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Early event related fields during visually evoked pain anticipation

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HIGHLIGHTS

- First countdown cue during pain anticipation evoked greater attention and alertness.
- Fronto-central P2 and N2 components mediate pain anticipatory phenomena.
- Neuromodulation techniques could be devised to target these early evoked components.

ABSTRACT

Objective: Pain experience is not only a function of somatosensory inputs. Rather, it is strongly influenced by cognitive and affective pathways. Pain anticipatory phenomena, an important limitation to rehabilitative efforts in the chronic state, are processed by associative and limbic networks, along with primary sensory cortices. Characterization of neurophysiological correlates of pain anticipation, particularly during very early stages of neural processing is critical for development of therapeutic interventions.
Methods: Here, we utilized magnetoencephalography to study early event-related fields (ERFs) in healthy subjects exposed to a 3 s visual countdown task that preceded a painful stimulus, a non-painful stimulus or no stimulus.
Results: We found that the first countdown cue, but not the last cue, evoked critical ERFs signaling anticipation, attention and alertness to the noxious stimuli. Further, we found that P2 and N2 components were significantly different in response to first-cues that signaled incoming painful stimuli when compared to non-painful or no stimuli.
Conclusions: The findings indicate that early ERFs are relevant neural substrates of pain anticipatory phenomena and could be potentially serve as biomarkers.
Significance: These measures could assist in the development of neurostimulation approaches aimed at curbing the negative effects of pain anticipation during rehabilitation.

1. Introduction

The experience of pain is multi-dimensional. Sensory components transmit information regarding location and intensity of stimuli, whereas affective-cognitive components modulate the suffering experience and play an important role in the process of pain chronification and associated disability (Lousberg et al., 1996; Melzack, 1999; Flor et al., 2002; Moseley, 2003). Therapeutic neuromodulatory interventions have largely neglected the affective component of pain, while targeting predominantly the sensory spheres (Machado et al., 2013). Novel treatment strategies based on neuro-modulation can be devised to target affective and cognitive neural networks to modulate pain experience and limit the disabling effects associated with the transition from acute to chronic pain state. Key correlates to this transition are pain anticipatory phenomena and pain avoidance behaviors, which can impair rehabilitative efforts after injury and therefore augment the extent of long-term pain-related disability (Machado et al., 2013; Plow et al., 2013). An important limitation to the development of strategies directed at modulating pain anticipatory

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phenomena is the lack of a reliable neurophysiological indicator, which could be detected with high temporal and spatial resolution during epochs immediately preceding incoming painful stimuli. A promising approach is to investigate event related brain activity during tasks that elicit pain anticipatory phenomena, such as with sensory stimuli that cue arriving/impending nociceptive stimuli. Event related neural activity reflects sensory, affective and cognitive processes elicited by the task (Luck and Kappenman, 2012), and by controlling for the sensory component, affective-cognitive spheres can be unambiguously drawn out. Several techniques can be used to this end, including electrophysiological and perfusion based techniques. However, magnetoencephalography (MEG) has been our technique of choice, given its high temporal resolution without compromising spatial integrity (Hansen et al., 2010).

Event-related fields (ERFs) acquired using MEG are a sequence of positive P and negative N deflections with specific timing/latency. They have been widely used to characterize sensory and cognitive neuronal processing in normal as well as patient populations (Luck and Kappenman, 2012). ERFs can be classified into short or long latency events, where latency varies with the sensory modality (i.e. auditory, visual, olfactory, and sensory) and the underlying contextual meaning of the cue used to evoke the field. In the case of visual ERFs, short latency or early events are labeled P1 and N1 occurring 100–200 ms and P2 and N2 occurring 200–350 ms. Long latency events are labeled P3, occurring >300 ms later (Olofsson et al., 2008). Later events are then classified as succeeding "slow waves". The early ERF components are generally associated with attentional and affective processing (Carretié et al., 2004; Carretié, 2014), whereas the late components are involved in cognitive aspects (Luck et al., 2000).

In our prior works, we investigated ERFs in the frequency domain during visually evoked pain anticipation (Machado et al., 2014; Gopalakrishnan et al., 2015). We showed that associative cortical areas such as the dorsolateral prefrontal cortex are critical in establishing the contextual meaning of visual cues that indicate incoming painful stimuli vs. non-painful stimuli. However, limbic and primary sensory cortical areas became significantly active once the contextual meaning was established, corroborating to the central role of these areas in the process of pain chronification. To date, pain anticipatory phenomena has been predominantly linked to late event-related components, in particular stimulus preceding negativity (SPN) (Poli et al., 2007; Brunia et al., 2012). It remains unknown whether anticipatory phenomena are processed by early event related components. In this study we (a) investigate early ERF components presented during a 3 s visual countdown preceding painful stimuli, non-painful stimuli or no stimuli and (b) assess whether early ERF components could serve as early biomarkers of anticipatory phenomena.

