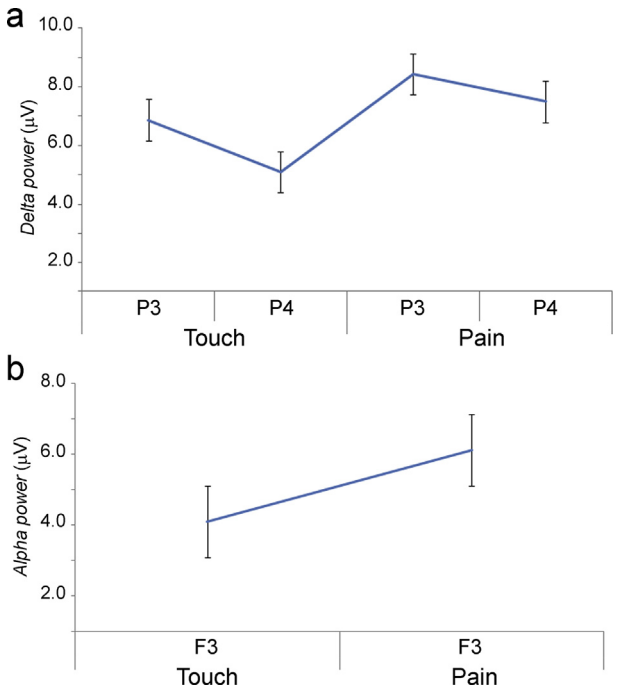

Fig. 2. EEG oscillatory activity (power values) in response to touch- and pain-related stimulation. (a) Delta activity over parietal sites. (b) Alpha activity over left frontal sites. Bars represent ± 1SE.

About alpha band, Stimulation × Electrode showed significant results ($F[14,20] = 7.55$, $p \leq 0.001$, $\eta^2 = 0.31$). Indeed post-hoc paired comparisons revealed greater left frontal (F3) alpha power (lower activation) for the pain-related stimulation than the touch-related one ($F[1,20] = 7.08$, $p \leq 0.001$, $\eta^2 = 0.31$ Fig. 2*b*).

No other effect was statistically significant.

3.2. Autonomic data

As shown by ANOVA for SCR, stimulation effect revealed significant results ($F[1,19] = 7.54$, $p \leq 0.001$, $\eta^2 = 0.30$), with increased SCR values in response to pain-related more than touch-related stimulation (Fig. 3a). The analysis of SCL data did not show significant results ($F[1,19] = 1.17$, $p = .23$, $\eta^2 = 0.09$).

In addition, moving to HR measures, somatic stimulation revealed increased values in response to pain more than simple touch ($F[1,19] = 6.11$, $p \leq 0.001$, $\eta^2 = 0.27$; Fig. 3b).

4. Discussion

The present study aimed at exploring the potential of metrics related to electrophysiological and autonomic activation profiles – namely, frequency-domain EEG modulations, skin conductance and heart rate measures – as markers of residual information-processing for touch- and pain-related pathways in VS patients. The analyses of EEG and ANS responses highlighted that both central and peripheral measurements might provide relevant information for the evaluation of patients' responsivity even via stimulation procedures that limit potential harm and stress. In particular, somatic stimulations relying on touch-related and pain-related pathways lead to measurable modulations of delta oscillations over frontal and parietal electrode sites, with a peculiar modulation of parietal activity in response to pain-related stimulations. Again, lower left frontal activation was observed when the simula-

