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Shaping Thalamo-cortical Plasticity: A Marker of Cortical Pain Integration in Patients With Post-anoxic Unresponsive Wakefulness Syndrome?

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ABSTRACT

Background: The distinctive feature of unresponsive wakefulness syndrome (UWS) is the dissociation between arousal and awareness. Cortico-cortical and thalamo-cortical connectivity and plasticity play a key role in consciousness. UWS patients do not usually show any "cortical" behavioral sign in response to painful stimulation. Nevertheless a "focal conscious" pain perception has been hypothesized.
Hypothesis: Since defective plasticity and connectivity within pain matrix could be striking mechanisms of non-conscious pain perception and, consequently, of non-cortical responses in UWS subjects, aim of our study was to investigate pain-motor plasticity in such patients through a specific paired laser associative stimulation protocol (L-PAS).
Methods: We enrolled 10 post-anoxic subjects and 10 healthy controls evaluating clinical and electrophysiological parameters before and after the application of such protocol.
Results: Some patient showed a restored pain-motor integration with a partial motor cortex excitability modification.
Conclusions: Although we studied a small cohort of post-anoxic UWS patients and the results obtained were short-lasting, L-PAS seems a feasible and suitable technique in order to induce plastic change within pain matrix in some UWS patients, allowing the production of "cortical" responses to painful stimuli, which are signs of at least partially ("focal") preserved consciousness. Cortico-thalamic plasticity could have also an important role in the emergence of pain perception as compared to other sensory modalities.

Introduction

The "unresponsive wakefulness syndrome" (UWS) is the consequence of a severe brain injury that disrupts brain higher cognitive functions. Cerebral hypoxia is a very common cause of UWS and leads to diffuse neuronal loss, especially evident in basal ganglia and thalamus [1]. The pathognomonic feature of such condition is the dissociation between arousal and awareness: patients in UWS seem to be awake but lack any sign of awareness of themselves or environment [2]. UWS has been demonstrated to mainly depend on cortico-cortical disconnection and cortico-thalamic deafferentation [3], which potentially lead to a continuous alternation between up- and down-states in the cortex, and thus to a long-term alteration of excitability within specific cortical circuits [4–6]. Cortico-thalamo-cortical loops contribute to the wide regulation of plasticity and functional connectivity at cortical and cortico-subcortical levels, and therefore play a crucial role in awareness, attention, consciousness, and conscious perception. The restoration – at least partial – of these networks, depending on wide dynamic plastic processes, is crucial for retrieving consciousness [7–9].

The issue of nociception and pain perception in patients with chronic disorders of consciousness (DOC) is of either ethic or clinical outstanding importance. Nociception is the conscious or not detection of noxious peripheral stimuli, whereas pain is "an unpleasant sensory and emotional experience associated with

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actual or potential tissue damage, or described in terms of such damage" [10,11]. Conscious pain perception is related either to the activity and connectivity within the pain matrix, or to the complex thalamo-cortical and cortico-cortical (in particular fronto-parietal) networks [12–15]. Indeed, UWS patients show the failure of these phenomena [16,17], i.e. cortical processes in the UWS may occur as disconnected. Hence, painful stimuli may be experienced in a non-integrated and unconscious manner [18]. Because of such failing integrative processes at cortical and cortico-subcortical levels, UWS patients do not usually show any "cortical" behavioral sign in response to painful stimulation [19,20].

On the other hand, it has been recently suggested that some UWS patients might somehow experience pain perception, i.e. high relevant stimuli may be still processed also in severe brain injury, since "pain perception represents a primary function for life persistence" [21,23]. Hence, it needs to be further investigated whether behavioral unresponsiveness to pain in UWS patients could depend on a dysfunctional pain-motor integration (PMI), on a lack of cortical plasticity related to PMI, on an abnormal descending pain modulatory-system, or on a motor output failure.

PMI is the (inhibitory) effect of experimental pain (e.g. induced through laser stimuli), at cortical level, on primary motor area (M1) output, i.e. the motor evoked potential (MEP) amplitude is reduced, in order to allow sub-cortical defensive reflex elicitation [24,25]. PMI has been demonstrated for the first-ever time in healthy subjects by means of a laser-transcranial magnetic stimulation (TMS) paired-pulse protocol by Valeriani and coworkers [24].

