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Assessing pain in patients with chronic disorders of consciousness: Are we heading in the right direction?



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ABSTRACT

The deterioration of sensory-motor integration within the pain matrix in patients with chronic Disorders of Consciousness (DoC) is one of the principal mechanisms responsible for non-conscious pain perception. The present study aimed to assess whether the variability in the inter-peak interval (IPI) between the N2 and P2 components of laser evoked potentials (LEP) could represent an objective marker of the behavioral responsiveness to nociceptive stimulation, as measured by the Nociception Coma Scale-Revised (NCS-R), and regardless of the sensory part of pain processing. We found that only IPI variability showed a significant correlation with NCS-R score, independently of the stimulation intensity (that influences the sensory part of pain processing). It was thus concluded that IPI variability might represent an objective measure of pain processing, which may help clinicians in the development of effective pain management strategies.

1. Introduction

Patients in a Minimally Conscious State (MCS) (Giacino et al., 2002) or exhibiting Unresponsive Wakefulness Syndrome (UWS) (previously referred to as Vegetative State), both belong to the chronic Disorders of Consciousness (DoC), and show inconsistent and only reflex responses, respectively, to all types of stimuli. However, the absence of a purposeful motor response to stimuli does not necessarily mean that a patient with a DoC lacks awareness (de Tommaso et al., 2013, 2015; Demertzi et al., 2009). In fact, advanced paraclinical approaches have revealed concealed command-following behaviors and residual higher-level cognitive capacities in patients who are otherwise defined as being in the UWS state (Bardin et al., 2011; Forgacs et al., 2014; Goldfine, Victor, Conte, Bardin, & Schiff, 2011; Monti et al., 2010; Owen et al., 2006; Stender et al., 2014). Such a condition can be better described as Motor-Cognitive Dissociation (MCD) (Schiff, 2015), although some authors refer to this condition as Functional Locked-In State or Vegetative State with residual islands of consciousness (Bruno, Vanhaudenhuyse, Thibaut, Moonen, & Laureys, 2011; Formisano, D'Ippolito, & Catani, 2013; Formisano, Pistoia, & Sarà, 2011; Formisano et al., 2011; Qiu, 2007; Schiff, Nauvel, & Victor, 2014). The condition of MCD also highlights the dissociation between the behaviors measured at the bedside (UWS or low-level MCS behavioral profile) and laboratory investigations (fMRI or electrophysiological evidence of command following) (Schiff, 2016). Although the neurophysiological basis of MCD is still unclear, it has been hypothesized that varying degrees of breakdown in cortical-subcortical-cortical connectivity across the mesocircuit described by Schiff may be responsible for MCD (Fernández-Espejo, Rossit, & Owen, 2015; Laureys & Schiff, 2012; Schiff, 2010, 2015, 2016).

The existence of such conditions has significantly complicated the management of pain in patients with UWS. Indeed, patients with UWS may feel pain but may be unable to communicate the fact (Calabrò et al., 2017; De Salvo et al., 2015; Naro, Leo,

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Bramanti, & Calabrò, 2015; Naro, Leo, et al., 2015; Naro, Russo, et al., 2015). Consequently, some authors recommend the prophylactic use of painkillers in all the patients with DoC (Bartolo et al., 2016; Schnakers & Zasler, 2007). However, more objective measures should be employed to study pain processing in patients with DoC.

There is a vast literature on the usefulness of laser-evoked potentials (LEP) in studying the integrity of the brain pathways involved in nociception and pain by delivering infrared laser stimuli to the skin (Mouraux, Guérit, & Plaghki, 2003). Laser stimuli activate type-II A δ mechano-heat nociceptors present on free nerve endings of the superficial layers of skin (Treede, Meyer, Raja, & Campbell, 1995). These receptors co-activate A δ - and C-fibers within the somatosensory pathways in the spinothalamic tract (Iannetti et al., 2003; Treede, 2003). The laser stimulation elicits cortical responses that are time locked to the onset of the laser stimulus, and some of these responses can also be detected in the human electroencephalogram (EEG) (Carmon, Mor, & Goldberg, 1976; Mouraux et al., 2003). These evoked signals derive from the activation of the primary (SI) and secondary (SII) somatosensory areas, anterior insula, and anterior cingulate cortex (ACC), which are fundamental to painful experience (Bushnell & Apkarian, 2005; Craig, 2009; Garcia-Larrea, Frot, & Valeriani, 2003). Among the brain evoked responses, the largest is the N2-P2 complex, which is made of a negative component (N2) followed by a positive one (P2), having peaks at about 200 and 330 ms, respectively, when stimulating the dorsum of the hand, with the maximal amplitude at the scalp vertex (Bromm & Treede, 1984). The N2-P2 complex arises from a wide network involving the bilateral opercular-insular regions and the ACC (Garcia-Larrea et al., 2003), and it is preceded by a smaller negative component (N1) peaking at approximately 160 ms, with maximal amplitude over the temporal region contralateral to the stimulated side (García-Larrea, Peyron, Laurent, & Mauguière, 1997). The N1 component probably arises from a network encompassing SI and the opercular-insular region contralateral to the stimulated side (Garcia-Larrea et al., 2003).