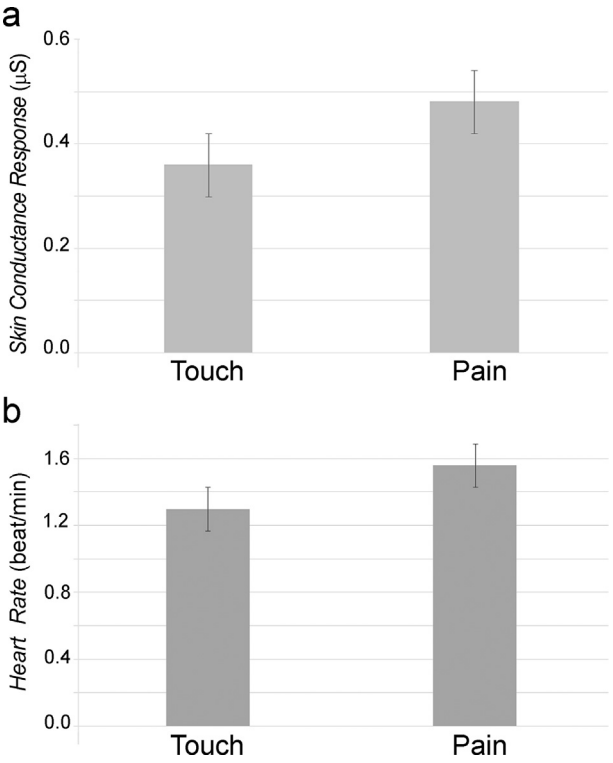

Fig. 3. Autonomic activity in response to touch- and pain-related stimulation. (a) Skin conductance responses. (b) Heart rate. Bars represent ± 1SE.

tions activated pain-related pathways. In addition, cardiovascular and electrodermal measures consistently presented a relevant modulation during the pain-related stimulation. Going down to specifics, signs of increased arousal were found both in SCR and HR measurements.

Starting from the observed increase of delta oscillations, it is crucial to note that such modulation followed a stimulation. Indeed, in clinical contexts heightened delta activity is globally deemed as a marker of inactivity, alteration of neural communication and unconsciousness. Nonetheless, modulations of delta power related to the occurrence of an event, such as sensory or cognitive stimulations, proved to be associated to perceptual and attention processes [54]. Such interpretation is further supported by the distribution of observed effects. Indeed anterior modulations of delta power are thought to mirror cognitive load related to information processing, whereas additional delta activity over posterior areas proved to occur following stimulations that have an emotional – positive/appetitive or negative/aversive – connotation [55,56]. Again, moving to limited though specific literature on frequency-domain EEG correlates of pain perception, it is worth noting that the modulation of delta oscillatory activity have been put in relation with affective-motivational aspects of pain-related stimulations [27].

Findings concerning frontal alpha modulations adds to those concerning posterior delta activity and helps sketching a clearer picture of covert responses to somatic and, in particular, nociceptive stimulations. The presence of alpha activity is indeed generally deemed as a marker of cortical idling and, when collected during a task, of inhibition of information-processing [57–59]. Starting from such hypothesis and according to the dual systems model of neural signatures of affective experience [60,61] greater left frontal alpha power following pain-related stimulation with respect to simple touch may mirror the inactivation of the left-lateralized prefrontal neural system, which mediates pleasant experiences and approach motivational drives. While a lack of activation of the leftward approach system is consistent with the aversive nature of pain-related stimuli, we suggest that the fact that we did not observe a complementary increase of activation of the rightward avoidance system is worth additional investigations. Such investigations would also enrich literature on lateralized prefrontal responses to approachable and aversive stimuli, since almost all available evidence regard induction methods based on visual and/or acoustic stimulations.

Taken together, findings concerning cortical activation following touch and nociceptive stimulation suggest that the latter is able to elicit a more consistent and informative pattern of EEG responses. Such remark is further supported by findings concerning ANS activity. The analysis of both skin conductance responses and heart rate indeed highlighted that pain-related stimulations were able to systematically induce clear autonomic activation. While the absence of significant modulations of SCL measures might mirror altered tonic electrodermal activity due to basic autonomic dysfunction, as often observed in DoC patients, the observed variations of skin conductance responses and heart rate elicited by pain-related stimulations may mirror preserved basic mechanisms regulating phasic changes of arousal and primal responses to the environment [62,63]. Those results are consistent with Keller, Hülsdunk and Müller [39] observations. Namely, the authors reported that even somatosensory stimulations (in their case, a tactile stimulation) could elicit relevant increase of SCR and HR indices in vegetative state patients. Again, while evidence concerning autonomic correlates of pain perception of DoC patients is not systematic, present findings are consistent with available studies with healthy participants, which reported activation of the sympathetic system as measured by increased cardiovascular and electrodermal activity following pain-inducing stimuli [43,45,48].

