A magnetoencephalography study of visual processing of pain anticipation

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Machado AG, Gopalakrishnan R, Plow EB, Burgess RC, Mosher JC. A magnetoencephalography study of visual processing of pain anticipation. J Neurophysiol 112: 276–286, 2014. First published April 30, 2014; doi:10.1152/jn.00193.2014.—Anticipating pain is important for avoiding injury; however, in chronic pain patients, anticipatory behavior can become maladaptive, leading to sensitization and limiting function. Knowledge of networks involved in pain anticipation and conditioning over time could help devise novel, better-targeted therapies. With the use of magnetoencephalography, we evaluated in 10 healthy subjects the neural processing of pain anticipation. Anticipatory cortical activity elicited by consecutive visual cues that signified imminent painful stimulus was compared with cues signifying nonpainful and no stimulus. We found that the neural processing of visually evoked pain anticipation involves the primary visual cortex along with cingulate and frontal regions. Visual cortex could quickly and independently encode and discriminate between visual cues associated with pain anticipation and no pain during preconscious phases following object presentation. When evaluating the effect of task repetition on participating cortical areas, we found that activity of prefrontal and cingulate regions was mostly prominent early on when subjects were still naive to a cue’s contextual meaning. Visual cortical activity was significant throughout later phases. Although visual cortex may precisely and time efficiently decode cues anticipating pain or no pain, prefrontal areas establish the context associated with each cue. These findings have important implications toward processes involved in pain anticipation and maladaptive pain conditioning.

magnetoencephalography; neuromatrix; pain; pain anticipation; visual cortex

CHRONIC PAIN IS ONE OF THE most common causes of disability in the industrialized world (Torrance et al. 2006). Pain, particularly chronic, is not merely sensory discrimination encoding the magnitude and site of potential tissue injury. Rather, it is represented by a complex neuromatrix, where affective and cognitive spheres play a fundamental role as well in determining the final pain experience (Melzack 1999). Therefore, individuals’ conditioning to pain and their anticipation can modify or exaggerate their perception (Flor et al. 2002; Lousberg et al. 1996). Although anticipation is adaptive, helping individuals avoid injury (Pfingsten et al. 2001), it can exaggerate disability in those who suffer from chronic pain, thus limiting recovery. Current therapies for chronic, medically refractory pain include neurostimulation as well as intrathecal infusion of drugs, with the primary aim of producing analgesia by modulating ascending or descending sensory-discriminative pathways. Unfortunately, these interventions only partially alleviate pain or restore function and in only approximately one-half of the patients (Kumar et al. 2008; Sears et al. 2011). New modalities that broaden targeting of the nervous system to include spheres of pain experience beyond somatosensory pathways are warranted instead to manage totality of pain experience. Clinical trials are under way to evaluate the efficacy of modulating neural networks that process affective information via invasive and noninvasive stimulation in managing chronic pain (Machado et al. 2013; Maeoka et al. 2012; Plow et al. 2013).

These efforts are, however, limited by our current understanding of what neural networks process anticipation of pain, how they modulate individual conditioning, and how they interact with the remaining neuromatrix. Importantly, the elucidation of the neural mechanisms of pain anticipation would provide insight into underlying mechanisms of novel interventions under way to target affective neural networks to influence pain outcomes. With this knowledge, novel therapies can be designed to target pain anticipation and conditioning specifically. In the present study, we evaluated for the first time in healthy individuals the neural processing of pain anticipation using magnetoencephalography (MEG). Specifically, visual cues that signified approaching painful stimulus (PS), in this case, thermal heat stimulus, served as our anticipatory painful condition, which was compared against control conditions. Here, we demonstrate for the first time that neural processing of visually cued pain anticipation involves the primary visual cortex (V1), as well as cingulate and frontal regions. Importantly, the visual cortex can independently encode and discriminate between visual cues associated with anticipation of pain and neutral stimuli during early preconscious perception.

MATERIALS AND METHODS

Ten subjects (seven men and three women; average age: 45 ± 15 yr) participated in the study after approval from the Cleveland Clinic Institutional Review Board. All subjects provided written, informed consent to participate. Participants did not have any neurological disorders or history of chronic pain.

