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Early Event Related Fields during Visually Evoked Pain Anticipation

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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 3s 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.

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Conflict of interest

Andre Machado has the following conflicts to declare, none of which are pertinent to this research project or to this manuscript: consultant, Spinal Modulation and Functional Neuromodulation. Potential distribution from intellectual property: Enspire DBS, Cardionomics and ATI. Other authors have no disclosures.

Significance—These measures could assist in the development of neurostimulation approaches aimed at curbing the negative effects of pain anticipation during rehabilitation.

Keywords

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 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 et al., 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 et al., 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 100–200ms and P2 and N2 occurring 200–350ms. Long latency events are labeled P3, occurring >300ms 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” (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 3s 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 3s 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 thermal where a hot thermode 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), 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, 2s 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 8–9s long including 1s baseline, 3s of pre-stimulus countdown or anticipatory period (Fig-1) and 4–5s 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.

2.2. Data pre-processing

MEG data were collected either at 1000 (DC to 330 Hz) or 2400 (DC to 800 Hz) samples/sec and processed through temporal signal space separation method (Taulu et al., 2006) to filter magnetic interferences and external artifacts. The raw data were downsampled to 200 Hz. All initial preprocessing were performed using fieldtrip toolbox (Oostenveld et al., 2011) and in-house built Matlab (The Mathworks, Natick, MA, USA) scripts. The data from 204 gradiometer pairs were parsed to the onset of PS/NPS to segregate 4s baseline and anticipatory period. Trials contaminated with SQUID jump artifacts were removed from analysis by means of thresholding the z-transformed value (Oostenveld et al., 2011). On average, 58 ± 2 (paradigm-1) and 52 ± 5 (paradigm-2) trials per block per subject underwent subsequent analysis. The trials were then subtracted for dc offset and band-pass filtered 1 – 70 Hz using a 4^{th} order butter-worth zero phase lag IIR filter in fieldtrip (Oostenveld et al., 2011). To account for the variances due to head motion, a generalized linear model (GLM) based head movement compensation algorithm (Stolk et al., 2013) was employed. The method modeled the non-linear effects of head movements

(from initial position) by including the linear, square and cubes of head movement and their derivatives, to compute 36 regression coefficients which were then subtracted from individual trials. Initial head position was set to the coordinates recorded at the beginning of first block in each extremity. Data trials from both extremities were clubbed together to form a combined set assuming anticipatory period is unaffected by the location of target stimuli.

2.3. Data analysis and statistics

Pre-processed data trials from each condition were subjected to evoked analysis using Fieldtrip (Oostenveld et al., 2011) to study the early ERF components (500ms from cue onset). Data from 204 paired orthogonal gradiometers were combined in each subject (using *ft_combineplanar* command in Fieldtrip) for all conditions studied. The ERFs were subjected to a non-parametric permutation statistics (Maris et al., 2007) implemented in Fieldtrip, to identify sensor pairs that show significant anticipatory effect. Event-related neural activity in the observed datasets between any two conditions was initially clustered, based on adjacency in space and time using dependent samples t-test, at a parametric threshold of $p<0.05$. The samples were then permuted a large number of times (5000). For each permutation, the cluster with the maximum sum of t-values was retained to compute the distribution histogram. Observed cluster sums that exceeded 95% confidence interval ($p<0.05$) of the permutation distribution were considered significant to compute Monte-Carlo estimate of t-statistics (Maris et al., 2007). The minimum cluster size was set to three sensors, with no maximum limit. The multiple comparison problem was controlled by evaluating the cluster-level statistics under the permutation distribution of the maximum cluster-level statistic. Cluster topographies were plotted in intervals of 20ms highlighting sensors that showed significant effect for contiguously for 10ms or more.

As shown in Fig. 1, there were four conditions, namely, PS, NPS, NOS1 (no stimulus condition associated with PS in paradigm-1) and NOS2 (no stimulus condition associated with NPS in paradigm-2). Our primary interest was to study the significant anticipatory effects upon ERFs in paradigm-1 (PS/NOS1) in comparison to those in paradigm-2 (NPS/NOS2). In addition, we were interested in studying within paradigm (PS vs. NOS1 and PS vs. NOS2) effects and the individual cue effects within each condition. Hence, the ERFs were compared at two levels. 1. Within-condition, where responses of first count-down cue was compared against second and third cues. 2. Between-conditions, where responses of each of the countdown cues in one condition was compared against corresponding cues in another condition, both within paradigm and across paradigms.

