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Pain perception in patients with chronic disorders of consciousness: What can limbic system tell us?

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HIGHLIGHTS

- Preliminary data exist for the presence of pain perception in some Unresponsive Wakefulness Syndrome (UWS) patients.
- Pain-induced γ-oscillations within limbic system are related with pain perception in disorder of consciousness patients.
- Limbic system activation was preserved in some UWS patients, suggesting that they perceive the affective component of pain.

ABSTRACT

Objective: Although it is believed that patients with Unresponsive Wakefulness Syndrome (UWS) do not feel pain, recent neuroimaging and neurophysiologic studies have demonstrated some residual traces of nociceptive processing.
Methods: To confirm this growing evidence, we evaluated 21 patients suffering from chronic disorders of consciousness (DOC) (both UWS, $n = 11$, and Minimally Conscious State – MCS –, $n = 10$), using an Event-Related Potential (ERP) Low-Resolution Brain Electromagnetic Tomography (LORETA) approach, based on nociceptive repeated laser stimulation (RLS). We delivered laser stimuli to the dorsum of both hands and analysed the γ-band LORETA activations and the ERP γ-power magnitude induced by laser stimulation, as well as the heart rate variability (HRV).
Results: We found partially preserved cortical activations and ERP γ-power magnitude in all MCS and two UWS individuals. These effects were paralleled by a purposeful behaviour, and a reduced HRV concerning nociceptive stimulation, whereas the two UWS individuals showed no more than reflex behaviours, besides a strong limbic activation.
Conclusions: Some UWS patients may somehow perceive the affective components of nociceptive stimulation.
Significance: The diagnosis of functional locked-in syndrome should be taken into account when dealing with DOC differential diagnosis.

1. Introduction

Whether or not and to what extent patients suffering from Unresponsive Wakefulness Syndrome (UWS) can perceive pain is still a great dilemma (Arbour, 2013; Demertzi et al., 2009; Chatelle et al., 2014; Schnakers et al., 2012). Indeed, clinical experience suggests that UWS individuals do not feel pain since they show no more than reflexive behaviours following nociceptive stimuli, whereas Minimally Conscious State (MCS) subjects show pain-oriented responses. Indeed, UWS patients have a repertoire of pain-induced responses, including grimacing and crying, which are similar to those that are seen in conscious individuals. Nonetheless, these responses are mediated by thalamic and limbic system circuits, which are not primarily involved in consciousness.

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Therefore, UWS individuals can process some aspects of nociceptive stimuli at an unaware level (Boly et al., 2005, 2008; Laureys et al., 2002). However, many authors claim that these patients may somehow feel pain since: (i) they show different types of facial reactions to various stimuli; (ii) some of them show large scale neural activations related to nociceptive stimuli processing when tested through paraclinical approaches (functional neuroimaging, neurophysiology) and even if they are unable to communicate and show no more than reflex responses to nociceptive stimuli (including aspecific body movements, sweating, tachycardia, and endocrinological phenomena) (Markl et al., 2013; Naro et al., 2015).

The lack of pain perception and of emergence from UWS may depend on a subcortical and limbic hyperconnectivity, aside from a cortical-thalamocortical connectivity breakdown (Rosanova et al., 2012; Massimini et al., 2009; Demertzi et al., 2013; Pistoia et al., 2010; Di Perri et al., 2013, 2016). Subcortical and limbic structures contribute to balance the activity between frontal-temporo-parietal (FTP) networks (which are related to awareness generation and maintenance) (Demertzi et al., 2013; Di Perri et al., 2013, 2016) and Central Autonomic Network (CAN) (whose functionality can be measured through modifications in the heart rate variability – HRV) (Riganello et al., 2012, 2013, 2016; Leo et al., 2016). Taking into account such issues, we hypothesized that a residual neural connectivity within the limbic system and the FTP networks might contribute to the preservation of nociceptive information processing in DOC patients. To this end, we measured the modifications of behavioural responsiveness using the Nociception Coma Scale (NCS), the Event-Related Potential (ERP) Low-Resolution Brain Electromagnetic Tomography (LORETA) values within γ frequency range, and the HRV following nociceptive repeated laser stimulation (RLS) paradigm, which is useful in entraining pain-related brain networks (Stancak et al., 2011).