2. Methods

Ten healthy subjects (7 males and 3 females, average age: 45 ± 15 years) participated in the study. Subjects were recruited through advertisements within the institution as well as through referrals from other research studies. Subjects were screened to not have any history of neurological or musculoskeletal condition that could lead to chronic pain. All research activities were approved by the Cleveland Clinic Institutional Review Board with signed informed consent This study was conducted in parallel to a clinical trial that investigates the use of deep brain stimulation (DBS) targeting affective networks to alleviate pain disability in patients with post-stroke (Plow et al., 2013). In order to facilitate future data comparisons, it is first necessary to understand pain anticipatory phenomena in the normal population. Subject enrollment in this study has been matched to the patient population to be best possible extent.

2.1. Data collection

The paradigm used in this study has been described elsewhere in greater detail (Gopalakrishnan et al., 2013; Machado et al., 2014). Briefly, subject's fiducials (nasion, left and right auricular) and head surface points were collected using Fastrack digitizer (Polhemus, Colchester, VT, USA) to allow for co-registration with MRI data. Before entering the MEG suite, subjects were degaussed to decrease unwanted magnetic fields arising from metallic objects external and internal to their body. The experimental paradigms (Fig. 1) were explained in detail. In short, subjects underwent MEG during anticipation to painful (PS), non-painful (NPS) and to no stimuli (NOS). Visual cues (250 ms) signaled the countdown to the stimulus and the nature of incoming stimulus. The countdown lasted for 3 s and was cued with numbers appearing on the screen in descending order as "3, 2, 1". The visual cues always correctly predicted the type of incoming stimulus. The type of incoming stimulus was indicated by the shape of the visual cue around the number. A tip down triangle warned of a PS or NPS, depending on the paradigm, while a tip up triangle symbolized NOS. PS was a thermal hot stimuli that was applied to the volar surface of the forearms using a contact heat-evoked potential stimulator (CHEPS) of the Medoc pathway system (Medoc Ltd., Ramat-Yoshai, Israel), whereas NPS involved electrical stimulation delivered to the median nerve using a stimulator (Grass Instruments). Subjects were instructed to (a) stay alert and focused on the cues and numbers to evoke anticipation, (b) avoid blinking during the countdown as much as possible and (c) remain as motionless as possible while recording data. Pain thresholds (Machado et al., 2014) were determined before MEG data collection using a ramp and hold pattern, with rise rate of 70 °C/s, 2 s hold at target temperature (range: 40–50 °C with 1 °C increments) and fall rate of 40 °C/s. Threshold was set at temperature at which subjects perceived the pain to be 8 out of 10 in a numerical rating scale.

1. *Paradigm-1:* Patients were seated upright in a 306 channel MEG array (Elekta, Stockholm, Sweden) with their head fully inserted into the helmet. While seated, subjects viewed visual cues presented. This first paradigm consisted of 4 blocks of 60 pseudo-randomized trials with 60% PS trials and 40% NOS trials. Nociceptive stimuli were applied to the left extremity for the first two blocks and then switched to the right extremity for the last two. Each trial in a block was 8–9 s long including 1 s baseline, 3 s of pre-stimulus countdown or anticipatory period (Fig. 1) and 4–5 s of post-stimulus (recovery) period before the next trial started.
2. *Paradigm-2:* The set up for experimental paradigm 2 repeated the same methods as for experimental paradigm 1, except PS was replaced by NPS. The electrode was affixed to the median nerve at the wrist. The intensity of stimulus (voltage) was increased stepwise until a thumb twitch was evident. Based on feedback from patients, the intensity was either maintained or lowered till subjects rated the sensation associated with stimulation as no more than 2 on a numerical rating scale of 0–10, while maintaining their attention.

Subjects were asked to report pain rating on a numerical rating scale of 0–10 at the end of data collection for each extremity. They were monitored continuously with a video camera to ensure alertness and continued attention to visual cues. If signs of inattentiveness were observed, subjects were alerted vocally through microphone. Additionally, subjects were allowed to take break, if needed, at the end of data collection from each extremity.