3. Results

The titrated temperature thresholds were 48.6 ± 1.58 °C and 48.6 ± 1.35 °C for left and right extremities respectively. Though the initial titrated pain rating was 8 out of 10, the final pain ratings for the left and right extremities were 6.85 ± 1.15 and 7 ± 1.31, respectively. The demographics, titrated target temperatures and final pain ratings of individual subjects have been reported elsewhere in greater detail (Machado et al., 2014). The visual anticipatory countdown cues evoked two types of responses in the MEG sensors, since they were presented with 250ms duration. First response was an ON response pertaining to the presentation of the cue, followed by OFF response pertaining to disappearance of the cue. In

both types of responses, early ERF components namely P1, N1, P2 and N2 components were evident, as shown in Fig. 2. In the following sections, we have added '-ON' and '-OFF' suffixes to differentiate the ERF components associated with ON and OFF responses. The temporal range of P1-ON, N1-ON, P2-ON and N2-ON from stimulus onset was 110 – 120ms, 150 – 170ms, 230 – 300ms and 320 – 360ms respectively. The temporal range of P1-OFF, N1-OFF and P2-OFF from stimulus onset was 360 – 380ms, 380 – 440ms and 440 – 500ms respectively. Since the OFF responses were elicited by cue disappearance, the ERF responses elicited were not as strong as ON responses. In addition, an N2-OFF component could not be identified.

3.1. Cross-paradigm comparison

PS vs. NPS—All three countdown cues in PS showed significant differences in comparison to corresponding cues in NPS during ON response (Fig. 2). The first countdown cue in PS elicited significant sensor clusters associated with MEG activity localized to anterior (fronto-central) sensors from 280 – 360ms (P=0.0004). This latency encompassed two important ERF components, namely P2-ON (280 – 320ms) transitioning into N2-ON (320 – 360ms) components, which is also referred to as "early posterior negativity" with associated frontal positivity. While the P2 peak was significant in sensors near the vertex (cingulate region), at the N2 peak the significance transitioned anteriorly with right lateralization to encompass sensors over DLPFC (Fig. 2). Though the N2 peak was evident in NPS condition, its amplitude was significantly lower compared to PS. Given the nature of our visual paradigm, N2 is the last component that could be detected prior to the OFF responses, where we did not find any significant findings. The second and third countdown cues in PS were associated with significant sensor clusters from 140 – 160ms (P=0.0412) and 140 – 180ms (P=0.0216), respectively, corresponding to N1 component. The origination of N1 components was mostly from frontal sensors (second cue) and sensors near the vertex (third cue).

NOS1 vs. NOS2—When comparing the NOS1 to NOS2, only the first countdown yielded a significant ON response cluster in NOS1 between 240 – 300ms (P=0.0180) corresponding to P2 component with fronto-central (cingulate and right DLPFC) localization (Fig. 3). Neither NOS1 nor NOS2 presented evidence of N2 component. The second and third cues did not yield any significant clusters.

3.2. Within paradigm comparison

PS vs. NOS1/NPS vs. NOS2—Within each paradigm, the stimulus condition (PS or NPS) was compared against no stimulus condition (NOS1 or NOS2). Interestingly, no significant clusters were identified in any of the three countdowns for both ON or OFF responses.

3.3. Within condition comparison

Within condition analysis results are summarized in Fig. 4, 5, 6 and 7.

PS—During PS, the first countdown cue showed three significant clusters in comparison to second countdown cue (Fig. 4, bottom 3 rows). The temporal location (from cue onset) of

the clusters was 230 – 320 ms for P2-ON (P=0.0036), 370 – 440 ms for N1-OFF (P=0.0308) and 440 – 500ms for P2-OFF (P=0.0132). The P2-ON initiated in the posterior vertex area followed by activation along temporal and parietal areas bilaterally (260 – 280ms). The N1-OFF component initiated in the posterior vertex area and, followed by activation along temporal areas. The P2-OFF localized fronto-temporally. When comparing the first countdown cue to the third cue, we noted two significant sensor clusters (Fig. 4, top two rows). The temporal location (from cue onset) of the clusters was 140 – 200ms for N1-ON (P=0.0168) and 200 – 320ms for P2-ON (P=0.0004). The P2-ON was similar to the response observed in comparison to the second cue, however with a broader significant temporal range. The N1-ON component was localized mostly along the vertex and frontal sensors. Interestingly, there was no evidence of significant N2-ON component during the first cue in the within condition comparison.

