Published in final edited form as:

Neuroscience. 2015 September 24; 304: 176–189. doi:10.1016/j.neuroscience.2015.07.049.

A Magnetoencephalography study of multi-modal processing of pain anticipation in primary sensory cortices

Raghavan Gopalakrishnan¹, Richard C. Burgess², Ela B. Plow¹, Darlene Floden¹, and Andre G Machado¹

¹ Center for Neurological Restoration, Neurological Institute, Cleveland Clinic Cleveland, OH 44195

² Epilepsy Center, Neurological Institute, Cleveland Clinic, Cleveland, OH 44195

Abstract

Pain anticipation plays a critical role in pain chronification and results in disability due to pain avoidance. It is important to understand how different sensory modalities (auditory, visual or tactile) may influence pain anticipation as different strategies could be applied to mitigate anticipatory phenomena and chronification. In this study, using a countdown paradigm, we evaluated with magnetoencephalography the neural networks associated with pain anticipation elicited by different sensory modalities in normal volunteers. When encountered with well-established cues that signaled pain, visual and somatosensory cortices engaged the pain neuromatrix areas early during the countdown process, whereas auditory cortex displayed delayed processing. In addition, during pain anticipation, visual cortex displayed independent processing capabilities after learning the contextual meaning of cues from associative and limbic areas. Interestingly, cross-modal activation was also evident and strong when visual and tactile cues signaled upcoming pain. Dorsolateral prefrontal cortex and mid-cingulate cortex showed significant activity during pain anticipation regardless of modality. Our results show pain anticipation is processed with great time efficiency by a highly specialized and hierarchical network. The highest degree of higher-order processing is modulated by context (pain) rather than content (modality) and rests within the associative limbic regions, corroborating their intrinsic role in chronification.

Keywords

Multimodal; anticipatory processing; visual; tactile; auditory

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Corresponding Author: Raghavan Gopalakrishnan, Center for Neurological Restoration, Cleveland Clinic, 9500 Euclid Avenue, S-31, Cleveland, OH 44195, Phone: (216) 445-9322, Fax: (216) 444-1015, gopalar@ccf.org.

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Disclosures

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.

1. Introduction

The experience of pain is a complex phenomenon reflecting not only the sensory encoding of tissue injury site and intensity but also emotional-affective and cognitive perception (Melzack 1999). While acute pain imposes a limited emotional load, with chronification cognitive and emotional-affective spheres become increasingly relevant and become salient during anticipation and fear of pain (Apkarian et al. 2005). Pain anticipatory phenomena are common in healthy individuals (Brown and Jones 2008; Machado et al. 2014; Worthen et al. 2011) likely representing an important evolutionary gain against tissue injury and environmental threats (Pfungsten et al. 2001). However, pain anticipation becomes maladaptive in painful states as individuals transition from acute to chronic pain, where anticipation may precipitate kinesiophobia and limb usage avoidance. Such behaviors result in worsened weakness or atrophy and exaggerate disability (Flor et al. 2002; Lousberg et al. 1996).

Better understanding of the mechanisms underlying pain anticipatory phenomena in the healthy state is important to establish a norm of pain anticipatory behavior and allow for future comparison with patient populations suffering from chronic pain conditions. Additionally, novel therapeutic approaches that can specifically target affective and cognitive neural networks, such as deep brain stimulation, could be directed towards modulation of anticipatory phenomena and promote pain deconditioning (Machado et al. 2013; Plow et al. 2013). Ultimately, a measurement index of pain anticipation could become a method to evaluate the efficacy of such treatments.

We have recently studied the neural processing of anticipatory visual cues signaling imminent noxious vs. non-noxious stimuli (Machado et al. 2014). We have found that the primary visual cortex as well as dorsolateral and cingulate areas were directly involved in processing the contextual meaning of these cues. Interestingly, once the contextual meaning was established, i.e. whether a stimulus was painful or non-painful, the primary visual cortex was able to independently process the cues not just specific to anticipation, but anticipation to pain, a feature that has been considered characteristic of only higher order cognitive-affective areas. These findings pose a new question: do all primary sensory areas show activation that signals anticipation to pain vs. no pain independent of the activation of associative areas? If yes, such findings would suggest direct involvement of primary sensory areas in processing affective and cognitive spheres of the pain neuromatrix (Melzack 1999), which has been traditionally attributed to “higher” cortical areas including the dorsal lateral prefrontal cortex (DLPFC), insula and cingulate cortex.

2. Experimental Procedures

Ten healthy subjects (7 males and 3 females, average age: 45 ± 15 years, range: 29 – 71 years) participated in the study. The study was approved by the Cleveland Clinic Institutional Review Board and all subjects provided written informed consent. Participants did not have any history of neurological or musculoskeletal condition that could lead to chronic pain.

2.1. Data Collection

In this study, three different modalities (visual - V, somatosensory/tactile - S and auditory - A) were used as conditioning stimulus to cue the subject of the imminent unconditioned stimulus during a 2s long countdown (Fig. 1), while they were seated upright in a 306 channel Neuromag MEG array (Elekta AB, Stockholm, Sweden).

