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DO UNRESPONSIVE WAKEFULNESS SYNDROME PATIENTS FEEL PAIN? ROLE OF LASER-EVOKED POTENTIAL-INDUCED GAMMA-BAND OSCILLATIONS IN DETECTING CORTICAL PAIN PROCESSING

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Abstract—It has been proposed that a neural signature of aware pain perception could be represented by the modulation of gamma-band oscillation (GBO) power induced by nociceptive repetitive laser stimulation (RLS). The aim of our study was to correlate the RLS-induced GBO modulation with the Nociception Coma Scale-Revised (NCS-R) scores (a validated scale assessing possible aware pain perception in patients with chronic disorders of consciousness), in an attempt to differentiate unresponsive wakefulness syndrome (UWS) patients from minimally conscious state (MCS) ones (both of them are awake but exhibit no or limited and fluctuant behavioral signs of awareness and mentation, and low and high NCS-R scores, respectively). In addition, we attempted to identify those among UWS patients who probably experienced pain at covert level (i.e. being aware but unable to show pain-related purposeful behaviors, which are those sustained, reproducible, and voluntary behavioral responses to nociceptive stimuli). Notably, the possibility of clearly differentiating UWS from MCS patients has outmost consequences concerning prognosis (worse in UWS) and adequate pain treatment. RLS consisted in 80 trains of three laser stimuli (delivered at 1 Hz), at four different energies, able to evoke Aδ-fiber related laser evoked potentials. After each train, we assessed the NCS-R score. EEG was divided into epochs according to the laser trains, and the obtained epochs were classified in four categories according to the NCS-R score magnitude. We quantified the GBO absolute power for each category. RLS protocol induced a strongly correlated increase in GBO power and NCS-R score (the higher the laser stimulation intensity, the higher the NCS-R, independently of stimulus repetition) in all the MCS patients, thus confirming the presence of aware pain processing. Nonetheless, such findings were present even in five UWS individuals. This could suggest the presence of covert pain processing in such subjects, despite the low NCS-R scores. In conclusion, RSL-induced GBO power evaluation could be helpful in the differential diagnosis between MCS and UWS patients, besides the clinical assessment, and in identifying covert pain perception in some UWS individuals.

Key words: gamma-band oscillations, laser-evoked potentials, Nociception Coma Scale-Revised, pain arousal, pain perception.

INTRODUCTION

Pain can be defined as an unpleasant experience that involves the conscious awareness of noxious sensations. The response to pain is an important aspect in the assessment at the bedside of patients with chronic disorders of consciousness (DOC) (Plum and Posner, 1983), since these have a limited repertoire of communication, but seem to be somehow able to process pain information (e.g. de Tommaso et al., 2013, 2015; De Salvo et al., 2015). In fact, it has been demonstrated that nearly all the unresponsive wakefulness syndrome (UWS) patients can show cortical responses to nociceptive stimuli even when other sensory responses are missing, thus somehow suggesting a potential pain experience, at least concerning the physical dimension of the nociceptive stimulus (Laureys et al., 2002; Kassubek et al., 2003; De Tommaso et al., 2015). In particular, minimally conscious state (MCS) patients show fluctuating, erratic, non-reproducible, but clearly aware-related behaviors following nociceptive stimulation, whereas UWS individuals usually show no more than reflexive behaviors (The Multi-Society Task Force on PVS, 1994). Such clinical responses are paralleled by a wide brain network activation following nociceptive stimulation in MCS individuals (similar to healthy subjects), thus suggesting a conscious pain experience, and by a lack of any complex inter-area activation in UWS patients, which prompts aware processes (Gosseries et al., 2011).

Nonetheless, lack of purposeful pain-related behaviors do not demonstrate that all the UWS patients are incapable of consciously feeling pain, since some among them may have a covert awareness, i.e. they could be aware but unable to behaviorally manifest it. In other words, they cannot show more than reflex behaviors, although aware of perceiving external stimuli

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Abbreviations: CRS-R, Coma Recovery Scale-Revised; DOC, disorders of consciousness; GBO, gamma-band oscillations; LEP, laser-evoked potentials; MCS, minimally conscious state; NCS-R, Nociception Coma Scale-Revised; RLS, repetitive laser stimulation; UWS, unresponsive wakefulness syndrome.

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(Formisano et al., 2011a,b, 2013; Demertzi et al., 2009; Bruno et al., 2011). Indeed, such individuals suffer from functional locked-in syndrome (fLIS), being thus unable to show purposeful motor behavior owing to a severe motor output impairment rather than a thalamo-cortical functional disconnectivity. On the other hand, "real" UWS individuals suffer from a profound impairment of the higher-order cortical networks sustaining awareness (Schiff et al., 2002).