A detailed description of data collection and preprocessing is provided elsewhere (Gopalakrishnan et al. 2013). Briefly, fiduciary points (nasion, right and left auricular), along with head surface points and head position indicator (HPI) locations, were first marked on each subject’s head using a Fastrak digitizer (Polhemus, Colchester, VT) to allow registration with their MRI anatomical data. Subjects were seated upright in a MEG array (Elekta Neuromag, Helsinki, Finland), such that each participant’s head was fully inserted into the helmet. The position of the head was monitored continuously via five HPI coils affixed to the scalp.
A contact heat-evoked potential stimulus thermode of the Medoc pathway system (Medoc, Ramat Yishai, Israel) was used to elicit pain. The thermode was attached to the volar surface of the forearm. Painful heat stimulus was titrated for each subject to determine his or her individual threshold. The thermode was heated and cooled repeatedly in a ramp-and-hold pattern (rise rate: 70°/s; hold 2 s; fall rate: 40°/s). Target temperatures, ranging between 40°C and 50°C, were presented in 1° increments after every 1 s. Subjects were instructed to stop titration when they felt that the temperature was painful enough to evoke anticipation. As a general rule, they were asked to report when their subjective perception of pain was approximately eight on a scale of zero to 10 (10 being the worst pain they could imagine). Subjects were specifically asked not to allow pain to reach severe or excruciating levels.

While seated in the MEG array, subjects viewed visual cues presented as a countdown. The cues signified the type of approaching stimulus: PS (Fig. 1, top), nonpainful stimulus (NPS; Fig. 1, middle), or no stimulus (NOS) at all (Fig. 1, bottom). The type of stimulus that would follow the countdown was symbolized by shape of the visual cue. A downward-pointing triangle warned of a PS or NPS, depending on the block of stimulation, whereas an upward-pointing triangle symbolized NOS. The countdown itself was 3 s long and was marked by numbers 3, 2, and 1, presented in descending order with each cue (whether a downward- or upward-pointing triangle). Visual cues always accurately represented whether PS, NPS, or NOS would follow. Subjects were instructed to stay alert and focus on cues and numbers presented during the countdown to evoke anticipation. They were also asked to avoid blinking during the countdown and remain as motionless as possible inside of the MEG array.

The paradigm was explained verbally to the subjects before data collection. The first paradigm consisted of four blocks of 60 pseudo-randomized trials, 60% of which signaled impending PS, whereas the remaining 40% signaled NOS. Nociceptive stimulus was applied to the left extremity for the first two blocks and then switched to the other extremity for the last two, regardless of hand dominance. Consecutive blocks for each extremity helped minimize any adjustments to position of the head inside of the array. Each trial in a block was 8–9 s long, including a 1-s baseline, 3 s of prestimulus countdown or anticipatory period, and 4–5 s of a poststimulus (recovery) period. In between blocks, subjects were asked (over an intercom) if they were ready to continue onto the next block. At the end, they were asked to rate the overall pain they experienced on a scale of zero to 10 for each extremity. Subjects were monitored continuously with a video camera to ensure alertness and continued attention to visual cues. MEG recordings were acquired continuously during the four blocks. The paradigm was repeated in a separate set of four blocks, but this time, electrical NPS was delivered to the median nerve at the wrist (Grass Technologies, Warwick, RI) instead of the PS. The intensity (voltage) of stimulation was increased gradually to the point where a thumb twitch was evident. Based on feedback from subjects, the voltage level was maintained or lowered until subjects rated pain associated with stimulation as zero on a scale of zero to 10, while maintaining their attention. The visual cues for NPS were identical to those for PS. Subjects were informed at the beginning of the block whether downward-pointing cues would signify approaching PS or NPS.

Data Model

All MEG data were collected at either 1,000 [direct current (DC) to 330 Hz] or 2,400 (DC to 800 Hz) samples/s. Although subject motion was monitored continuously through the MEG HPI system, the data were not postprocessed to correct for motion; as discussed in GOPalakrishnan et al. (2013), the vendor’s motion-compensation algorithm decreases the dimensionality of the data and hence, possibly its information content. Initial, simple temporal prewhitening was performed using a two-point difference operator to attenuate the strong low frequencies. The data were downsampled to 200 samples/s using the Matlab (MathWorks, Natick, MA) “resample” command. The 60-Hz artifact was removed by modeling the sinusoid and subtracting it from the data. The data were parsed visually to identify and reject trials that exceeded 3 SD from the mean. On average, 141 PS/NPS trials and 92 NOS trials were used for analysis. Finally, a low-order (10th) autoregressive model was used to reintegrate lower frequencies originally suppressed by the difference operator, flattening the overall spectrum. The 1-s period preceding the anticipatory period was used as a baseline to evaluate the spatial noise covariance.

