Cool evoked potentials in patients with disorders of consciousness: a new bedside approach to probe spino-thalamic pathways in non-communicative patients.

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Objective

Pain management in patients with prolonged disorders of consciousness (DOC) raises ethical and quality of life issues. Because these patients are unable to communicate verbally, pain management is highly problematic and, most probably, often inadequate or insufficient. Therefore, there is an urge to implement tools that do not require patient collaboration and can be used at bedside to assess their potential ability to perceive pain.

Recent studies reported brain responses in patients with DOC elicited by laser heat stimuli [1,2]. If these responses seem to be a good marker of saliency rather than a marker specific for pain (because similar responses can be elicited by non-nociceptive stimuli provided that they are salient), these results suggest that nociceptive stimulation can elicit measurable brain responses in severely brain-injured patients, even in unresponsive wakefulness state/ vegetative state (UWS/VS).

In this study, we used a new approach to probe spinothalamic pathways using innocuous cutaneous cold stimulation. Brisk cooling of the skin activates cool-sensitive A-delta fiber afferents. Even though these stimuli are not perceived as painful, they are conveyed to the brain by the spino-thalamic system, such as noxious heat stimuli. A prerequisite to recording time-locked brain responses such as event-related potentials (ERPs) is to generate a transient, well-synchronized afferent volley. This is possible using a new cold stimulator based on micro-peltier elements, able to achieve very steep cooling ramps of up to 300° C/s (see Fig.1 – Methods section). In healthy subjects, ERPs elicited by cool stimulation are similar to those obtained after transient laser heat stimulation [3]

Here, we present this new methodology, that has never been used in patients with DOC, to evaluate specifically the integrity of spino-thalamic pathways through cool-evoked potentials.

Method & Analysis

Population

10 patients with a DOC or evolving from a prolonged DOC, evaluated for their level of consciousness based on the Coma Recovery Scale – Revised (CRS-R) administered just before the stimulation session and classified as:

- In an Unresponsive Wakefulness Syndrome (UWS) (n=3)
  - 2 TBI, 1 Anoxic
- In a Minimally Conscious State (MCS) (n=4)
  - 2 TBI, 2 Vascular
- Emerging from MCS (EMCS) (n=3)
  - 3 TBI

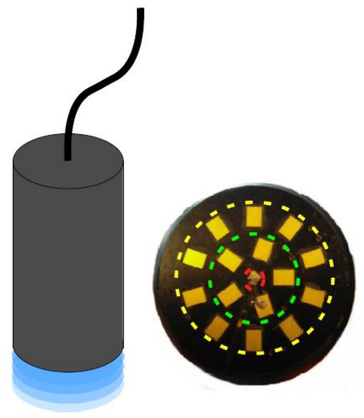


Fig.1 The Thermal Cutaneous Stimulator uses micro peltier element to generate a cooling ramp up to +/- 300° C/s and is able to cool down the skin up to 5° C

Recording

- 32 channels surface EEG
- 60 stimulations (2 blocks of 30 stimulations), delivered on the distal part of the volar forearm with a random interstimulus interval from 6 to 10 seconds.

Stimulations characteristics

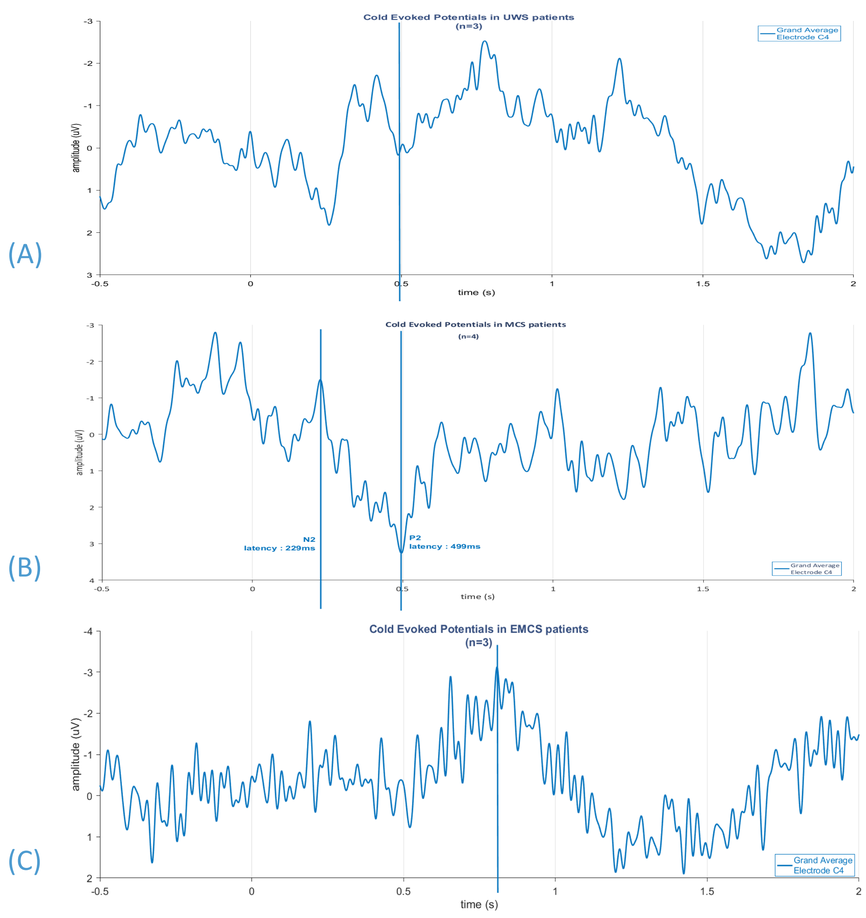
- Area of stimulation : 115mm²
- Stimulus duration : 100ms
- Cooling ramp : 200° C/S
- Baseline temp. : 31° C
- Skin cooling : 17° C