NPS—During NPS, the first countdown cue presented only one significant cluster in comparison to the second cue (Fig. 5, bottom row) that was evident between 220 – 320ms (P2-ON; P=0.0004). The first countdown cue also presented two significant clusters in comparison to the third cue (Fig. 5, both rows), evident between 140 – 180ms (N1-ON; P=0.0076) and 240 – 320ms (P1-ON; P=0.0048). The spatial localization of these components was similar to those observed in PS. No significant clusters were recorded during OFF responses in NPS condition.

NOS1—Interestingly, both NOS1 and NOS2 conditions showed similar patterns of activity as for PS and NPS, respectively (Figs. 6 and 7). During NOS1, the first countdown cue elicited MEG activity associated with significant sensor clusters corresponding to N1-ON (P=0.0416), P2-ON (P=0.0004) and N1-OFF (P=0.0416) in comparison to the third cue (Fig. 6, top three rows), and P2-ON (P=0.0016) and P2-OFF (P=0.0348) in comparison to second cue (Fig. 6, second and fourth row).

NOS2—Similarly, during NOS2, the first countdown cue showed significant clusters corresponding to N1-ON (P=0.0060) and P2-ON (P=0.0084) in comparison to the third cue (Fig. 7, top two rows), and P2-ON (P=0.0044) and N1-OFF (P=0.0392) in comparison to second cue (Fig. 7, bottom two rows). The spatial localization of all these components was similar to those observed in PS and NPS conditions.

4. Discussion

The purpose of this study was to investigate early ERF components and their evolution during pain anticipation. In a countdown paradigm like ours, one would imagine that the last countdown cue is the most important for its cumulative anticipatory build-up. However, in the current study, we found that the first countdown cue was critical in terms of both attention and alertness, while the cues that followed were redundant. In all four conditions studied, the first (countdown) cue elicited a significant P2-ON component compared to rest of the cues. In addition, the first cue during pain anticipation (PS) elicited a significantly greater P2-ON and a N2-ON component originating from fronto-central sensors that could serve as a biomarker of pain anticipation.

The present data corroborates the involvement of early ERF components in pain anticipatory process. Early ERF components have been shown to process visual stimuli of positive and negative valence, both facial and otherwise (Holmes et al., 2008, Olofsson et al., 2008, Bublatzky et al., 2010). Here, we show that abstract visual cues that correctly predict a pain outcome can also modulate early ERF components. Modulation of early ERF components, specifically P2 and N2 were significantly dependent on the contextual meaning of the visual cue i.e. whether it predicted a painful stimulus or a non-painful stimulus. Interestingly, these components localized to fronto-central sensors, involving cingulate and prefrontal cortex. This indicates that early ERFs are involved in the contextual classification of pain anticipatory cues and corroborates our prior findings regarding the extraordinary time-efficiency with which the neuromatrix identifies and correctly classifies pain-related anticipatory cues (Machado et al., 2014).

Our earlier work (Machado et al., 2014) based on MEG data collected from normal subjects reported that the primary visual cortex (V1) is capable of independently distinguishing between visual anticipatory cues signaling painful or non-painful stimuli once associative/limbic areas establish the contextual meaning of these cues. We showed that activity in the associative/limbic areas is dominated by gamma band oscillations during early stages of anticipation. These findings in the spectral domain motivated the present work aimed at evaluating the neural correlates of pain anticipatory phenomena at sensor level in the temporal domain. We are particularly interested in the P2/N2 component during ON response, which has been associated with affect processing and memory encoding (Lefebvre et al., 2005, Finnigan et al., 2011, Paulmann et al., 2013, Carretié, 2014).

The most widely reported event related component associated with pain anticipation is the stimulus preceding negativity (Brown et al., 2008a, Clark et al., 2008, Seidel et al., 2015). This is a slow component that occurs at >500ms latency and has been reported to occur during the anticipatory process of an imminent sensory event that is emotionally significant (Brunia et al., 2012). When anticipating with certainty, as in our study, stimulus preceding negativity has been localized to anterior prefrontal cortex, inferior frontal cortices and cingulate cortex (Brown et al., 2008a). Contingent negative variation (CNV) is another slow anticipatory component that occurs when a cue signals an expected voluntary motor or mental activity (Bares et al., 2007). Though CNV has not been reported in relation to pain anticipation, the early or orienting component of CNV that occurs immediately after the cue has been thought to reflect neural substrates of SPN (Brown et al., 2008a) or affective processes (Carretié et al., 2001). While prior studies have reported early evoked component such as P2 in the context of pain processing (Brown et al., 2008a, Brown et al., 2014, Seidel et al., 2015) such findings were not associated with a anticipatory conditioning stimuli but, rather, from the noxious, target stimuli (i.e. pain evoked responses).