Source Model

With the use of Brainstorm’s algorithms and data models (Tadel et al. 2011), the tessellated pial surface of a surrogate brain template [Montreal Neurological Institute (MNI), Quebec, Canada] was morphologically warped to each subject, using the subject’s scalp data as the reference. This MNI MRI phantom has 88 predefined patches or
regions of interest (ROIs), based on standard anatomical nomenclature (Tzourio-Mazoyer et al. 2002), and thus the ROIs were warped automatically into the appropriate regions for each subject. After warping, the MEG leadfield matrix for 15,000 cortical dipoles sampled on the phantom pial surface was computed for each subject, using the overlapping spheres head model (Huang et al. 1999).

We focused the analysis to ROIs in the calcarine (V1), orbitofrontal cortex (OFC), dorsolateral prefrontal cortex (DLPFC; midfrontal and superior frontal gyrus), cingulate cortex [anterior (ACC), mid (MCC), and posterior (PCC)], and insula (Fig. 2). The frontal, cingulate, and insular regions were chosen based on their involvement in pain and pain-anticipation processing (Brown and Jones 2008; Clark et al. 2008; Hauck et al. 2007); V1 was included in the analysis because the anticipatory cues were visual objects. Although MEG has been shown to be sensitive in lateralizing medial occipital sources, such as the V1 (Gavaret et al. 2013), discrimination between right and left in the cingulate cortex sources can be difficult with MEG due to the midline location. For this reason, we did not attempt to distinguish cingulate activity between right and left.

**Data Analysis**

**Combined analysis.** Across the ROIs, evoked (“phase-locked”) (Tallon and Bertrand 1999) analysis was performed to evaluate oscillatory activity in the 8- to 100-Hz range. Data from left and right extremities were pooled, assuming that anticipatory phenomena are independent of the site stimulated. We compared the anticipatory period for PS vs. NPS conditions. There were no differences in the shape of the visual cues for the site stimulated. We compared the anticipatory period for PS vs. NPS were pooled, assuming that anticipatory phenomena are independent of activity in the 8- to 100-Hz range. Data from left and right extremities were analyzed to evaluate oscillatory activity between right and left.

**Source space analysis.** The averaged trials in each condition were source estimated using the minimum-norm estimate (MNE) technique (Baillet et al. 2001) with regularization parameter λ set to 9. MNE source estimates or time series were computed for each dipolar source, assuming the orientation of sources to be constrained and fixed normal to the cortex. The dominant orientation of sources within each ROI was identified, and time series from each of the sources were sign flipped to align with the dominant direction before taking an average across all source estimates within a ROI.

**Time-frequency analysis.** The average time series from each parcel was subjected to a time-frequency analysis using complex Morlet wavelets with a time bandwidth of 7. Each frequency was then z scored with respect to the baseline period at that frequency. A nonparametric permutation analysis was performed to compare the different conditions and detect statistical significance within each subject. Subsequently, a grand average was performed to evaluate if there was sustained predominance of oscillations (rather than isolated oscillations) spanning the β- and γ-frequency domains across participants.

**RESULTS**

**Subject Attention and Pain Experience**

Overall, all subjects were attentive to visual cues. Although the initial pain rating was eight out of 10 during thresholding/titration, this was well tolerated because each PS was short in duration. Subjects’ overall pain rating varied at the end of test blocks corresponding to each extremity. We believe this primarily may have been due to conditioning and accommodation to pain, given that stimulation was first applied to the left and then to the right. Table 1 shows demographics, titrated target temperature, and subjects’ final pain ratings.