Unconditioned stimulus (US)—A contact heat-evoked potential stimulator thermode (Gopalakrishnan et al. 2013) of the Medoc pathway system (Medoc Ltd., Ramat-Yoshai, Israel) was used to elicit 2s long noxious painful hot stimulus (PS) or non-noxious non-painful cold stimulus (NPS). The presentation of no stimulus (NOS) was also tested as an added control.

The thermode was always attached to the volar surface of the dominant forearm. Painful hot stimulus was titrated prior to the beginning of the study (Machado et al. 2014), whereas non-painful stimulus was set to 8 degrees below the baseline temperature of 30 degrees to deliver a pleasant sensation. Throughout the manuscript we take the liberty to address noxious stimulus as painful stimulus, and non-noxious stimulus as non-painful stimulus.

Conditioning stimulus (CS)—The visual, auditory or tactile cues were presented prior to the unconditioned stimuli. For the visual cues, a STIM2 stimulus presentation system (Compumedics Neuroscan, Charlotte, NC, USA) was used. The type of incoming unconditioned stimulus was symbolized by the shape of the visual cue. A downward pointing triangle symbolized upcoming PS, a horizontal-pointing triangle symbolized NPS and an upward pointing triangle symbolized NOS. The countdown was marked by numbers-2, 1- presented in descending order with each cue (whether downward, sideway or up-pointing triangle). The visual cues appeared for 250ms on top of the background gray screen with cross-hairs (refer Fig.1).

For the tactile cues, somatosensory air puffs were generated using a pneumatic stimulator (James Long Company, NY) delivered using 0.25 inch nycoil polyurethane tubing. The air puffs were applied to the skin overlying the first dorsal inter-osseous muscle (of subject's non-dominant hand). The length and number of air puffs cued the incoming unconditioned stimuli. One 50ms long puff cued NOS; two 50ms long puffs applied at an interval of 150ms cued NPS, while three 50ms long puffs delivered at intervals of 50ms cued approaching PS. For the auditory cues, 50ms long 4 kHz pure tones (STIM2, Compumedics Neuroscan, Charlotte, NC) were used in a similar fashion as the air puffs described above. The tones were delivered bilaterally using MEG/fMRI compatible foam ear phones. The tones were embedded in pure white noise background to attenuate auditory contamination of sound generated by air puffs. When tactile or auditory cues were presented, the participants were shown neutral gray screen with cross hairs.

To summarize, the study consisted of a total of 9 conditions (Fig. 1): visual cues that signaled no stimulus (Vnos), non-painful stimulus (Vnps), and painful stimulus (Vps); somatosensory/tactile cues that signaled no stimulus (Snos), non-painful stimulus (Snps), and painful stimulus (Sps); and auditory cues that signaled no stimulus (Anos), non-painful stimulus (Anps) and painful stimulus (Aps).

2.2.Paradigm

The paradigm consisted of 15 blocks of 63 psuedo-randomized trials consisting of the above 9 conditions such that a total of 105 trials per condition were collected, making each block less than 9 minutes long. Two of the subjects completed only 13 blocks due to time constraints. Prior to the start of the paradigm, the subjects went through a familiarization session consisting of 63 trials where target stimulus was not delivered, instead following anticipatory cues, text appeared on the screen indicating the type of the target stimulus that would have been delivered in a real trial. We used text (painful, non-painful and no stimulus) during familiarization in order to help subjects learn to associate the cue with the nature of stimulus. During testing, each trial in a block was 8s long including 1s baseline, 2s pre-stimulus countdown or anticipatory period and 5s stimulus/recovery period (Fig. 1). In order to ensure alertness and continued attention to the cues, during each block, subjects were asked to count the number of painful stimuli they perceived, and report the same at the end of each block along with their overall experienced pain rates on a numerical rating scale of 0 – 10. In addition, subjects were also monitored continuously with a video camera. Otherwise, MEG recordings were acquired continuously during the 15 blocks.

The cues always correctly predicted the target stimulus i.e. there was no uncertainty regarding CS – US relationship at any given time. The paradigm was explained verbally to the subjects prior to data collection. Subjects were instructed to stay alert and focus on cues presented during countdown, to evoke anticipation. They were also asked to avoid blinking during the countdown and remain as motionless as possible inside the MEG array. Considering the length of the paradigm, subjects were given an option to take a 5 min break at midpoint or at any other point in time; they were asked to not take more than two total breaks.

2.3.Data Pre-processing

All MEG data were collected 2400 (DC to 800 Hz) samples/sec and processed using Neuromag Max-filter (Taulu and Simola 2006) to filter magnetic interferences and external artifacts. All initial preprocessing were performed using open source Matlab (The Mathworks Inc., Natick, MA, USA) toolbox fieldtrip (Oostenveld et al. 2011) and in-house built Matlab scripts. Only data from planar gradiometers were chosen for subsequent analysis because they are more sensitive to activity from local sources directly under them and less sensitive to noise from distance sources. The data from 204 gradiometer pairs were parsed/time locked to the onset of conditioned stimulus to segregate 3s (baseline and the anticipatory period) preceding all 9 conditions (Fig. 1). Trials with SQUID jump artifacts were removed from analysis by means of thresholding the z-transformed value of the raw data (Oostenveld et al. 2011). On average, 93 ± 7 trials per condition per subject underwent subsequent analysis. The trials were then subtracted for DC offset and band-pass filtered 1 – 100 Hz using default filter settings in fieldtrip (Oostenveld et al. 2011).