4.1. N1 component is indicative of anticipatory attention

ERF components P1 and N1 have been associated with attention to spatial selection (Hillyard et al., 1998a, Luck et al., 2000) and attention-related amplification of electrophysiological response (Hillyard et al., 1998b). Our results do not show evidence of P1 involvement in pain anticipatory processing. However we noted increased N1 component

during the first countdown cue in all conditions studied (Figs.4 – 7). This points to a heightened attentional state to the initial cues during the countdown process. A similar phenomenon was noticed during the second and third cues in the PS condition, in comparison to NPS (Fig. 2), perhaps indicating that N1 is more pronounced in response to cues that have already been classified but still deserve attention. Interestingly, the N1 component was localized to sensors encompassing dorsolateral prefrontal cortex and cingulate cortex, which could reflect the role of these regions in processes such as alertness (Posner et al., 1990, Carretié et al., 2001), cognitive control/task setting (MacDonald et al., 2000, Floden et al., 2011), or emotion regulation (Beauregard et al., 2001, Ochsner et al., 2004, Kalisch et al., 2005).

4.2. The role of P2 in pain anticipation

When comparing within conditions, the first countdown cue elicited a significant P2 component during the ON response compared to the second and third cues. This indicates that once the first cue was characterized, the second and third cues became irrelevant and redundant. The topography of sensors indicated an origin at vertex with spread into frontal and temporal areas (Fig. 4, second row). Though P2-ON was elicited in all conditions (whether painful, non-painful or no stimulus), P2-ON recorded during PS and NOS1 had a significantly greater magnitude compared to NPS and NOS2 conditions, respectively (Fig. 2 and 3). It was localized to fronto-central sensors indicating a role of the cingulate cortex and pre-frontal dorsolateral cortices, key areas of the pain neuromatrix. These findings could indicate that P2-ON is associated with a state of high degree of vigilance expected of subjects during paradigm-1 compared to paradigm-2. Paradigm-1 had greater salience since it involved delivery of painful stimuli. The P2-ON component seems to have an important role in pain alerting and anticipation, especially in an environment where there is an ongoing pain threat.

4.3. The role of N2 in pain anticipation

One of the most interesting findings of this study was the presence of a unique anteriorly localized N2 component (Fig. 2) during the first cue in PS exclusively attributed to pain anticipation. Several studies have reported N2 using different terminologies (such as N2a, N2b, N2c, early posterior negativity) depending on the type of task and modality (Schupp et al., 2006, Folstein et al., 2008). N2 has also been reported as homologous to early orienting component of CNV (Carretié et al., 2001). Though fronto-central N2 has been associated with cognitive control, response inhibition, visual novelty or odd-ball kind of response (Folstein et al., 2008), our findings seem to reflect anticipatory alertness to visual stimuli of negative salience reported by Carretie et al. (Carretié et al., 2001, Carretié et al., 2004). Interestingly, these studies reported that N2 associated cortical activity decreased as negative saliency of the target stimuli increased. On the contrary, we recorded greater N2 when anticipating pain (high salience) than a non-painful stimulus (low salience). This discrepancy could be attributed to the nature of the target emotional stimulus, which was a mere visual stimulus of negative salience (i.e. psychological) in the reported studies compared to pain (both psychological and physiological) in our study.

4.4. Conclusions and Clinical Implications

Event related brain fields or potentials, in particular P3 and late components have been widely used for clinical purposes in a variety of cognitive and psychotic disorders (Pfefferbaum et al., 1984, Polich, 1992, 2004, Duncan et al., 2009). To date, neurophysiological indicators of pain anticipation have relied mostly on late phases of cue processing (Brown et al., 2008a, Brown et al., 2008b), when cue classification has already been completed and processed by higher order cortical areas. This delay is a significant limitation to the development of novel interventions aimed at modulating pain anticipatory phenomena and its effects on pain chronification and disability. Our data indicate that P2 represents the increased attention/vigilance, while N2 represents the anticipatory component that distinguishes cues signaling incoming painful from non-painful stimuli. This study was conducted on healthy subjects and we recognize the limitation that this population differs from chronic pain population. However, we believe that understanding the pain anticipatory phenomena in normal controls will establish a platform to compare patient data against, which will be a topic for future communication. We speculate that these early electrophysiological correlates – biomarkers - of pain anticipatory phenomena will be useful to develop new approaches aimed at modulating pain anticipatory phenomena in very early stages of processing, before information regarding the salience of a cue is passed on to associative cortical areas. Such therapies could benefit chronic pain rehabilitative efforts by curbing the negative effects of kinesiophobia and other anticipatory pain behaviors that amplify the duration and severity of pain-related disability.

