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ORIGINAL RESEARCH

Vigilance to Painful Laser Stimuli is Associated with Increased State Anxiety and Tense Arousal

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Introduction: Pain is frequently accompanied by enhanced arousal and hypervigilance to painful sensations. Here, we describe our findings in an experimental vigilance task requiring healthy participants to indicate when randomly timed moderately painful stimuli occur in a long train of mildly painful stimuli.

Methods: During a continuous performance task with painful laser stimuli (CPTpain), 18 participants rated pain intensity, unpleasantness, and salience. We tested for a vigilance decrement over time using classical metrics including correct targets (hits), incorrectly identified non-targets (false alarms), hit reaction time, and false alarm reaction time. We measured state anxiety and tense arousal before and after the task.

Results: We found a vigilance decrement across four 12.5-minute blocks of painful laser stimuli in hits [$F_{3,51}$=2.91; p=0.043; time block 1>block 4 (t=2.77; p=0.035)]. Both self-report state anxiety ($t_{paired,17}$=3.34; p=0.0039) and tense arousal ($t_{paired,17}$=3.20; p=0.0053) increased after the task. We found a vigilance decrement during our laser pain vigilance task consistent with vigilance decrements found in other stimulus modalities. Furthermore, state anxiety positively correlated with tense arousal.

Discussion: CPTpain acutely increased tense arousal and state anxiety, consistent with previous results implicating the reciprocal interaction of state anxiety and acute painful sensations and the role of pain in augmenting tense arousal. These results may indicate a psychological process which predisposes the hypervigilant to developing greater acute pain, resulting in positive feedback, greater pain and anxiety.

Keywords: continuous performance task, false alarms, pain, vigilance, salience

Introduction

Pathological vigilance to painful and pain-related stimuli is linked to individual burden of chronic pain and predictive of post-op pain.[1–3] This burden of pain is in turn related to increased anxiety and arousal.[4,5] Despite the clinical importance of hypervigilance to painful stimuli, most studies reporting effects of pain on attentional mechanisms use visual attention-bias tasks to pain-related stimuli such as pain-related words or faces of those in pain, or self-report measures such as the Pain Vigilance and Avoidance Questionnaire.[6–9] These tools are subjective and reflect attentional bias toward pain-related semantic or visual stimuli and do not incorporate painful stimuli.[9,10] Furthermore, these tests do not measure changes in behavior over time, a core characteristic of vigilance.[11] Meta-analyses of attention bias studies show evidence of mixed or small effects indicating that attention bias is increased in chronic pain patients compared to control populations.[8,9,12]

Previously, our group examined behavior, performance, and self-reported characteristics of painful thermal stimuli in an experimental model of vigilance. We reported a decrement in vigilance performance over time on task during a continuous performance task requiring discrimination of painful targets from non-targets (CPTpain).[13] This decrement was also observed during sustained attention to target stimuli in other sensory modalities.[11,13–15] We reported that tense arousal during the CPTpain positively correlated with pain unpleasantness, consistent with negatively valenced stimuli

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and affective states or moods driving tense arousal.[5,16] Furthermore, tense arousal was related to state anxiety, but not trait anxiety, consistent with the dynamic nature of increased tense arousal in headache pain.[5,17]

Modifying our task to use a laser stimulus made it possible to selectively evoke activation of Aδ- and C-fiber nociceptors without activation of Aβ primary afferents evoked by the ongoing physical contact of a thermode.[18–20] When evaluating evoked potentials measured with scalp electroencephalography, laser evoked potentials have the benefits of being comparable to larger body of evidence and allow more precise temporal resolution given the short duration stimulus.[21–24]

According to the biased competition model of attention, task-directed and stimulus-driven mechanisms impinge on task performance.[25] Painful stimuli are both aversive and inherently salient, suggesting psychological elements associated with painful stimuli result in cognitions related to stress and threat.[4,5,25,26] Consistent with this hypothesis, we predicted increases in both state anxiety and tense arousal, which we measured immediately before and after the CPT with painful laser stimuli.[5,27] Furthermore, consistent with our prior reports, we predicted state anxiety and tense arousal would be correlated during the experience of painful stimuli.[13]

Materials and Methods

Participant Recruitment

We recruited 24 healthy volunteers from neighbors, staff, students, and trainees of the Johns Hopkins Hospital and University. Participants who were enrolled included 8 women (18 to 47 years old) and 16 men (18 to 75 years old). Exclusion criteria included active neurological conditions, including the presence of or self-report of history of chronic pain, psychiatric conditions, and medical conditions. All participants gave written informed consent before the study, all study procedures were approved and renewed yearly by the Johns Hopkins School of Medicine Institutional Review Board, and the study complied with the Declaration of Helsinki.