Tessellated pial surface and their corresponding parcellations (Desikan et al. 2006) were generated for each subject from 3T MPRAGE T1 images using Freesurfer (Dale et al. 1999; Fischl et al. 1999) and were used to create the source model. The individual heads/ parcellations were then read into open source Matlab toolbox Brainstorm (Tadel et al. 2011)

along with isotrak head points to refine MRI registration. In Brainstorm, fiducials were manually chosen and 15,000 dipoles were generated on the cortical surface. Using the T1 images and transformation matrix generated from above, forward model was computed for each subject using a realistic single shell volume conductor model (Nolte 2003).

2.4. Regions of Interest

Out of the 68 parcellations or regions of interest (ROI) provided by the Desikan-Killany (DK) atlas (Desikan et al. 2006), we focused our analysis on to the following ROIs for their involvement in sensory processing and/or pain/pain anticipation as pointed out in the references:

- Sensory areas: Primary visual cortex V1 (Machado et al. 2014), auditory cortex A1 and somatosensory cortex S1 (Worthen et al. 2011) for their direct involvement in processing the cues. The V1, S1 and A1 areas are termed as pericalcarine, post-central and transverse temporal respectively in DK atlas.
- Associative areas: Dorsolateral pre-frontal cortex DLPFC (Lorenz et al. 2003), orbito-frontal cortex OFC (Rolls et al. 2003) and insula (Brown et al. 2008). The DLPFC is divided and termed as rostral and caudal middle-frontal in DK atlas, whereas the OFC is divided into medial and lateral regions.
- Limbic areas: The cingulate cortices (Brown and Jones 2008; Vogt 2005). The nomenclature used here is consistent with the four-region neurobiological model of human cingulate cortex (Vogt 2005; Vogt et al. 2005). Hence, areas noted in DK atlas as rostral anterior cingulate cortex was re-termed anterior cingulate cortex (ACC), caudal part of anterior cingulate cortex and posterior cingulate cortex together was termed as mid-cingulate cortex (MCC) and isthmus cingulate cortex was termed as posterior cingulate cortex (PCC). We did not attempt to lateralize the midline regions taking into account their close proximity and MEG's spatial resolution at larger distances from the sensors closer to the center of the head.

2.5. Data Analysis

We focused our analysis primarily on evoked (as opposed to induced) responses. The rationale for this approach is multifold.

1. Pain anticipation is a phenomenon that protects from external threats and imminent danger. Hence, our interest lies in the early responses to anticipatory cues that highlight rapid mental processing of incoming information. In this paper, our focus was on the 500ms following the presentation of each conditioning cue (visual, auditory or tactile) that lasted for 250ms or less. This time epoch is rich in phase locked components.
2. Our hypothesis was to investigate the direct effects of anticipatory cues on the default state of the neuronal assemblies, rather than indirect non-linear effects (David et al. 2006). In comparison to induced responses, early evoked responses, especially in the gamma band are modulated by cognitive processes, and hence represent not only bottom-up, but also top-down neural processes (Debener et al. 2003; Herrmann et al. 2010).

3. For the above reasons, we kept the anticipatory cues very simple without involving complex deciphering and cognitive load.

The time locked filtered data trials from each of the 9 conditions were averaged to compute evoked activity for each subject. For the tactile modality, two subjects who were left hand dominant had to be excluded from the analysis because of lateralization confounds.

The averaged trials were source localized using the minimum-norm (MNE) technique (Baillet et al. 2001). The SNR used to compute regularization parameter was set to 3 (Tadel et al. 2011). The 1s period preceding the anticipatory period was used as a baseline to evaluate the spatial noise covariance. MNE source estimates or time series were computed for each dipolar source for all three orientations (unconstrained) and then projected to its strongest orientation i.e. the direction that explains most of the source variance. Time series of the sources within each ROI were then averaged.

Time-frequency (TF) analysis was focused on beta (12 – 30 Hz) and gamma (30 – 90 Hz) bands. These bands have been often implicated with cognitive functions and related sensorimotor transformations that serve as neural signatures for pain and pain anticipation (Engel and Fries 2010; Jensen et al. 2007; Schulz et al. 2012; Senkowski et al. 2011). The average time series from each ROI was subjected to a time-frequency analysis using complex Morlet wavelets (time-bandwidth parameter $F_b = 7$ and central frequency $F_c = 1$ Hz). A time bandwidth product of 7 has been shown to provide good compromise between time and frequency resolutions (Grimm and Pfurtscheller 2006; Jensen and Hesse 2010; Tallon and Bertrand 1999). Each frequency was then z-scored with respect to the baseline period at that frequency. A non-parametric statistics (described below) 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 predominance of evoked frequency components across participants.