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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.

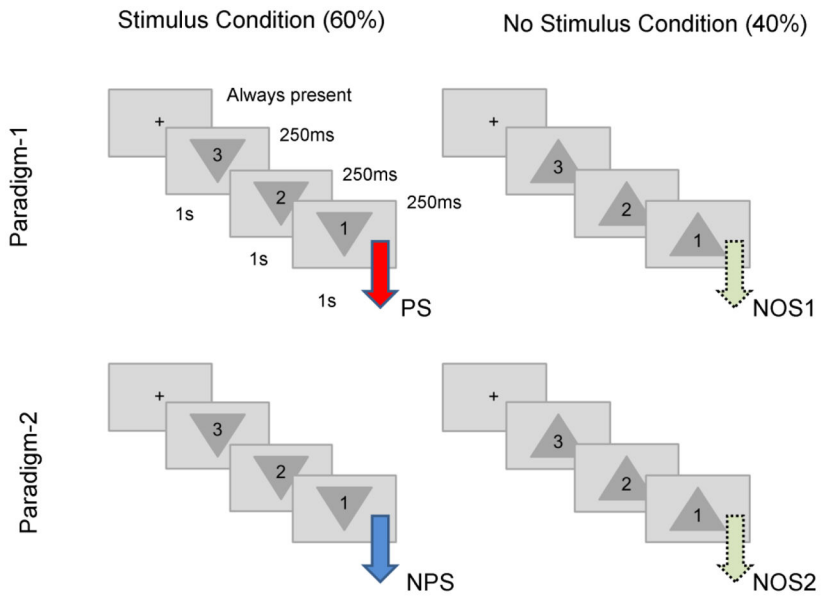

Figure 1.

Paradigms-1 and 2 illustrated schematically. Top row shows paradigm-1 where visual countdown cues preceding painful stimulus (PS) were presented as down pointing triangle, whereas those preceding no stimulus (NOS) condition were presented as up pointing triangle. Bottom row shows paradigm-2, which is similar to paradigm-1 except non-painful stimulus (NPS) was given in place of PS. NOS1 and NOS2 refers to no stimulus condition in paradigm-1 and 2 respectively.

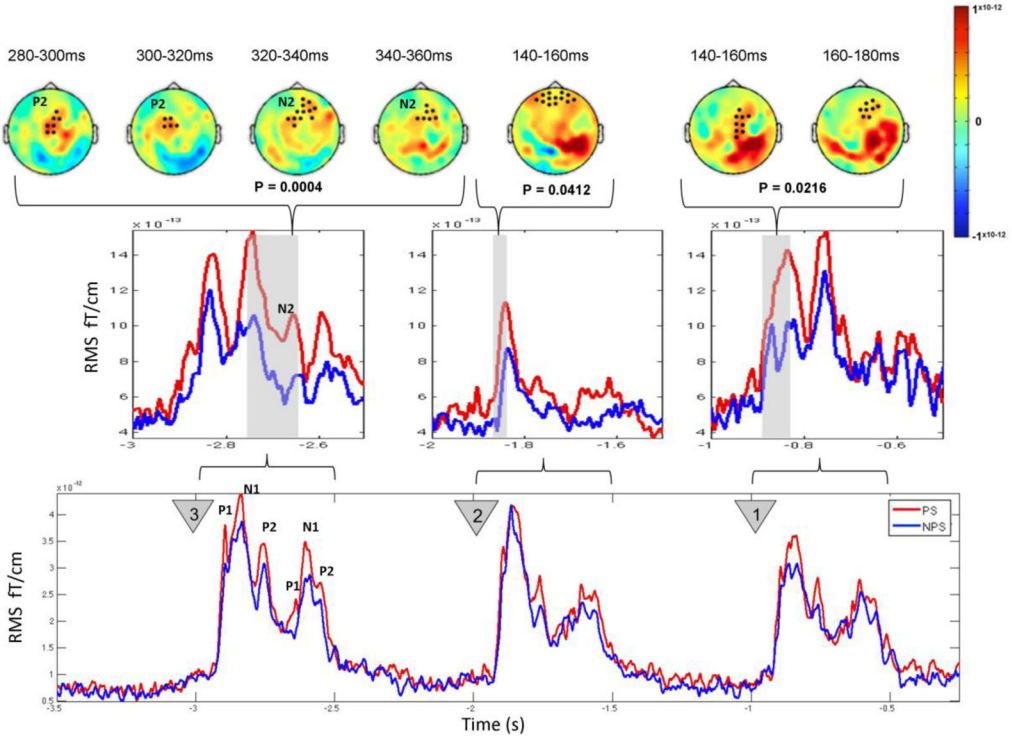

Figure 2.