**Combined Analysis**

The results of combined evoked analysis during the anticipatory period are shown in the region of V1 and frontal areas in Figs. 3–6. The left calcarine cortex showed sustained, high γ oscillations (centered ~65 Hz) for the PS condition. This finding was significant whether activity of either control condition—NOS or NPS—was subtracted, indicating that this is unlikely to be merely attentional (Fig. 3). The left side also uniquely encoded the NOS condition in a separate frequency
band. Visual cues associated with NOS, when comparing against NPS and PS, were encoded exclusively with θ-band oscillations. The NPS condition was mostly encoded on the right-side calcarine. Interestingly, visual cues associated with NPS were encoded in a unique frequency band, which can be characterized as high θ band, lying between θ and γ bands associated with NOS and PS conditions (Fig. 3).

The DLPFC on the right side encoded the PS condition with oscillations in the γ band in a fashion similar to that seen in the V1. The DLPFC on the left side showed activity predominantly associated with the NPS conditions, encoded between the β and γ bands, in a fashion similar to the right V1. The NOS condition was encoded in the β band but mainly by DLPFC on the right (Fig. 4). Analysis of the data corresponding to the OFCs reveals a difference in frequency-dependent encoding of contextual information (Fig. 5). Unlike V1 and DLPFC areas, right OFC encoded the PS condition with oscillations mostly in the β band. These findings were consistent regardless of whether PS was compared with NOS or NPS conditions. There was no characteristic, sustained activity for the left OFC, which is unlike V1 and DLPFC areas that were actively involved in response to at least one of the conditions (Figs. 3 and 4). Lastly, the same source-level analysis was carried out for the cingulate cortices (ACC and MCC). MCC did not present sustained oscillatory activity in response to anticipation in the PS condition. However, it presented sustained θ-band activity associated with the NPS condition compared with PS, as well as NOS conditions (Fig. 6). Sustained, higher θ-band oscillations were associated with the NOS condition only when subtracted from the PS condition but not when compared against NPS and PS.

Table 1. Demographics, titrated target temperature, and subject’s final pain rating

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age (Gender)</th>
<th>Threshold Temperature (in °C)</th>
<th>Final Overall Pain Rating</th>
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<tr>
<td></td>
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<td>Left Right</td>
<td>Left Right</td>
</tr>
<tr>
<td>1</td>
<td>43 (M)</td>
<td>50 50</td>
<td>5 5</td>
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<tr>
<td>2</td>
<td>51 (F)</td>
<td>45 46</td>
<td>7 7</td>
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<tr>
<td>3</td>
<td>36 (M)</td>
<td>47 47</td>
<td>7.5 7.5</td>
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<tr>
<td>4</td>
<td>28 (M)</td>
<td>50 50</td>
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<td>5</td>
<td>51 (M)</td>
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<td>70 (M)</td>
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<td>10</td>
<td>35 (F)</td>
<td>48 48</td>
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Fig. 3. Time-frequency subtraction spectrograms of evoked minimum-norm estimate (MNE) time series from left and right calcarine cortices. Top: cortical activity when the anticipatory period preceding NOS is subtracted from that preceding NPS. Middle: cortical activity when the anticipatory period preceding NOS is subtracted from that preceding PS. Bottom: activity when the anticipatory period preceding NPS is subtracted from activity preceding PS. Blue hatches indicate significance of NOS, NOS, and NPS in the top, middle, and bottom, respectively. Red hatches indicate significance of NPS, PS, and PS in the top, middle, and bottom, respectively. Significance was based on nonparametric permutation analysis (P < 0.01). Arrows represent overall findings. Red arrows in the middle and bottom indicate that high γ oscillations were seen in PS vs. NPS or NOS conditions. Green arrows indicate that β oscillations were seen in NOS vs. NPS or PS conditions. Yellow arrows indicate high β oscillations seen in the NPS condition in the top and bottom. The color bar indicates SD from baseline (−4 to −3 s).
against the NPS condition. We did not observe sustained characteristic activity in response to any of the conditions in the ACC.

Because of the relevance of the data from V1 and visual nature of our anticipatory cues, we also analyzed the dataset in the time (power) domain to assess for possible differences across conditions (Fig. 7). The visually evoked fields (VEFs) from visual cues for PS and NPS were analyzed while subtracting those for NOS. The left calcarine area exhibited most activity associated with the NPS and PS conditions; VEF peaks associated with the PS condition had significantly greater power across subjects. This occurred predominantly in the first countdown. Likewise, a trend was observed for higher power during the presentation of NPS-related visual cues, but these were not significant.