Although basic LEP parameters, including amplitude and latency, do not correlate *per se* with behavioral responsiveness or awareness (De Salvo et al., 2015; de Tommaso et al., 2013, 2015), yet single LEP components express specific parts of the pain-motor process. In particular, N1 represents an early stage of sensory processing occurring independently of the conscious awareness of the nociceptive stimulus (Lee, Mouraux, & Iannetti, 2009), whilst the N2-P2 complex is considered to express the readiness of defensive motor responses (N2) and the saliency and the intensity of the perception (P2), rather than the intensity of the stimuli (Legrain, Iannetti, Plaghki, & Mouraux, 2011; Moayedi et al., 2015; Ronga, Valentini, Mouraux, & Iannetti, 2013; Valentini, Torta, Mouraux, & Iannetti, 2011). In other words, the magnitude of the P2 component elicited by a first stimulus may predict the conscious detection of a second one. Furthermore, the level of attention, abnormalities in sensory processing, and variations in arousal (which are common in DoC patients) together influence the absolute latency and the amplitude of N2 and P2 components (Franz, Nickel, Ritter, Miltner, & Weiss, 2015).

Therefore, LEP parameters that are independent of such biasing factors must be tested. The variability in the inter-peak interval (IPI) between N2 and P2 components could be helpful in objectively quantifying pain-related behavioral output in patients with DoC. In fact, IPI is argued to represent an index of connectivity between different areas belonging to the pain matrix. Specifically, it represents the time spent in generation of motor output based on the sensory information originating from the parallel sensory processing in SI and SII and the hierarchical sensory processing from SI to SII, insula, and ACC (Franz et al., 2015; Garcia-Larrea et al., 2003; Pistoia, Sacco, Stewart, Sarà, & Carolei, 2016; Torta, 2015). Such amount of time is independent of the sensory component of the processes mentioned above and the level of attention (Garcia-Larrea et al., 2003). Therefore, IPI variability may represent an electrophysiological correlate of the behavioral responsiveness to nociceptive stimulation (as measured, e.g., by the Nociception Coma Scale-Revised, NCS-R). To provide support for this hypothesis, we measured the latency, amplitude, IPI variability of N2 and P2 components, and the NCS-R score in 20 patients with DoC, and 10 healthy controls (HC) by using two different laser stimulation intensities.

2. Methods

2.1. Participants

We included in the study 10 patients with UWS (age range 29–73 years, 6 females and 4 males, 4 post-anoxic and 6 post-traumatic brain injury), whose time since injury ranged from 5 to 37 months. There were also 10 patients with MCS (age range 30–70 years, 5 females and 5 males, 5 post-anoxic and 5 post-traumatic brain injury), whose time since injury ranged from 12 to 22 months, and 10 HCs (6 females and 4 males; age 46 ± 3 years) included in the study. Clinical-demographic characteristics are summarized in Table 1.

The patients were diagnosed independently by two DoC-skilled physicians, using the JFK Coma Recovery Scale-Revised (CRS-R) (Giacino, Kalmar, & Whyte, 2004), consecutively for 30 days, at a frequency of 3–5 times per day, at different schedules every day. Most of the patients were treated with baclofen, L-DOPA, antiepileptic drugs, and analgesics. Specific inclusion criteria were as follows: patients with post-anoxic or post-traumatic MCS and UWS; no history of neuromuscular function blockers and sedation; enrollment at least 1 week prior to the commencement of the study; absence of any pre-existing severe chronic neurological disorder; absence of any current acute illness or severe cardiopulmonary instability; and no contraindication for the execution of LEP.

The study was approved by the local Ethics Committee. Written informed consent was obtained from the patient's legal surrogates and all HCs.

2.2. Clinical assessment

The level of responsiveness in patients with DoC was clinically defined using the CRS-R. The CRS-R is a reliable and standardized

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