PS vs. NPS cross-paradigm comparison results. Bottom row: The bottom row shows the RMS evoked responses in femto-Tesla/cm to three countdown cues from parieto-occipital sensors to indicate the various event related components pertaining to ON and OFF responses. The first set of P1, N1, P2 and N2 refers to ON response, followed by OFF response components. Middle row: Corresponding to each visual cue, the middle row shows RMS evoked responses from sensor cluster that showed significant response in PS vs. NPS comparison. Sensors were picked from the time point that display largest cluster on the topographical difference maps (PS – NPS) in the top row. Top row: Topographical difference maps from onset to end of the significant effect in increments of 20ms. The black dots in the topography indicate the spatial location (sensors) of the significant effect on the surface. The gray shaded areas in the middle row show the corresponding temporal range where significance was found.

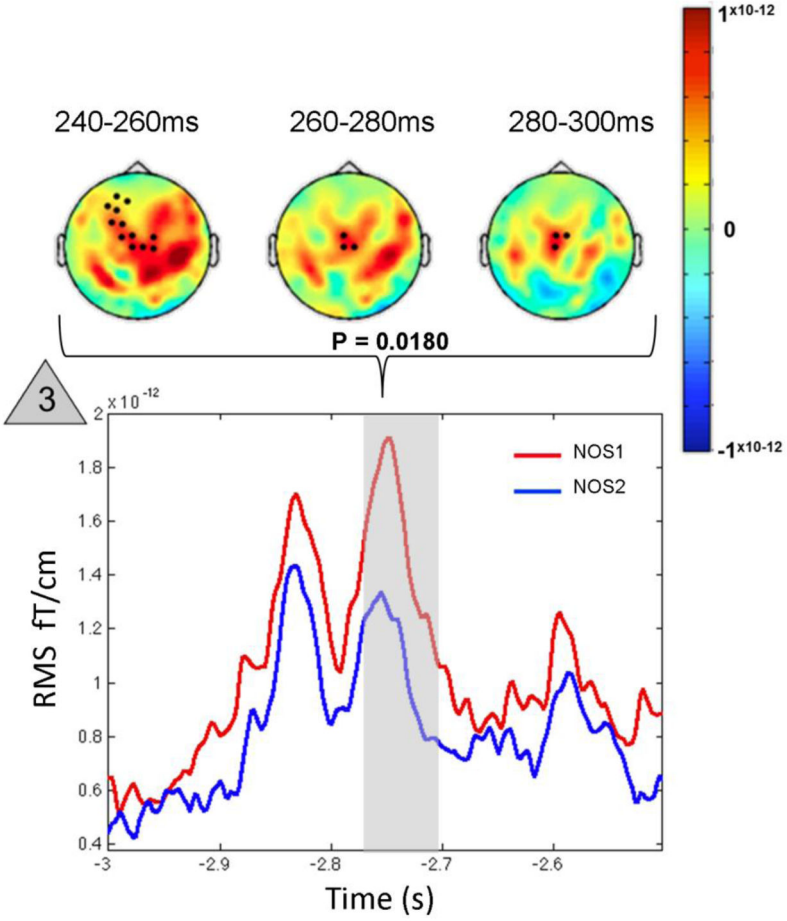

Figure 3.

NOS1 vs. NOS2 cross-paradigm comparison results displaying P2 component. Significant results were observed only during the first count-down cue (starting at -3s). The bottom plot shows the RMS evoked responses in femto-Tesla/cm from sensor cluster that showed significant response in NOS1 vs. NOS2 comparison. Sensors were picked from the time point that display largest cluster on the topographical difference maps (NOS1 – NOS2) in the top row. The black dots in the topography on the top row indicate the spatial location (sensors) of the significant effect on the surface. The gray shaded areas show the temporal range where significance was found.