**Early vs. Late Analysis**

The earlier results had indicated that the V1 was directly encoding the contextual meaning of the visual cues associated with NOS, NPS, and PS. However, because all data from the four blocks (60 trials each) had been combined, they did not indicate whether V1 or other cortical areas had been actively involved in visual-cue processing throughout all of the trials. In the early vs. late analysis, we evaluated the activity of each cortical area of interest by presentation block to evaluate for possible effects of experience with the task on cortical activity. All cortical areas of interest were analyzed. Because the size of the sample block is reduced fourfold in this analysis, not all cortical areas that may have been active (in the combined analysis) will show significant changes in activity across epochs. Only data from regions that showed sustained activity confined to one or more of the four phases are shown here (Figs. 8 and 9).

**Painful condition.** Significant, high γ activity seen in left calcarine in the PS condition during the combined analysis occurred throughout the phases of the experiment and was not confined to any one phase. However, right calcarine revealed greater epoch-dependent activity, with a sustained, 40-Hz oscillation seen exclusively during ME and LT phases (Fig. 8). Several cortical areas, including the OFC bilaterally, left DLPFC, and ACC, presented with strong and sustained oscillatory activity during the ER phase compared with ML and LT phases. This activity was mostly in the higher β band (ACC and right OFC) or γ band (DLPFC). However, with the exception of disorganized β-band activity during the ML phase in the left OFC area, these cortical areas were mostly silent during post-ER phases, in sharp contraposition to the calcarine area. Of note, significant ACC activity was not noted during the combined analysis and was apparent exclusively during the ER block in the early vs. late analysis.

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Fig. 4. Time-frequency subtraction spectrograms of evoked MNE time series from left and right DLPFC using the same analysis as for Fig. 3 (see Fig. 3 legend). Significance was based on nonparametric permutation analysis (P < 0.01). Red arrows indicate γ oscillations seen in the PS condition; the green arrow indicates β oscillations seen in the NOS condition; and yellow arrows indicate γ oscillations seen in the NPS condition. The color bar indicates SD from baseline (−4 to −3 s).
NPS condition. Figure 9 shows the same regions as shown in Fig. 8 for the NPS condition. The right and left OFC presented with activity similar to that of the PS condition, with organized \( \gamma \) activity and \( \beta \)-oscillatory activity (respectively) mostly restricted to the ER phase. None of the other cortical regions showed significant changes in oscillatory activity during the post-ER study epochs, with the exception of higher \( \beta \)-band activity during the ML phase in the right OFC.

DISCUSSION

Here, we discuss across healthy individuals the neural processing of pain anticipation using MEG. We have found that the V1, as well as frontal regions, including DLPFC, OFC, and cingulate cortices, encodes visual cues signaling PS. These regions encode anticipation to pain differently than to NPS or NOS via separate cortical oscillatory patterns. One of the most relevant findings of our study is that V1 can independently encode and distinguish with great time efficiency visual cues, predicting imminent PS from those associated with approaching NPS or NOS. Such a finding indicates that a cortical region processing a primary sensory modality—in this case, visual—also possesses the higher-order ability to anticipate pain, a property that has traditionally been attributed to associative prefrontal and cingulate cortices.

Pain anticipation is an important part of the cognitive-affective sphere of pain experience. Whereas pain anticipation may have been important in helping protect against environmental threats or predators in evolution, these anticipatory behaviors can become pathological and maladaptive in chronic pain conditions, sensitizing individuals to PS and forcing them to avoid meaningful behaviors. For example, patients with allodynia may develop pain habituation from repetitive contact, which may predispose to limited use of the affected limb prolongation of disability and loss of function. Previous electroencephalographic studies have shown that patients presenting with heightened pain responses demonstrate increased anticipatory processing in the cingulate cortex (Brown and Jones 2008). In addition, changes in activity in the PCC have been observed during pain anticipation (Höfle et al. 2013).