Given available evidence, present findings suggest that both somatic stimulations induced measurable central responses that might mirror basic attention orientation and perceptual processes. Nonetheless, they also suggest that the nociceptive stimulation in particular could have been able to induce a more consistent and informative pattern of covert activation response. Even if we used a mild pain-induction procedure – devised to cause minimal harm and stress to the patients – such form of stimulation showed an interesting potential for the investigation of responsivity of VS patients. While potential implications concerning ethics of such induction procedure may be worthy, we nonetheless acknowledge that our observations are still preliminary and need to be further strengthened by replication to be rightly used to inform practice. Moreover, we think it is worth noting that the need for replication is a crucial point for future investigations also due to the paucity of available literature on specific autonomic and frequency-domain EEG correlates of nociceptive information processing in both clinical and non-pathological conditions (see, for example, [27–29]; but also [30]).

Disclosure of interest

The authors report no conflict of interest.

Disclosure statement

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jocn.2018.09.020.

References

[1] Cruse D, Owen AM. Consciousness revealed: new insights into the vegetative and minimally conscious states. Curr Opin Neurol 2010;23:656–60. https://doi.org/10.1097/WCO.0b013e32833fd4e7.
[2] Bernat JL. Chronic disorders of consciousness. Lancet 2006;367:1181–92. https://doi.org/10.1016/S0140-6736(06)68508-5.
[3] Chiappa KH, Hill RA. Evaluation and prognostication in coma. Electroencephalogr Clin Neurophysiol 1998;106:149–55. https://doi.org/10.1016/S0013-4694(97)00118-1.
[4] Balconi M, Arangio R. The relationship between coma near coma, disability ratings, and event-related potentials in patients with disorders of consciousness: a semantic association task. Appl Psychophysiol Biofeedback 2015;40:327–37. https://doi.org/10.1007/s10484-015-9304-y.
[5] Balconi M, Arangio R, Guarnerio C. Consciousness and N400 ERP measures in response to a semantic task. J Neuropsychiatry Clin Neurosci 2013;25:237–43. https://doi.org/10.1176/appi.neuropsych.12090227.
[6] Boly M, Faymonville ME, Peigneux P, Lambermont B, Damas F, Luxen A, et al. Cerebral processing of auditory and noxious stimuli in severely brain injured patients: differences between VS and MCS. Neuropsychol Rehabil 2005;15:283–9. https://doi.org/10.1080/09602010443000371.
[7] Boly M, Faymonville ME, Schnakers C, Peigneux P, Lambermont B, Phillips C, et al. Perception of pain in the minimally conscious state with PET activation: an observational study. Lancet Neurol 2008;7:1013–20. https://doi.org/10.1016/S1474-4422(08)70219-9.
[8] Laureys S, Faymonville ME, Peigneux P, Damas P, Lambermont B, Del Fiore G, et al. Cortical processing of noxious somatosensory stimuli in the persistent vegetative state. Neuroimage 2002;17:732–41. https://doi.org/10.1006/nimg.2002.1236.
[9] Rosanova M, Gosseries O, Casarotto S, Boly M, Casali AG, Bruno MA, et al. Recovery of cortical effective connectivity and recovery of consciousness in vegetative patients. Brain 2012;135:1308–20. https://doi.org/10.1093/brain/awr340.
[10] Massimini M, Boly M, Casali A, Rosanova M, Tononi G. A perturbational approach for evaluating the brain's capacity for consciousness. Prog Brain Res 2009;177:201–14. https://doi.org/10.1016/S0079-6123(09)17714-2.
[11] Demertzi A, Soddu A, Laureys S. Consciousness supporting networks. Curr Opin Neurobiol 2013;23:1–6. https://doi.org/10.1016/j.conb.2012.12.003.
[12] Pistoia F, Mura E, Govoni S, Fini M, Sarà M. Awakenings and awareness recovery in disorders of consciousness: is there a role for drugs? CNS Drugs 2010;24:625–38. https://doi.org/10.2165/11535940-000000000-00000.