2. Methods

2.1. Subjects

Twenty-one patients with DOC (eleven UWS and ten MCS) and ten healthy controls (HC) (six females and four males, mean age ± SD 39 ± 6 years, range 31–47) participated in the experiment (Table 1), according to magnetic resonance imaging (MRI) and medical criteria. The level of consciousness was assessed through the Coma Recovery Scale-Revised (CRS-R) (Giacino et al., 2004). Patients had MRI patterns consistent with an anoxic brain injury following cardiac arrest, post-traumatic diffuse axonal injury, subarachnoid haemorrhage, or multiple petechial haemorrhages. Patients who had very severe brain atrophy were excluded from the study (Galton et al., 2001; Bekinschtein et al., 2011), as well as those with a history of neurological disorders, were in critical conditions or could not submit to laser stimulation. Each HC individual and legal of patient with DOC gave his/her informed consent in written form. Our ethical committee approved the study, which was carrier according to the Declaration of Helsinki.

2.2. Clinical assessment

DOC individuals were evaluated daily through the JFK CRS-R for 30 consecutive days prior to study enrolment, in order to define the level of consciousness. CRS-R is a standardized tool to differentiate coma, MCS, and UWS (vegetative state) (Bodien et al., 2016). The CRS-R evaluates different domains (including visual, verbal, auditory, motor function, communication, and arousal). To date, the CRS-R is considered the gold standard for evaluating consciousness and functional recovery (Gerrard et al., 2014).

NCS was used to evaluate conscious pain perception (Chatelle et al., 2012). This scale rates different behavioural patterns (facial, motor, verbal, and visual) related to pain perception in patients with DOC. A score of four indicates the DOC patient capable of differentiating a noxious from a non-noxious stimuli.

2.3. Laser-induced ERP

The experimental procedure was carried out while subjects were lying on a bed, wearing protective earplugs and goggles. A Nd:YAG laser (Electronic Engineering, Florence, Italy) is used to generate radiant-heat stimuli (1.34 μm wavelength, 7 mm beam diameter, 38 mm^2, 4 ms pulse duration). The right and left hand dorsum was stimulated in two distinct sessions in a day in order to increase trial number and signal-to-noise ratio. We employed two stimulus energies in a classic oddball paradigm (non-target condition: threshold + 0.5 J, E_1; target condition: threshold + 3 J, E_2). The threshold was determined in the HC sample (1.3 ± 0.3 J), and the mean value was applied to the DOC sample. Thus, DOC patients received a laser intensity of at least 40% higher than the HC individuals. In each session, two runs of 40 trains (32 non-target and eight target stimuli) were delivered at 0.1 Hz, with an interruption of two minutes between the runs. HC rated the non-target and target laser stimuli-induced pain, if observed, on a 0–10 visual analogic scale. We measured the NCS after each laser stimulus in DOC patients.

A 19-electrode standard electroencephalogram (EEG) was performed during RLS. Mastoid served as common reference, the forehead as ground. Two surface electrodes were placed over the lower eyelid and 1 cm laterally to the outer corner of the orbit in order to monitor ocular movements and eye blinks. Signals were amplified, digitized at 1028 Hz, and band-pass filtered at 0.3–70 Hz with 50 Hz notch (System Plus; Micromed, Mogliano Veneto, Italy).

The open-source EEGLAB toolbox was used to analyse EEG data concerning ERP analysis (Delorme and Makeig, 2004). An independent component analysis algorithm was used to correct artefacts (Delorme and Makeig, 2004). Artefact-free data were divided into epochs of 1-s [$-$100;1000]ms with regard to the stimulus, and the first pre-stimulus interval was used for baseline correction. Then, we averaged and locked to stimulus onset the episodes. Thereafter, two averaged ERP waveforms (i.e., for non-target – E_1 – and target – E_2 and channel) were obtained by averaging individual ERP waveforms from C3/C4-nose into group-level waveforms. We set the time windows for ERP analysis (peak-to-peak amplitude in μV, peak latency in ms, and absolute γ-band power within 35–70 Hz) of each individual on the ERP grand-average. Absolute γ-band power at ERP peak was calculated applying a Fast Fourier Transform. We first computed a time–frequency representation of single epochs using a windowed Fourier transform for each single trial (giving a single-point and 1 Hz time–frequency spectral estimate within [$-$100;1000]ms and [35;70]Hz). Thus, we averaged C3 and C4 single power values to obtain the mean GBO-power. We focused on such a γ-band range given that these may express the intensity of subjective pain and reflect the inner representations of the stimuli to be preferentially processed (Gross et al., 2007; Zhang et al., 2012; Hu et al., 2014; Peng and Tang, 2016; Naro et al., 2016). Further, significant ERP γ-power magnitude modulation may be a marker of awareness because it may both reflect cognitive and post-perceptual processing (through "bottom-up" binding and "top-down" synchronization processes involving the activation, retrieval, and maintenance of internal representations) (Tallon-Baudry and Bertrand, 1999; Aru et al., 2012; Pitts et al., 2014) or constitute a marker of large-scale brain connectivity (which potentially sustains awareness generation and maintenance) (Laureys and Schiff, 2012; Wijnen et al. 2007).