Statistics—Anticipatory period was compared between PS vs. NPS and PS vs. NOS conditions within each modality (visual, tactile and auditory). By having a neutral (i.e. NOS) as well as positive (i.e. NPS) control conditions, cortical activity change due to attention was better accounted for and results related due to pain anticipation could be isolated. Comparisons across modalities was neither the purpose of the study nor possible because anticipatory phenomena recorded was modality specific.

Statistical significance of one condition over another was tested using a non-parametric cluster based permutation analysis (Maris and Oostenveld 2007). Observed TF maps computed from each of the ROIs were compared between two conditions under study (e.g. PS vs. NPS) using t-score maps. TF points that exceeded a threshold corresponding to $p=0.05$ were identified to form spectro-temporal clusters. One positive and one negative cluster with the largest sum of t-value were retained separately for the beta and gamma bands, which was tested for significance. This step took care of the multiple comparison problem. At a subject level, single trials from the two conditions were combined to form a combined pool. The two conditions were repopulated by drawing trials randomly from this combined pool to form test data 1000 times. The entire data analysis pipeline (section 2.5)

was performed on the test data to compute 1000 TF maps per condition per subject. Similar to observed data, largest positive and negative cluster were identified on these 1000 TF maps to compute histogram. The significance of the observed TF clusters were evaluated under the permutation distribution of maximum cluster statistic at $p < 0.05$. Because first and second cue of the CS evoked different responses, cluster analysis was performed separately for the first and second cue.

3. Results

3.1. Subject Performance

Participants were in general attentive to the visual, tactile and auditory cues. Initially, at titration, average initial pain rating was 8 out of 10. Though the subjects were monitored continuously using a video camera for attentiveness and alertness, the counting task served as a secondary measure to check not just attentiveness but also effect of pain anticipation in performance of a mental arithmetic task. A total of 146 blocks from 10 subjects were collected. Data from each block for each subject (Table-1) showed that, as pain rating increased, the accuracy in reporting number of painful stimuli decreased (Pearson's correlation using student's t-distribution for transformation of coefficient; $r = -0.2882$, $p = 0.0004$).

3.2. Evoked Analysis

We report here only the ROIs that showed significant differences in evoked oscillations between the conditions studied.

Visual modality—The results of the evoked analysis for the visual modality are shown in Figure 2, 5 and 6. The visual cues evoked an ON response in the first 250ms followed by an OFF response. During Vps, the first cue evoked a greater beta band response in left V1 and gamma band (40 – 60 Hz) oscillations in the right V1. However, during second cue, the right V1 showed a robust gamma (40 – 60 Hz) in a standalone fashion. The Vnps and Vnos anticipatory conditions mostly evoked beta band oscillations during first cue in the right V1 and second cue in left V1. Apart from the V1, Vps evoked greater response in associative and limbic areas. PCC and insula activations in beta and gamma band (40 – 60 Hz) were exclusively recorded in the visual modality during PS. In addition, left caudal DLPFC (beta), right rostral DLPFC (40 – 60 Hz), and MCC (beta and gamma) showed greater responses.

Interestingly, visual modality not only activated the V1, but also S1 and A1 (Fig. 7). The ipsilateral S1 and left A1 showed cross-modal activations in the gamma band.

Tactile modality—The results of the evoked analysis for the tactile modality are shown in Figure 3, 5 and 6. Similar to left V1, the first cue evoked a greater beta band response in the ipsilateral S1 during Sps. The second cue evoked greater response in Snps both in beta and gamma band. The contralateral S1 did not show any significant findings. Apart from S1, Sps showed greater response in MCC (beta), left caudal and rostral DLPFC (40-60Hz).

Interestingly, the left V1 (30 – 40 Hz), right V1 (60 – 80 Hz) and both A1 (30-40 Hz) were also activated by Sps (Fig. 8).

Auditory modality—The results of the evoked analysis for the auditory modality are shown in Figure 4, 5 and 6. Auditory modality did not evoke a specific pattern of activation in the primary cortex. The first auditory cue evoked higher beta band oscillations on the right side in Aps (vs. Anos) and on the left side in Aps (vs. Anps). The second cue corresponding to Aps did not evoke any significant response. However, second cue corresponding Anos and Anps evoked greater activation on the right side in gamma band (30 – 50 Hz). Apart from A1, Aps showed greater activation of MCC and left rostral DLPFC in gamma band (40 – 60 Hz) during only the second cue. The auditory modality did not evoke any cross-modal oscillatory responses in other sensory cortices.

4. Discussion

The most striking finding of this study was the ability of the visual modality to elicit a wide network of cortical activity in the gamma band not just in the associative and limbic areas, but also in all primary sensory cortices (cross-modal) during pain anticipation. This activity was evident in the associative areas early on (<250ms) leading to robust activity in V1 itself (>250ms) during both countdown cues reiterating its independent processing capability. The tactile and auditory modality elicited gamma activity during pain anticipation in the associative areas early on (<250ms) during first and second cue respectively, but lacked independent processing ability. These findings from healthy controls will form a basis to compare results from chronic pain patients, which will be a topic for future communications.