[13] Di Perri C, Bastianello S, Bartsch AJ, Pistarini C, Maggioni G, Magrassi L, et al. Limbic hyperconnectivity in the vegetative state. Neurology 2013;81:1417–24. https://doi.org/10.1212/WNL.0b013e3182a43b78.
[14] Di Perri C, Bahri MA, Amico E, Thibaut A, Heine L, Antonopoulos G, et al. Neural correlates of consciousness in patients who have emerged from a minimally conscious state: a cross-sectional multimodal imaging study. Lancet Neurol 2016;15:830–42. https://doi.org/10.1016/S1474-4422(16)00111-3.
[15] Calabrò RS, Naro A, Manuli A, Leo A, De Luca R, Lo Buono V, et al. Pain perception in patients with chronic disorders of consciousness: what can limbic system tell us? Clin Neurophysiol 2017;128:454–62. https://doi.org/10.1016/j.clinph.2016.12.011.
[16] Groenewegen HJ, Uylings HBM. The prefrontal cortex and the integration of sensory, limbic and autonomic information. Prog Brain Res 2000;126:3–28. https://doi.org/10.1016/S0079-6123(00)26003-2.
[17] Gusnard DA, Raichle ME. Searching for a baseline functional imaging and the resting human brain. Nat Rev Neurosci 2001;2:685–94. https://doi.org/10.1038/35094500.
[18] Price DD. Central neural mechanisms that interrelate sensory and affective dimensions of pain. Mol Interv 2002;2:392–403. https://doi.org/10.1124/mi.2.6.392.
[19] Derbyshire SW. Exploring the pain "neuromatrix". Curr Rev Pain 2000;4:467–77. https://doi.org/10.1007/s11916-000-0071-x.
[20] de Tommaso M. Response: Commentary: Cortical responses to salient nociceptive and not nociceptive stimuli in vegetative and minimal conscious state. Front Hum Neurosci 2015;10:1–14. https://doi.org/10.3389/fnhum.2016.00012.
[21] Garcia-Larrea L, Frot M, Valeriani M. Brain generators of laser-evoked potentials: from dipoles to functional significance. Neurophysiol Clin 2003;33:279–92. https://doi.org/10.1016/j.neucli.2003.10.008.
[22] Iannetti GD, Zambreanu L, Cruccu G, Tracey I. Operculoinsular cortex encodes pain intensity at the earliest stages of cortical processing as indicated by amplitude of laser-evoked potentials in humans. Neuroscience 2005;131:199–208. https://doi.org/10.1016/j.neuroscience.2004.10.035.
[23] Varotto G, Fazio P, Rossi Sebastiano D, Duran D, D'Incerti L, Parati E, et al. Altered resting state effective connectivity in long-standing vegetative state patients: an EEG study. Clin Neurophysiol 2014;125:63–8. https://doi.org/10.1016/j.clinph.2013.06.016.
[24] Wu DY, Cai G, Yuan Y, Liu L, Li GQ, Song WQ, et al. Application of nonlinear dynamics analysis in assessing unconsciousness: a preliminary study. Clin Neurophysiol 2011;122:490–8. https://doi.org/10.1016/j.clinph.2010.05.036.
[25] Gosseries O, Schnakers C, Ledoux D, Vanhaudenhuyse A, Bruno M-A, Demertzi A, et al. Automated EEG entropy measurements in coma, vegetative state/unresponsive wakefulness syndrome and minimally conscious state. Funct Neurol 2011;26:25–30.
[26] Cruse D, Chennu S, Chatelle C, Bekinschtein TA, Fernández-Espejo D, Pickard JD, et al. Bedside detection of awareness in the vegetative state: a cohort study. Lancet 2011;378:2088–94. https://doi.org/10.1016/S0140-6736(11)61224-5.
[27] Chang PF, Arendt-Nielsen L, Chen ACN. Dynamic changes and spatial correlation of EEG activities during cold pressor test in man. Brain Res Bull 2002;57:667–75. https://doi.org/10.1016/S0361-9230(01)00763-8.