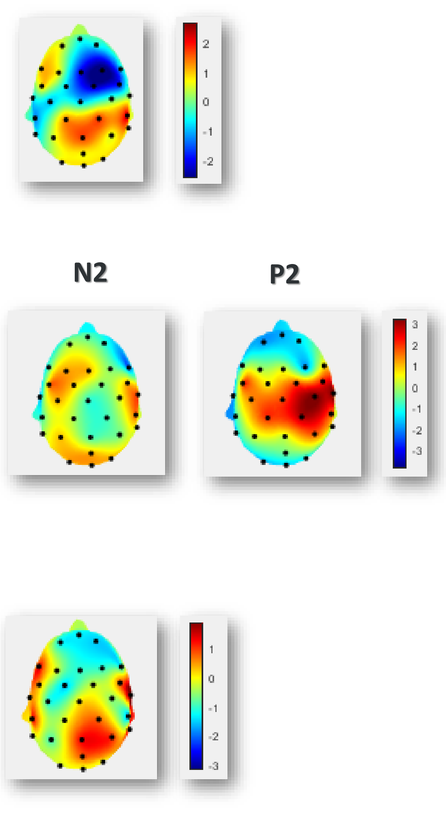
Analysis

- iFFT bandpass filter (0.5-40Hz)
- Segmentation from -2 to +3sec relative to onset
- Visual artifacts rejection
- Spatial filtering by ICA
- Baseline correction (-0,5 to 0 sec)

Results & Interpretation

Group Level Results
(A) UWS (B) MCS (C) EMCS





Results

In the UWS group (n=3) (A), no clear peak can be identified. However, we represented the scalp topography of the signal power, based on electrodes coordinates. While the amplitude of the response is low, its topography matches with the expected P2 peak.

In the MCS group (n=4) (B), a N2 peak is identified at 229ms and a P2 peak is identified at 499ms, with a maximal signal power on the central right part of the scalp. No N1-P1 complex could be identified (data not showed)

In the EMCS group (n=3) (C), no clear peak could be identified, although a significant deflection can be seen in the EEG, its significance is doubtful, according to the scalp topography and its timing.

Interpretation

A clear brain response related to brisk cooling of the skin can be observed only in MCS patients at the group level, while such response in the other group seems dubious. In the UWS group, the low number of patients (n=3) might be a reason why the peak has an unsufficient averaged power, while the lower level of consciousness and the absence of access to a cortical integration of the cold stimuli might be another one. The hypothesis to explain the absence of such response in EMCS patients could be the technical difficulties to register scalp EEG in those agitated patients, that are clearly reacting unpredictabily to the stimuli, resulting in a low signal-to-noise ratio. In general, the heterogeneity of the etiologies and the lesions result in variable central conduction time, which could lead to a lower amplitude of the averaged event related brain responses.

Conclusion

The **primary aim** of this preliminary study was to demonstrate the achievability of the use of a cool stimulator generating a very steep cooling-ramp to elicit time-locked brain responses in DOC patients .

Thenceforth, eliciting cool evoked potential (CEP) could be a valuable methodology to investigate the integrity of spino-thalamic pathways in DOC patients. Like laser evoked potential (LEP), which are more representative of the concept of saliency than specific to pain perception, cool stimuli are processed by the same pathways as noxious heat stimuli without generating a painful perception. Therefore, CEP could be more specific to a spino-thalamic tract lesion than LEP. Moreover, unlike laser stimuli, the use of cool stimuli is not painful and can be generated by a device that is usable at bedside, highly portable and relatively low cost as compared to CO_2 laser devices.

In the near future, our work aims to characterizing CEP according to the level of consciousness but also according to the etiology of the DOC. This methodology could also be used to identify spino-thalamic tract lesion, which could lead to neuropathic pain, a specific kind of pain that can only be alleviated by specific analgesics. Therefore, we should find means or develop alternative methods to increase signal-to-noise ratio and make possible the interpretation of our results at a single subject level.

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