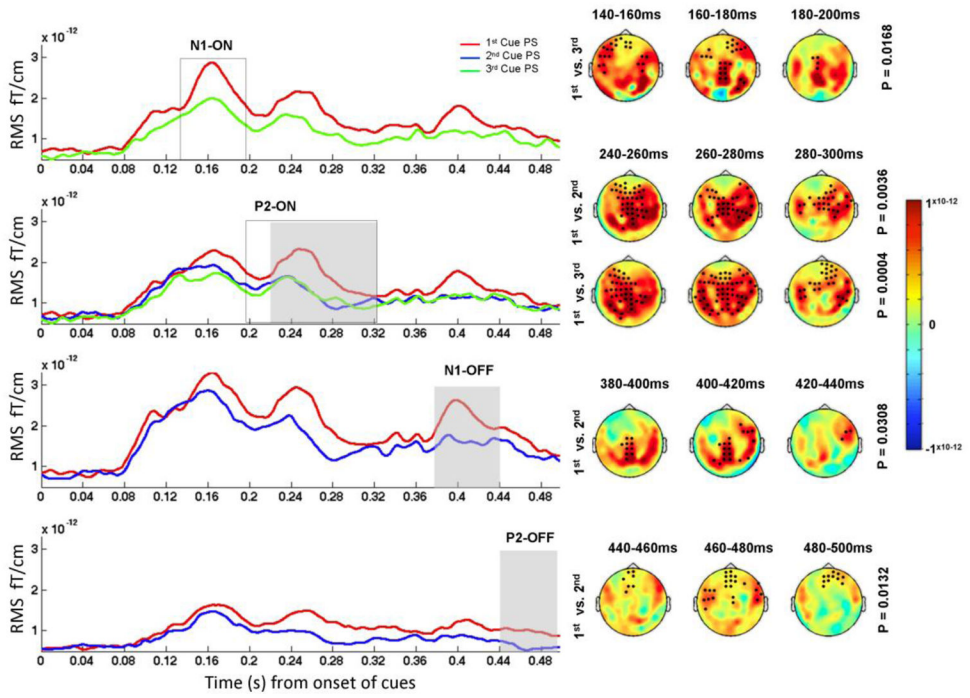

Figure 4.

Within condition comparison results in PS. Four clusters were observed corresponding to N1-ON (top row), P2-ON (row below top), N1-OFF (row above bottom) and P2-OFF (bottom). Panel on the left shows the RMS evoked responses in femto-Tesla/cm from sensor cluster that showed significant responses in the comparison of first cue (starting at −3s) vs. second (starting at −2s) and third cues (starting at −1s). Time axis shown here are relative to the starting point of each cue. Sensors were picked from the time point that display largest cluster on the corresponding panel on the right that displays topographical difference maps. Black windows display the temporal range of significant cluster for comparison of cue-1 vs. cue-3, whereas shaded windows display the temporal range of significant clusters for comparison of cue-1 vs. cue-2. Topography is displayed only for three temporal intervals that showed maximal effect. Black dots on the topography display significant sensor clusters on the surface.

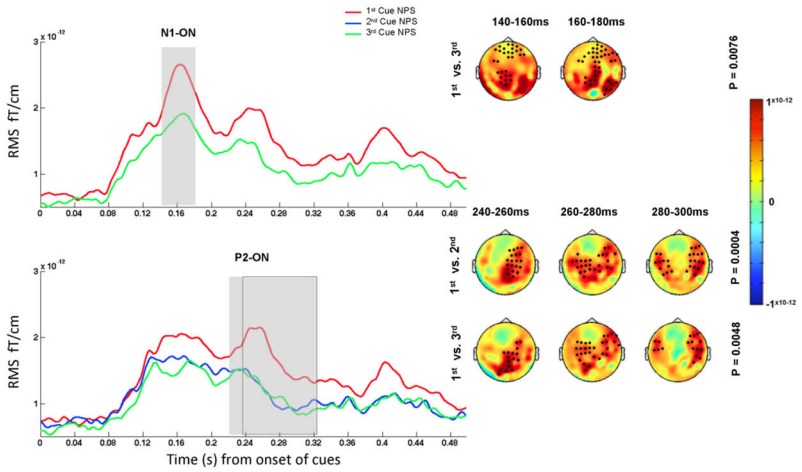

Figure 5.

Within condition comparison results in NPS. Two clusters were observed corresponding to N1-ON (top row) and P2-ON (bottom row). Panel on the left shows the RMS evoked responses in femto-Tesla/cm from sensor cluster that showed significant responses in the comparison of first cue vs. second and third cues. Time axis shown here are relative to the starting point of each cue. Sensors were picked from the time point that display largest cluster on the corresponding panel on the right that displays topographical difference maps. Black windows display the temporal range of significant cluster for comparison of cue-1 vs. cue-3, whereas shaded windows display the temporal range of significant clusters for comparison of cue-1 vs. cue-2. Topography is displayed only for three temporal intervals or less that showed maximal effect. Black dots on the topography display significant sensor clusters on the surface.