One of the recent outstanding questions in pain research is how different sensory modalities modulate neuronal processes in pain anticipation and their role in cross modal shaping of pain experience (Senkowski et al. 2014). Till date, several animal studies have reported learning induced plasticity in primary (Weinberger 2004) and secondary sensory cortices (Sacco and Sacchetti 2010) during fear conditioning using visual and auditory modalities, however pain anticipation elicited by different modalities in humans is poorly studied. Specifically, somatosensory/interoceptive stimuli and their role in fear conditioning has been poorly studied (De Peuter et al. 2011). Here, we present a comprehensive examination demonstrating mechanisms elicited by three different anticipatory cue modalities – visual, auditory and tactile – signaling imminent painful, non-painful or no stimuli and how they are processed by primary sensory, associative and limbic networks. We are in particular concerned with the response of primary sensory cortices to pain anticipatory cues, a function currently attributed to higher cortical areas.

The anticipatory cues, in this study, were presented in the form of a two-step countdown. We speculate that as the subjects encountered the first countdown, the response evoked might reflect anticipation with a novelty factor (due to randomized design of blocks), whereas, the second countdown appropriately prepared them for the upcoming US. Since the CS-US associations were known to the subjects prior to testing, we cannot rule out the memory related effects of early responses reported here. Repetition suppression, an automatic phenomenon, where repeated presentation of a stimulus results in decreased

neural response, is a natural consequence of countdown paradigms. However, we believe our design evokes considerable repetition priming effect which could lead to improved time-efficient cognitive and behavioral performance through neural synchronization (Dobbins et al. 2004; Gotts et al. 2012) that will have an effect on anticipation.

4.1. Visual Modality

Consistent with our earlier report (Machado et al. 2014), visual cues representing PS were represented by the V1 in the gamma band (Fig-2). In fact, visual modality was the only modality in this study that evoked significant gamma band oscillations in V1 and other associative/limbic areas that were exclusively attributed to PS condition i.e. Vps in this study (Fig.2, 5 and 6). We believe that the beta responses seen in V1 (as seen in all conditions) is related to sensory processing of visual cue, whereas gamma noted in the right V1 has cognitive implications, including attention and memory (Jensen et al. 2007). The findings in Figs.2, 5 and 6 make us speculate that as soon as first visual cue in Vps was processed in the left V1, the rostral DLPFC and insula play a vital role in interpreting the contextual meaning of the cue and affect respectively, followed by subsequent processing in cingulate and right V1. Hence, during the second visual cue, the V1 interpreted the contextual meaning of visual cue (along with cingulate) without any assistance from DLPFC. The robust gamma activation could imply a memory match (Herrmann et al. 2004) in visual short term memory and subsequent preparatory processing to counter the incoming painful stimulus. The chain reaction of events reported here in the V1 engaging a wide network involving insula, DLPFC, cingulate cortex and back to V1 are in consensus with visual shaping of pain reported by Senkowski et.al. (Senkowski et al. 2014).

4.2. Tactile Modality

The anticipatory effect of tactile CS on US that are also tactile has been poorly studied (De Peuter et al. 2011). Results of such studies will definitely need to take into account the confounding effects because both CS and US involve the same cortex, unlike visual and auditory modality. Hence, our design involved CS applied to one limb, while US was expected on the other limb. The contralateral S1 has been known to be the primary cortical recipient of sensory information via bottom-up pathways. However, interestingly contralateral S1 (to CS) did not show any significant differences in tactile conditioning cues, whereas all significant findings were confined to ipsilateral S1 (to CS). As pointed earlier, due to the nature of our design the ipsilateral S1 to CS was contralateral to US. Hence, the significant findings in ipsilateral S1 could have been facilitated because of expectation of painful stimulus on the other extremity. In support of this view, prior studies have shown that anticipation to a tactile stimulus evoke similar response to the tactile stimulus itself i.e. heightened contralateral activity (Carlsson et al. 2000) which was attributed to tactile memory of sensation prior to its arrival. There was a possibility that subjects in our study experienced similar sensations. During the first cue (Fig.3), apart from significant beta activity before 250ms which could be sensory by nature, the ipsilateral S1 also evoked a brief gamma band oscillation during Sps around 300ms, however not as robust as V1. From Figs.5 and 6, it is evident that both caudal and rostral DLPFC evoked gamma oscillations as soon as the first sensory cue was perceived followed by activation of cingulate cortex and

S1. The tactile modality in this study evoked a sequence of network activity involved the DLPFC and cingulate cortex, but did not include insula.

4.3. Auditory modality

In addition to the visual modality, auditory modality has been widely used in conditioning paradigms (Sehlmeyer et al. 2009), but also have been attributed with poor short term learning, recognition and encoding capabilities in A1 (Bigelow and Poremba 2014). In this study, A1 presented a different pattern of activation compared to V1 and S1. During Aps, the beta band sensory processing was evident in both right (vs. Anos) and left A1 (vs. Anps). Contrary to other modalities, the gamma band activation was non-specific in A1 occurring in Aps (right A1; first cue) Anos (left A1; first cue) and Anps (right A1; second cue) conditions (Fig.4). Whereas, in V1 and S1, this gamma band activation was exclusively reserved during pain anticipation. Another interesting observation was the activation pattern of DLPFC and cingulate cortex during Aps, where they were confined to the second cue, rather than the first cue as in the case of visual and tactile (Figs.5 and 6). In addition, all associated gamma oscillations evoked by auditory modality occurred early (within 250ms from cue onset). These findings imply that 1. Auditory modality may be capable of evoking a time efficient processing in A1, but not specific to pain anticipation, 2. Auditory anticipation to pain might be amplified toward the end of countdown process, rather than at the beginning.