Our long-term goals are to study the anticipatory phenomena of patients with chronic pain conditions, such as complex regional pain syndrome and central pain syndromes. We expect to identify unique phenomena in these populations that may be associated with pain conditioning and habituation. The understanding of “abnormal” pain anticipation will require comparisons with normal anticipatory phenomena in healthy individuals. To this end, the present data represent the first magnetoencephalographic characterization of pain-anticipatory phenomena with this paradigm of visual cues. By analyzing presentation of block-dependent changes in activity of anticipatory networks, our findings describe the evolution of antic-
ipatory behavior, from naive to conditioned/sensitized. Since cortical activity patterns during anticipation within the pain matrix have long remained poorly characterized, our study aids better understanding of cortical processing underlying pain anticipation or habituation and can thus lead to novel, targeted therapies aimed at modifying these phenomena and pain-related disability (Machado et al. 2013).

The Visual Cortex Independently Encodes Pain-Related Cues

To the best of our knowledge, our study is the first to describe the critical role of the V1 in pain anticipation. Whereas other cortical areas, including the cingulate cortex, have been shown to process pain-related information (Brown and Jones 2008), we questioned whether the visual cortex...
Fig. 8. Early vs. late responses in PS. Top to bottom shows time-frequency contour plots from left calcarine, right calcarine, left OFC, right OFC, left DLPFC, and ACC respectively. Left to right indicates early (ER), mid-early (ME), mid-late (ML), and late (LT) phases. Sustained, significant oscillations are shown in dotted boxes. Black contours indicate significant oscillations between ER and LT, red hashes indicate significant oscillations between ER and ML, and dark-blue hashes indicate significant oscillations between ER and ME phases. The color bar indicates SD from baseline (−4 to −3 s).
Fig. 9. Early vs. late responses in NPS. Top to bottom shows time-frequency contour plots from left calcarine, right calcarine, left OFC, right OFC, left DLPFC, and ACC respectively. Left to right indicates ER, ME, ML, and LT phases. Sustained, significant oscillations are shown in dotted boxes. Black contours indicate significant oscillations between ER and LT, red hashes indicate significant oscillations between ER and ML, and dark-blue hashes indicate significant oscillations between ER and ME phases. The color bar indicates SD from baseline (−4 to −3 s).
could have a direct or indirect role in interpreting the contextual meaning of visual information cuing imminent pain.

The visual cortex, including the V1, has the intrinsic ability to interpret the meaning and context of visual information. V1 interactions with frontal-associative areas are not constructed on a unidirectional hierarchy in which V1 merely feeds information to higher processing areas. Rather, the processing of visual information is distributed such that higher-order areas relay information “back” to the V1, while simultaneously, the V1 feeds information to higher cortical areas (Bullier et al. 2001; Hupe et al. 1998; Mirabella et al. 2007; Supèr 2003). In addition to processing of information, microelectrode recordings of V1 in nonhuman primates have shown neural activity consistent with storage of information for working memory (Supèr et al. 2003), which maintains behaviorally relevant information. Recent advances in understanding V1 neural activity point to its role in not only segregating and storing information (i.e., working memory) but also in the overall perceptual experience of an object (Supèr 2002).

We have found that V1 independently encoded and distinguished with great time efficiency visual cues predicting approaching PS from NPS or NOS. The PS condition was encoded exclusively in the high γ band on the left calcarine. Whereas the NPS condition was cued with the same visual object as for the PS condition, it was not similarly encoded in the visual areas. The visual cortices were capable of distinguishing the contextual meaning of each cue within the duration of the visually evoked potential itself. Because unique oscillatory patterns were attributed to each control condition (NOS and NPS), distinctively from the oscillatory activity related to PS, it is unlikely that these findings merely reflect attentional states (Fig. 3). We then evaluated the activity of the V1 in the time (power) domain. The visual areas exhibited a significantly greater power of VEFs elicited by presentation of the PS visual cues than other conditions, particularly at the beginning of each countdown.

Combined, the results indicate that V1 can independently distinguish the pain context of visual cues during the period of anticipation. The extreme time efficiency seen across time and frequency domains indicates that V1 not only encoded visual cues accurately but also did so before interactions with higher cortical areas. This extraordinary time efficiency may represent a significant evolutionary gain, allowing for quick identification of threatening vs. nonthreatening visual objects. However, it may also participate in maladaptive responses and pain conditioning during preconscious states of pain anticipation. Information that is preconsciously encoded by V1 can be readily passed on to higher cortical areas of the pain neuromatrix, such as insular or cingulate cortices, via tightly integrated networks (Modha and Singh 2010). It is important to note that this analysis was conducted with data from all phases of the experiment, i.e., the combined analysis, and hence, cannot indicate at which moment V1 gained functional independence for encoding pain cues. This was evaluated further in the early vs. late analysis.