Recently, laser-evoked potentials (LEP) have been employed in DOC samples in an attempt to assess nociceptive cortical responsiveness (de Tommaso et al., 2013, 2015; De Salvo et al., 2015). Nevertheless, LEP cannot furnish evidence concerning pain perception, as they arise from different cortical zones involved in the processing of multimodal and somatosensory non-nociceptive stimuli, according to the salience of the stimulus employed (Garcia-Larrea et al., 2003; Mouraux and Iannetti, 2009).

In previous studies, it has been shown that the magnitude of gamma-band oscillation (GBO) power within the primary sensory area can be modulated by repetitively delivering single nociceptive stimuli, according to specific stimulus saliency and inter-stimulus intervals (Gross et al., 2007; Tiemann et al., 2010; Schulz et al., 2011; Valentini et al., 2012). In particular, it has been proposed that the magnitude of GBO power elicited by a 1-Hz repetitive laser stimulation (RLS) protocol, at different energies (in order to reduce the novelty of the repeated stimuli and to elicit graded intensities of pain perception), correlates with the subjective pain intensity and reflects the cortical activity related to pain perception (Zhang et al., 2012). Of note, RLS has the advantage of avoiding habituation effect, being thus the GBO-modulation independent of the stimulus saliency and the inter-stimulus interval. Hence, GBO modulation in humans seems to predict the amount of the pain perceived by a human being, independently of the stimulus novelty, and reflect the cortical activity directly related to the emergence of painful percepts (Gross et al., 2007; Schulz et al., 2011; Zhang et al., 2012). Therefore, any potential change in pain-related responses (assessed through the Nociception Coma Scale-Revised, NCS-R) following RLS would be related to an aware pain-related behavioral output modulation. GBO assessment could be thus helpful in detecting pain perception at an aware level in the DOC individuals who cannot clearly communicate pain experience.

The aim of our study was to assess RLS-induced GBO power variations in a DOC sample, and correlate the GBO values with the pain clinical scores assessed by means of the NCS-R (Chatelle et al., 2015), in an attempt to differentiate MCS from UWS patients, and to identify those among UWS individuals who probably experienced pain, but were unable to communicate it.

EXPERIMENTAL PROCEDURES

Subjects

We enrolled 33 DOC patients who attended our Neurorehabilitation Center during a period of two years. All the patients met the following inclusion criteria: post-anoxic or post-traumatic brain injury; no neuromuscular function blockers and no sedation within the 24 h preceding the study; periods of eye opening, indicating preserved sleep-wake cycles and emergence from coma. The exclusion criteria were: pre-existing severe chronic neurological disorders, current acute illness, severe cardiopulmonary instability. Patients were independently diagnosed by two DOC-skilled physicians, using the Coma Recovery Scale-Revised (CRS-R) (Giacino et al., 2004), which was consecutively administered for 30 days, at different times of the day. Thus, patients were operationally divided into MCS (15 individuals: five post-anoxic and ten post-traumatic brain injury) and UWS (18 subjects: eight post-anoxic and ten post-traumatic brain injury). The local Ethics Committee approved the study, and the patients' legal surrogates gave their written informed consent.

Clinical assessment

DOC individuals were clinically evaluated through the JFK CRS-R. This scale is a reliable and standardized tool, which integrates neuropsychological and clinical assessment, and includes the current diagnostic criteria for coma, vegetative state, and MCS, allowing the clinician to assign the patient to the most appropriate diagnostic category (Bodien et al., 2015). The CRS-R assesses auditory, visual, verbal, and motor functions, as well as communication and arousal level. The total score ranges between zero (worst) and 23 (best). The CRS-R has shown superior performance in detecting the vegetative state and MCS as compared to other scales. Thus, the CRS-R is considered as an appropriate measure for characterizing the level of consciousness and for monitoring the neurobehavioral function recovery (Gerrard et al., 2014).

Pain perception at conscious level was specifically assessed by means of the NCS-R (Chatelle et al., 2015), which has been developed for assessing pain in severely brain-injured patients. This scale allows a better specification of the conscious behavioral patterns linked to pain experience in MCS and vegetative state patients. It consists in the observation of motor, verbal, and facial responses to painful stimulation. The total score ranges from zero to nine. A cut-off of four has been proposed to differentiate the patients receiving a noxious stimulation from those receiving a non-noxious stimulation.

LEP

The experimental procedure was carried out at the patient's bedside. Participants wore protective goggles and earplugs. Radiant-heat stimuli were generated by a Nd:YAG laser (Electronic Engineering, Florence, Italy) with a wavelength of 1.34 μm, a beam diameter of 7 mm (38 mm^2), and a pulse-duration of 4 ms. Laser pulses were directed to the dorsum of the right and left hands, in two different sessions in the same day, in order to increase the total number of trials and maximize the signal-to-noise ratio. We employed four stimulus energies (E_1: 2J; E_2: 2.5J; E_3: 3J; and E_4: 3.5J). For