4.4. Cross-modal Processing

In addition to processing of conditioning stimulus in their respective cortices, we observed an interesting cross-modal interaction phenomenon. This was not a surprising observation in light of the recent finding that all primary sensory cortices are in fact multimodal (Liang et al. 2013). However, interestingly we found consistent activations across modalities were only observed during pain anticipation. For instance, from Fig.8 all three primary sensory cortices evoked spectro-temporally matched 30-40 Hz oscillation in response to first tactile cue of the Sps (vs. Snos) condition. Similarly, from Fig.7, S1, A1 and V1 all responded in the gamma band to both visual countdown cues of Vps (vs. Vnos). Though A1 displayed strong cross-modal processing, the inability of A1 to translate significance in PS vs. NOS to PS vs. NPS during the first countdown cue was evident. This once again reiterates non-specific pattern of processing in A1 in response to harmful vs. non-harmful stimulus.

Increased early evoked gamma oscillations have been implicated in cross-modal multisensory processing (Schneider et al. 2008; Schneider et al. 2011; Senkowski et al. 2009), particularly due to enhanced coherence among neurons (Senkowski et al. 2008) when matching or highly relevant information is encountered. However, most of the studies (Senkowski et al. 2008) have only used conditioning and target stimuli that have a semantic relationship and encountered in the peripersonal space during daily routines. Here, we show that abstract conditioning cues that carry a contextual meaning relating to upcoming painful stimulus are capable of evoking a synchronous oscillatory pattern in all primary sensory cortices, especially when incoming stimuli were tactile or visual in nature. The data suggests that visual/tactile inputs are more likely to prepare other cortical areas for the anticipation of

pain than, for example, auditory cues. This may represent an evolutionary gain aimed at priming these areas for “readiness” for pain-related cues during flight-or-fight states.

4.5. Hierarchical Processing of Pain Anticipation

The results presented here indicate all primary sensory cortices upon receiving a threatening conditioning stimulus (painful) from their corresponding modality interact with higher order pre-frontal and cingulate areas to understand the contextual meaning of the cue. This represents an important strategy for time-efficiently avoiding tissue injury once the contextual meaning of a cue has been established with prior experience. While this capability seems to be shared by the three primary sensory cortical areas evaluated in this study, significant differences related to timing of this activity must be noted. V1 and S1 showed interactions with associative and limbic areas in a time efficient manner early during the countdown process, whereas A1 presented interaction with the associative areas late in the countdown. Only the visual modality was able to maintain pain anticipation throughout the countdown period, which could be due to the robust involvement of V1. Table-2 summarizes the gamma band activations evoked by each modality, from which it is clear that visual modality stands on top of the hierarchy followed by tactile and auditory.

In our opinion, visual modality presented superiority over tactile and auditory modalities, in engaging pain neuromatrix areas for efficient processing of pain anticipation. Tactile modality was superior over auditory. However, the cross-modal activation of A1 in both visual and tactile modalities suggests that auditory cortex may play an important facilitative role.

4.6. Cingulate and Associative Cortical Areas

In agreement with the findings of our prior study (Machado et al. 2014), DLPFC and cingulate cortex were active during the presentation of cues associated with painful stimuli. The cingulate cortex has been associated with a number of behavioral manifestations including processing of fear and anger (Vogt 2005). Likewise, it has been shown to have a central role in mediating the affective sphere of chronic pain (Ballantine et al. 1967; Vogt 2014). Significant cingulate activity was also reported (Brown and Jones 2008) during pain anticipation in healthy subjects. Therefore, it is not surprising that our data shows the cingulate cortex to be involved in pain anticipatory phenomena in a ubiquitous and modality-unspecific fashion.

4.7. Pain Anticipation and Attentional Task

The effect of pain and pain anticipation on attentional/cognitive performance has been well studied (Babiloni et al. 2004; Seminowicz and Davis 2007b). In this study, we used a simple attentional task where subjects were asked to report number of painful stimuli perceived. While percentage accuracy fell as pain rating increased, it is difficult to assess whether the decline was due to pain itself or anticipation to pain. Irrespectively, we believe that the mental counting task could not have affected the pain anticipatory task, but the opposite was a possibility. Several studies have reported that hyper-vigilance to upcoming pain gains precedence over and interrupts simple attentional tasks (Crombez et al. 1998; Crombez et al. 2005) and this interruptive activity was attributed to the MCC (Brown and Jones 2008).

Other studies have also reported that pain anticipation and simple attentional task can go hand-in-hand due to the multi-tasking nature of affective networks (Babiloni et al. 2003; Seminowicz and Davis 2007a). The consistent activity of MCC reported here during PS condition could have played a role in interrupting the attentional task.

4.8. Limitations

The study has several limitations regarding the design aspects which should be acknowledged. The experimental setup was deliberately designed to be simple and make sure there was least conflict between different modalities presented.