[28] Goudman L, Laton J, Brouns R, Nagels G, Huysmans E, Buyl R, et al. Cortical mapping of painful electrical stimulation by quantitative electroencephalography: unraveling the time-frequency-channel domain. J Pain Res 2017;10:2675–85. https://doi.org/10.2147/JPR.S145783.
[29] Shao S, Shen K, Yu K, Wilder-Smith EPV, Li X. Frequency-domain EEG source analysis for acute tonic cold pain perception. Clin Neurophysiol 2012;123:2042–9. https://doi.org/10.1016/j.clinph.2012.02.084.
[30] Huber MT, Bartling J, Pachur D, Woikowsky-Biedau SV, Lautenbacher S. EEG responses to tonic heat pain. Exp Brain Res 2006;173:14–24. https://doi.org/10.1007/s00221-006-0366-1.
[31] Wijnen VJM, Heutink M, Boxtel GJMV, Eilander HJ, Gelder BD. Autonomic reactivity to sensory stimulation is related to consciousness level after severe traumatic brain injury. Clin Neurophysiol 2006;117:1794–807. https://doi.org/10.1016/j.clinph.2006.03.006.
[32] Turkstra LYNS. brain injury. Brain Inj 1995;9:61–80. https://doi.org/10.3109/02699059509004573.
[33] Dindo L, Fowles DC. The skin conductance orienting response to semantic stimuli: significance can be independent of arousal. Psychophysiology 2008;45:111–8. https://doi.org/10.1111/j.1469-8986.2007.00604.x.
[34] Sokolov EN. Higher nervous functions: the orienting reflex. Annu Rev Physiol 1963;25:545–80. https://doi.org/10.1146/annurev.ph.25.030163.002553.
[35] Barry RJ. Habituation of the orienting reflex and the development of Preliminary Process Theory. Neurobiol Learn Mem 2009;92:235–42. https://doi.org/10.1016/j.nlm.2008.07.007.
[36] Lang PJ, Bradley MM, Cuthbert BN. Emotion, attention, and the startle reflex. Psych Rev 1990;97:377–95. https://doi.org/10.1037/0033-295X.97.3.377.
[37] Bauer RM. Autonomic recognition of names and faces in prosopagnosia: a neuropsychological application of the guilty knowledge test. Neuropsychologia 1984;22:457–69. https://doi.org/10.1016/0028-3932(84)90040-X.
[38] Hildebrandt H, Zieger A, Engel A, Fritz KW, Bussmann B. Differentiation of autonomic nervous activity in different stages of coma displayed by power spectrum analysis of heart rate variability. Eur Arch Psychiatry Clin Neurosci 1998;248:46–52. https://doi.org/10.1007/s004060050016.
[39] Keller I, Hülsdunk A, Müller F. The influence of acoustic and tactile stimulation on vegetative parameters and EEG in persistent vegetative state. Funct Neurol 2007;22:159–63.
[40] Riganello F, Cortese MD, Dolce G, Lucca LF, Sannita WG. The autonomic system functional state predicts responsiveness in disorder of consciousness. J Neurotrauma 2015;32:1071–7. https://doi.org/10.1089/neu.2014.3539.
[41] Pattoneri P, Tirabassi G, Pelá G, Astorri E, Mazzucchi A, Borghetti A. Circadian blood pressure and heart rate changes in patients in a persistent vegetative state after traumatic brain injury. J Clin Hypertens (Greenwich) 2005;7:734–9. https://doi.org/10.1111/j.1524-6175.2005.04780.x.
[42] Tobaldini E, Toschi-Dias E, Trimarchi PD, Brena N, Comanducci A, Casarotto S, et al. Cardiac autonomic responses to nociceptive stimuli in patients with chronic disorders of consciousness. Clin Neurophysiol 2018;129:1083–9. https://doi.org/10.1016/j.clinph.2018.01.068.
[43] Loggia ML, Juneau M, Bushnell MC. Autonomic responses to heat pain: Heart rate, skin conductance, and their relation to verbal ratings and stimulus intensity. Pain 2011;152:592–8. https://doi.org/10.1016/j.pain.2010.11.032.
[44] Lavigne GJ, Zucconi M, Castronovo V, Manzini C, Veglia F, Smirne S, et al. Heart rate changes during sleep in response to experimental thermal (nociceptive) stimulations in healthy subjects. Clin Neurophysiol 2001;112:532–5. https://doi.org/10.1016/S1388-2457(00)00558-7.