On the other hand, PMI plasticity is necessary for purposeful behavior actuation, according to the stimulus type [26,27]. PMI plasticity has been interestingly investigated in healthy individuals through an original paired repetitive laser/TMS protocol, defined as laser paired associative stimulation (L-PAS) by Suppa and coworkers [26]. Repetitive TMS (rTMS) is a well-known non-invasive and painless method that allows to investigate MEP amplitude after-effects related to long-term potentiation (LTP) and depression (LTD) like plasticity within M1 [28]. Further, repeated paired (i.e., associated) stimuli, over a certain period, may increase or decrease the excitability of corticospinal output, depending on the inter-stimulus interval (ISI) applied. These effects may represent a form of associative LTP or LTD according to a spike-timing dependent plasticity (STDP) mechanism. Suppa and coworkers showed that repeated heat-evoked pain stimulation paired with rTMS can elicit M1 long-lasting LTP/LTD-like plasticity concerning PMI [26]. L-PAS on M1 induces first an MEP amplitude decrease, i.e. an LTD-like inhibitory effect, that is followed by an increase, i.e. a homeostatic LTP-like increase of cortical excitability [26]. In analogy with classic PAS [29,30], the neurophysiological basis of L-PAS effects may rely on STDP in M1, depending on the ISI between pre- (laser) and post- (TMS) synaptic inputs on cortical layers II and III [26]. The pain-dependent inhibitory inputs on the MI area are likely to arise from the II somatosensory area (SSII) neurons reached by the nociceptive pathways [24]. Moreover, L-PAS effects are based on NMDA-dependent glutamatergic transmission [26]. It has been suggested that PMI plastic changes L-PAS induced may reflect the functional connectivity between pain and cortical motor areas within the pain matrix [26,31], mainly between SSII/posterior insula and M1 [24,26]. Recent works suggested that inter-area functional connectivity is also dependent on multiple and integrated cortico-thalamo-cortical loops [16,17].

Since L-PAS represents a suitable method to test STDP engaged in PMI processes within pain areas and M1 (in which also thalamo-cortical plasticity may be involved), primary aim of our study was to investigate PMI plasticity in post-anoxic UWS patients, in an attempt to find new insights concerning pain processing in severe DOC patients.

The secondary aim was to identify if even UWS patients are able to "appropriately" respond to painful stimuli, since L-PAS protocol might enhance residual pain-M1 areas connectivity leading to purposeful behavior.

Materials and methods

Subjects

We enrolled 10 post-anoxic subjects (7 females and 3 males, mean age 61.2 ± 5.4 years) who met the international criteria for VS (vegetative state) diagnosis [32], and 10 healthy controls (HC) (5 females and 5 males, mean age 35.3 ± 7.2 years). The disease duration was of 19.3 ± 5 months. The post-anoxic condition was a consequence of prolonged cardiac arrest and nuclear magnetic resonance imaging (MRI) pattern displayed a diffuse cortico-subcortical T2-hyperintensity.

Exclusion criteria were: cutaneous or systemic disease contra-indicating LEP execution; critical conditions, e.g. unable to breathe independently, hemodynamic instability; administration of analgesic substances or notoriously modifying cortical-excitability drugs; presence of pace-maker, aneurysms clips, neurostimulator or brain/subdural electrodes; left handedness; spinal cord and peripheral nervous system damage. The present study was approved by the Local Ethics Committee and written informed consent was obtained from the legal guardian of each patient.

Experimental design

At baseline (T_{PRE}), after clinical evaluation, including neurological examination, Coma Recovery Scale-Revised (CRS-R) [33] and Nociception Coma Scale (NCS) [34], each enrolled patient was tested for resting motor threshold (rMT), MEP amplitude, PMI strength, and latency and amplitude of laser evoked potential (LEP) N2P2 component. The same electrophysiological parameters were tested in HC group. Thus, the L-PAS protocol was applied. During L-PAS protocol, we measured MEP amplitude after 60 coupled stimuli ($T_{L\text{-}PAS60}$) and PMI strength after 30 and 60 pairs ($T_{L\text{-}PAS30}$, $T_{L\text{-}PAS60}$). After 90 pairs we measured rMT and PMI strength (T_0). Finally, NCS scoring, MEP amplitude, PMI strength, and LEP latency and amplitude were tested 10′ after the end of the conditioning protocol (T_{10}). The same electrophysiological measures were performed during and after L-PAS in HC. Figure 1 resumes the experimental design.

Clinical assessment

The neurological examination showed a predominantly pattern of spastic tetraparesis. Patients were also clinically evaluated through the CRS-R by at least two independent neurologists, skilled in DOC diagnosis. This scale is a reliable and standardized tool, which integrates neuropsychological and clinical assessments, and includes the current diagnostic criteria for coma, VS and MCS (minimally conscious state), allowing the patient to be assigned to the most appropriate diagnostic category. Thus, the CRS-R is a valuable measure for characterizing the level of consciousness and for monitoring the neurobehavioral function recovery.

Pain perception was specifically assessed by means of the NCS. This tool consists of the observation of motor, verbal, visual, and facial responses to painful stimulation. The total score varies from 0 to 12. NCS have been developed for assessing pain in severely brain-injured patients, and allows a better specification of the conscious behavioral patterns linked to pain experience in MCS and VS patients [35]. We used a laser painful stimulus (as perceived in normal subjects) to induce motor response and activate the same