1. The visual cues were presented centrally, the tactile cues were presented unilaterally and the auditory cues bilaterally. This asymmetrical presentation could have deployed different spatial attention. While this is a limitation, conditions within a modality were aligned so their spatial and temporal characteristics were consistent. Also, the comparisons in this study are within modality and not between modalities.
2. While tactile and auditory cues were essentially same during the first and second cue, the visual cues had changing numbers while maintaining the shape of the cue (which conveyed the contextual meaning). This may have had an effect in the anticipatory process specific to visual input.
3. In order to better match the visual modality, the auditory cues could have been three different tones for three different conditions and somatosensory cues could have been non-painful electrical stimulation of three different intensities. However we opted for a different design because, though the current study was conducted on normal healthy people, we anticipate repeating the same on patients with chronic pain. While normal healthy population may not have difficulty distinguishing subtle differences in the conditioned stimulus (e.g. tones), chronic pain patients may suffer from sensory and cognitive disabilities.
4. The different conditions within auditory and tactile modalities had different number of tones and puffs, respectively. However, we made sure the puffs/tones whether 1, 2 or 3 were always presented in the first 250ms of the countdown and there was no temporal mismatch in the evoked responses to the cues. This is evident from the source time series presented in Figs 2, 3 and 4. In addition the stimuli were quick. Though they were perceived separately they did not evoke separate responses.
5. We used a two-step countdown cues to build the anticipatory phenomena. While our past studies (Machado et al. 2014) and others (Brown and Jones 2008) have used more than two countdown cues, we resorted to 2 countdowns to minimize the recording time and subject boredom due to repetitive nature of the task. Additionally, to counter the effects of long recording time, the subjects were asked to perform an attentional task to report at the end of each block. In addition, subjects were allowed to break and refresh, if needed in order to keep their attention sustained.

5. Conclusions

Our results suggest dominance for visual cueing during pain anticipation. Although primary regions were sensitive to cross-modal activation in relation to their corresponding and non-corresponding sensory cues, associative and limbic-cognitive-affective regions as DLPFC and cingulate cortex showed greater activity in pain anticipation regardless of the modality. With this, our study supports a multi-modal yet hierarchical processing of pain anticipation that is highly specialized and time-locked (hence time efficient) at the level of primary sensory cortices while the highest degree of abstract processing (i.e. processing of context) rather than content (modality), rests with the associative limbic regions in line with their intrinsic role. These findings imply that, in the future, it may be possible to target neuro-modulatory techniques at areas processing pain anticipatory phenomena. Modulation of pain anticipation could have a significant role in the management of kinesiphobia and other behavioral manifestations that limit rehabilitation from chronic pain conditions.

Acknowledgments

Grants

This work was supported by National Institutes of Health New Innovator Award under award number DO006469A. The content is solely the responsibility of the authors and does not represent the official views of the National Institutes of Health.

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Highlights

1. V1 could process pain related cues after learning the contextual meaning
2. Unlike V1, S1 and A1 may not independently process pain related cues
3. Only visual and tactile cues engaged the associative and limbic areas early on
4. During visual and tactile cues, cross-modal activation was evident
5. DLPFC and MCC play a significant role regardless of modality

Figure 1.

Paradigm: Visual, tactile and auditory cues preceding no stimulus (NOS), non-painful stimulus (NPS) and painful stimulus (PS) conditions. Top row shows NOS where visual cues (flashed for 250ms) were presented in upright triangle and one 50ms beep/puff signaled tactile/auditory cue respectively. Middle row shows NPS condition where visual cues were presented in horizontal triangle and two 50ms beeps/puffs separated by 150ms signaled tactile/auditory cues respectively. Bottom row shows PS condition where visual cues were presented in inverted triangle and three 50ms beeps/puffs separated by 50ms signaled tactile/auditory cues respectively. The neutral screen with crosshairs was present all the time, except when visual cues were flashed. BL-baseline (1s), AP – Anticipatory period (2s), PR – post-recovery (5s), V – visual, A – Auditory and S – tactile/somatosensory, CS – conditioning stimulus and US – unconditioned stimulus

Figure 2.

Time frequency subtraction spectrograms of min-norm time series evoked by the visual cues in V1. Left column shows response from left V1, whereas right column shows response from right V1. Top row shows Vps – Vnos subtraction plot, while bottom row shows Vps – Vnps subtraction plot. Each panel has three sub-sections displaying time frequency plot on the top and corresponding time series on the bottom. The left most sub-section displays the representative baseline period from –2.5 to –2s, the middle sub-section displays the first 500ms response to first countdown cue and the right most sub-section displays the first 500ms response to second countdown cue. Only the oscillations pertaining to significant clusters are shown, while the statistically insignificant clusters were masked. Significance was based on non-parametric permutation analysis ($p < 0.01$). Color bar indicates SD from baseline (–3 to –2s), whereas the plots displays baseline from –2.5s for simplicity.

Figure 3.

Time frequency subtraction spectrograms of min-norm time series evoked by the tactile cues in S1 utilizing the same technique as for figure-2. Left column shows activity in ipsilateral (Left) S1 and right column shows activity in contralateral (right) S1. Top row shows Sps – Snos subtraction plot, while bottom row shows Sps – Snps subtraction plot. Refer Fig.2. caption for rest of the details.