[45] Kregel BYKC, Seals DR, Callister R. Sensation by Kevin c. kregel, Douglas R. seals. Physiology 1992;454:359–71. https://doi.org/10.1113/jphysiol.1992.sp019268.
[46] Möltner A, Hölzl R, Strian F. Heart rate changes as an autonomic component of the pain response. Pain 1990;43:81–9. https://doi.org/10.1016/0304-3959(90)90052-F.
[47] Fujita T, Fujii Y, Okada SF, Miyauchi A, Takagi Y. Fall of skin impedance and bone and joint pain. J Bone Miner Metab 2001;19:175–9. https://doi.org/10.1007/s007740170038.
[48] Schestatsky P, Valls-Solé J, Costa J, León L, Veciana M, Chaves ML. Skin autonomic reactivity to thermoalgesic stimuli. Clin Auton Res 2007;17:349–55. https://doi.org/10.1007/s10286-007-0446-8.
[49] Rappaport M, Hall KM, Hopkins K, Belleza T, Cope DN. Disability rating scale for severe head trauma: coma to community. Arch Phys Med Rehabil 1982;63:118–23.
[50] Rappaport M. The disability rating and coma/near-coma scales in evaluating severe head injury. Neuropsychol Rehabil 2005;15:442–53. https://doi.org/10.1080/09602010443000335.
[51] McQuillen MP. Can people who are unconscious or in the "vegetative state" perceive pain. Issues Law Med 1991;6:373.
[52] Schnakers C, Zasler N. Pain assessment and management in disorders of consciousness. Curr Opin Neurol 2007;20:620–6. https://doi.org/10.1097/WCO.0b013e3282f169d9.
[53] Jaspers HH. The ten-twenty electrode system of the International Federation. Electroencephalogr Clin Neurophysiol 1958;10:370–5.
[54] Güntekin B, Başar E. Review of evoked and event-related delta responses in the human brain. Int J Psychophysiol 2016;103:43–52. https://doi.org/10.1016/j.ijpsycho.2015.02.001.
[55] Balconi M, Lucchiari C. EEG correlates (event-related desynchronization) of emotional face elaboration: a temporal analysis. Neurosci Lett 2006;392:118–23. https://doi.org/10.1016/j.neulet.2005.09.004.
[56] Balconi M, Brambilla E, Falbo L. BIS/BAS, cortical oscillations and coherence in response to emotional cues. Brain Res Bull 2009;80:151–7. https://doi.org/10.1016/j.brainresbull.2009.07.001.
[57] Niedermeyer E. Alpha rhythms as physiological and abnormal phenomena. Int J Psychophysiol 1997;26:31–49. https://doi.org/10.1016/S0167-8760(97)00754-X.
[58] Pfurtscheller G, Lopes da Silva FH. Event-related EEG/MEG synchronization and desynchronization: basic principles. Clin Neurophysiol 1999;110:1842–57. https://doi.org/10.1016/S1388-2457(99)00141-8.
[59] Klimesch W. Alpha-band oscillations, attention, and controlled access to stored information. Trends Cogn Sci 2012;16:606–17. https://doi.org/10.1016/j.tics.2012.10.007.
[60] Anterior Davidson RJ. Cerebral asymmetry and the nature of emotion. Brain Cogn. 1992:125–51.
[61] Balconi M, Grippa E, Vanutelli ME. What hemodynamic (fNIRS), electrophysiological (EEG) and autonomic integrated measures can tell us about emotional processing. Brain Cogn 2015;95:67–76. https://doi.org/10.1016/j.bandc.2015.02.001.
[62] Mendes WB. Assessing autonomic nervous system activity. In: Harmon-Jones E, Beer JS, editors. Methods Soc. Neurosci.. New York: Guilford Press; 2009. p. 118–47.
[63] Bari DS, Aldosky HYY, Tronstad C, Kalvøy H, Martinsen G. Electrodermal responses to discrete stimuli measured by skin conductance, skin potential, and skin susceptance. Ski Res Technol 2018;24:108–16. https://doi.org/10.1111/srt.12397.