Frontal Cortical Areas As Well As Cingulate Cortex Also Process Contextual Information

The role of the DLPFC, ACC, and MCC in processing the information mediating the affective and cognitive spheres of pain has been studied extensively. In the present work, we found that the right and left DLPFC actively engages in distinguishing visual cues associated with each painful or control condition (Fig. 4). The cingulate cortices did not seem to encode the PS condition directly but interestingly, presented a unique oscillatory pattern in response to the NPS condition (Fig. 6). This finding points to the biological need not only to identify accurate and timely cues signaling impending pain but also cues that predict that the stimulus will not be painful. It is possible that the final pain-anticipatory experience associated with the PS condition stems from the combined activation of PS-related patterns in the DLPFC areas, as well as absence of NPS-related MCC activity. Another novel finding was noted when analyzing OFC activity. Whereas PS condition was uniquely associated with γ-band activity in the right DLPFC, it was associated with β-band oscillations in the right OFC. These two areas are highly connected anatomically but encoded the same information at different frequency bands. We speculate that both areas process information at different frequency bands in response to the same PS condition. Such parallel, distinctive processing of the same input speaks to the nature of computation across pain networks. The “anticorrelation” across functionally connected regions could be as important in determining the final experience as ordinary, resonant oscillations across connected areas.

Associative and Limbic Cortical Areas Were Active Almost Exclusively during Early Anticipation

Whereas our data suggest that V1 independently processed and encoded incoming pain-related or unrelated cues, the data do not support the visual area’s ability to learn independently the contextual meaning of each cue. Rather, a more likely explanation is that higher cortical areas, typically involved in learning and attributing context, were initially engaged in processing these signals. However, once the meaning of each cue was well established, V1 gained independence and hence, greater efficiency in attributing contextual values to each cue. The present early vs. late analysis provides results that are consistent with our working hypothesis. Indeed, after parsing the sequence of visual presentation associated with the PS condition into quartiles, we note that the ACC, DLPFC, and OFC areas were highly active and presented cue-specific oscillatory activity almost exclusively during the ER phase. To the contrary, the right visual area presented with limited activity in the ER phase only to gain meaningful activity in later phases. The results suggest that the right calcarine engaged in cue encoding after the context had been established. The left calcarine was active throughout all phases of the experiment. It is important to note that this area presented with the most robust responses during the combined analysis as well. Whereas the present data cannot confirm it, it is possible that the left visual area acquired cue-encoding independence at relatively early phases. Because our analysis combines data from one-quarter of the trials in each phase of the experiment, it is not possible to distinguish the moment when the left calcarine gained cue-encoding independence within the ER phase. Other limitations of this study include the smaller sample size and unimodal nature of the anticipatory cues.

Although contextual, abstract visual cues (shapes, colors, countdowns, etc.) are widely used to elicit anticipation to pain,
a number of studies have used other types of sensory cues, such as auditory cues (Brown and Jones 2008; Hauck et al. 2007) and somatosensory cues (Otsuru et al. 2011). Based on the findings in this study, it might be interesting to determine whether similar encoding phenomena are observed in the auditory or somatosensory cortices. We are currently studying these phenomena with different sensory modalities, and this will be a topic for future discussion.

In conclusion, the present data indicate that 1) V1 can independently encode visual cues leading to pain anticipation; 2) the higher cortical-associative areas process these visual cues with distinct oscillatory activity; and 3) these areas are actively engaged in visual-cue processing when their contextual meaning is not yet well established, becoming less active thereafter. Novel therapies may target visual or prefrontal networks to modulate the contextual meaning of visual cues of pain anticipation and promote deconditioning.

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DISCLOSURES

The content is solely the responsibility of the authors and does not represent the official views of the National Institutes of Health. A. Machado has the following conflicts to declare (none of which is pertinent to this research project or to this manuscript): consultant: Functional Neuromodulation and Spinal Modulation; potential distribution from intellectual property: Enspire Medical, Cardionomics, and ATI; Fellowship support: Medtronic. The other authors have no conflicts of interest.

AUTHOR CONTRIBUTIONS


REFERENCES