Figure 4.

Time frequency spectrograms of min-norm time series evoked by the auditory cues in A1 utilizing the same technique as for figure-2. Left column shows activity in Left A1 and right column shows activity in right A1. Top row shows Aps – Anos subtraction plot, while bottom row shows Aps – Anps subtraction plot. Refer Fig.2. caption for rest of the details.

Figure 5.

Outline of significant (beta and gamma) clusters identified in associative and limbic areas when comparing PS vs. NOS. Instead of showing positive and negative clusters with opposing colors on the same plot, the plot here shows positive and negative clusters from a particular ROI in the same color but on different (top row vs. bottom row) plots. Top row shows the contour representation of positive clusters (PS), whereas bottom row shows corresponding negative clusters (NOS). Left column shows visual modality, middle shows tactile and right column shows auditory modality. The ROIs are shown in different colors. Each panel has three sub-sections displaying time frequency contour plot as described in Fig.2. rDLPFC is rostral dorsolateral prefrontal cortex (right for visual, left for other modalities), MCC – midcingulate cortex, PCC – posterior cingulate cortex, LcDLPFC – Left caudal dorsolateral prefrontal cortex and L. Insula – left insular cortex

Figure 6.

Outline of significant (beta and gamma) clusters identified in associative and limbic areas when comparing PS vs. NPS. Instead of showing positive and negative clusters with opposing colors on the same plot, the plot here shows positive and negative clusters from a particular ROI in the same color but on different (top row vs. bottom row) plots. Top row shows the contour representation of positive clusters (PS), whereas bottom row shows corresponding negative clusters (NPS). Left column shows visual modality, middle shows tactile and right column shows auditory modality. The ROIs are shown in different colors. Each panel has three sub-sections displaying time frequency contour plot as described in Fig.2. rDLPFC is rostral dorsolateral prefrontal cortex (right for visual, left for other modalities), MCC – midcingulate cortex, PCC – posterior cingulate cortex, LcDLPFC – Left caudal dorsolateral prefrontal cortex and L. Insula – left insular cortex

Figure 7.

Significant gamma band clusters from cross modal activations seen in S1 and A1 in response to visual countdown cues. Clusters are saturated with one color (red or blue) for simplicity. Left column shows response from S1, whereas right column shows response from A1. Top row shows Vps – Vnos subtraction plot, while bottom row shows Vps – Vnps subtraction plot. Each panel shows clusters from both left and right sides of the corresponding cortex (see legend). Red filled contours indicate positive clusters and blue filled contours indicate negative clusters. The unfilled red contours are outline of significant positive clusters from V1 shown here for reference. No significant negative gamma band clusters in V1 were found as reported in Fig.2. The dotted box highlights the similarity in responses between the cortex presented and the visual cortex. The red arrows highlight the oscillations significant in Vps in comparison to Vnos and Vnps.

Figure 8.

Significant gamma band clusters from cross modal activations seen in V1 and A1 in response to tactile countdown cues. Clusters are saturated with one color (red or blue) for simplicity. Left column shows response from V1, whereas right column shows response from A1. Top row shows Sps – Snos subtraction plot, while bottom row shows Sps – Snps subtraction plot. Each panel shows clusters from both left and right sides of the corresponding cortex (see legend). Red filled contours indicate positive clusters and blue filled contours indicate negative clusters. The unfilled red and blue contours are outlines of significant positive and negative clusters from S1 shown here for reference. The dotted box highlights the similarity in responses between the cortex presented and the somatosensory cortex. The red arrows highlight the oscillations significant in Sps in comparison to Snos and Snps.

Table 1

Demographics and experimental parameters for each subject.

Subject	Age (gender)	% mean accuracy within blocks	Final overall average pain rating (Initial rating was 8/10)	Temperature in °C titrated for PS
1	43 (M)	95.3	5	49
2	51 (F)	96.2	7.3	49
3	36 (M)	85.2	7.9	48
4	28 (M)	99.7	6.9	50
5	51 (M)	98.5	5	50
6	66 (F)	100	7.5	49
7	41 (M)	98	6.1	50
8	30 (M)	98.9	5.7	49
9	70 (M)	89.2	9	49
10	35 (F)	72.5	7.5	48

Note: NPS was always set to 22°C (8°C below baseline 30°C)

Table-2

Hierarchical processing of pain anticipation

Modality	1. Visual			2. Tactile			3. Auditory			
	First Cue		Second Cue	First Cue		Second Cue	First Cue		Second Cue	
	vs. NOS	vs. NPS	vs. NOS vs. NPS	vs. NOS	vs. NPS	vs. NOS vs. NPS	vs. NOS	vs. NPS	vs. NOS	vs. NPS
Engaged the following areas in gamma band in PS										
V1	X	X	X	X	X	X				
S1	X	X	X	X						
A1	X		X	X		X	X			
DLPFC	X	X		X	X	X			X	X
Cingulate	X	X	X	X	X	X			X	X
Insula	X		X							

Note: Red check marks indicate <250ms processing, else >250ms processing