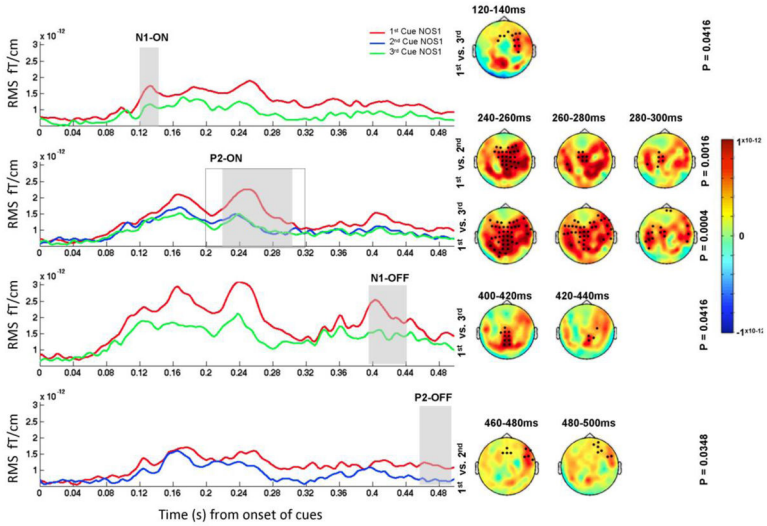

Figure 6.

Within condition comparison results in NOS1. Four clusters were observed corresponding to N1-ON (top row), P2-ON (row below top), N1-OFF (row above bottom) and P2-OFF (bottom). Panel on the left shows the RMS evoked responses in femto-Tesla/cm from sensor cluster that showed significant responses in the comparison of first cue vs. second and third cues. Time axis shown here are relative to the starting point of each cue. Sensors were picked from the time point that display largest cluster on the corresponding panel on the right that displays topographical difference maps. Black windows display the temporal range of significant cluster for comparison of cue-1 vs. cue-3, whereas shaded windows display the temporal range of significant clusters for comparison of cue-1 vs. cue-2. Topography is displayed only for three temporal intervals that showed maximal effect. Black dots on the topography display significant sensor clusters on the surface.

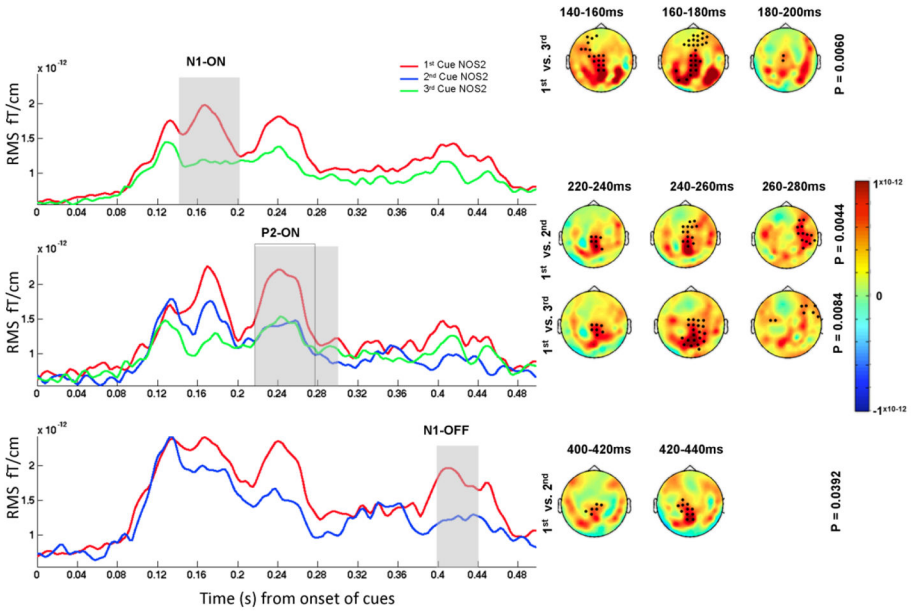

Figure 7.

Within condition comparison results in NOS2. Three clusters were observed corresponding to N1-ON (top row), P2-ON (middle row) and N1-OFF (bottom row). Panel on the left shows the RMS evoked responses in femto-Tesla/cm from sensor cluster that showed significant responses in the comparison of first cue vs. second and third cues. Time axis shown here are relative to the starting point of each cue. Sensors were picked from the time point that display largest cluster on the corresponding panel on the right that displays topographical difference maps. Black windows display the temporal range of significant cluster for comparison of cue-1 vs. cue-3, whereas shaded windows display the temporal range of significant clusters for comparison of cue-1 vs. cue-2. Topography is displayed only for three temporal intervals or less that showed maximal effect. Black dots on the topography display significant sensor clusters on the surface.