Stimuli Determination and Psychophysical Characterization

Laser stimuli were produced using a Nd:YAP 1340 nm wavelength laser (El.En. Group, Florence, Italy). Laser parameters included a 10mm-diameter beam with 20ms-pulse duration and energies ranging from 10J to 15J (fluence = 12.74 to 19.11 J/cm^2). Laser parameters of a 10mm diameter beam with 20ms pulse duration with 14.5J intensity regularly failed to fire, therefore the staircase included intensities from 10 to 14J in 0.5J increments. When choosing a target laser intensity, we used 15J only when stimuli of 13J were painful but still rated below 1.5 out of 10 on a numerical rating scale (NRS). Laser stimuli were applied to the distal half of the dorsal forearm and dorsum of the hand. The time between each successive stimulus on the same area of skin during any trial series was at least 3 minutes.

Participants were fitted with laser protective glasses and experienced a staircase of laser intensities (10 to 14J in 0.5J increments) which they perceptually classified as “none”, “warm”, or “pain”. The staircase started at the median energy of 12J, ascended to 14J, and then descended and ascended two more times. For those stimuli classified as “pain”, participants rated the salience, pain intensity and pain unpleasantness all on a 0–10 computerized NRS. Participants who did not endorse any of the stimuli as consistently painful were excluded. Mild (2 to 3/10 NRS) and moderate (4 to 5/10 NRS) pain stimulus energies were selected.

Training, Habituation and Continuous Performance Task

We have previously shown that the presentation order of habituation and continuous performance task with painful stimuli (CPTpain) within a similar experimental protocol had no effect on pain intensity of the first block of habituation or CPTpain.[13] Furthermore, there was no effect of order on the change in pain intensity, change in pain unpleasantness or change in salience. Therefore, we kept the order of habituation and CPTpain fixed to avoid long-term sensitization or habituation effects of the 480 stimuli over the hour of the CPTpain.

Next, participants were instructed:

> For this next test, the skin will rapidly increase in temperature and a word on the monitor will indicate whether the stimulus is a ‘high’ stimulus or a ‘low’ stimulus. Please concentrate on learning the association of the stimulus with the classification. Please put on the headphones and stare at the crosshairs.

Participants experienced a random train of 20 stimuli (10 mild, 10 moderate). Three seconds before receiving the stimuli they were shown either the word "high" for the moderate stimulus or "low" for the mild stimulus (Figure 1). After this "training" session, participants rated pain intensity, pain unpleasantness, and salience of the stimuli as well as degree of mind-wandering, and tense arousal. Participants were instructed on the meaning of pain intensity, pain unpleasantness and salience using a standard script (adapted from):[28]

> There are three aspects of your perception which we are interested in measuring: the intensity – how strong the stimulus feels, the unpleasantness – how disturbing the stimulus is for you, and the salience – how much the stimulus is able to attract or grab your attention. The distinction between these aspects of perception might be made clearer if you think of listening to a sound, such as a radio. As the volume of the sound increases, I can ask you how loud it sounds, how unpleasant it is to you, or how much you are distracted by the sound. The intensity of the stimulus is like loudness; the unpleasantness of the stimulus depends not only on intensity, but on other factors which may affect you; and the salience of the stimulus is the ability of the stimulus to attract your attention. Although some sensations may be equally intense and unpleasant and salient, we would like you to judge these aspects of your pain independently. Please put the headphones on and stare at the crosshairs.

To verify discrimination of mild and moderate pain stimuli, participants experienced a series of 20 stimuli (10 mild, 10 moderate) where they were instructed:

> For this next test, the skin will rapidly increase in temperature. Please press the button on the response pad as soon as you detect the more intense stimulus. Please be as accurate as you can but press the button as quickly as you are able to. Please press the button only once. Please put on the headphones and stare at the crosshairs.

Participants performed the training task during a series of 20 stimuli up to 4 times, until they achieved a performance of 16 out of 20 correct trials. If the participant performed below 0.8 (80%) correct trials after two series of stimuli, the increment between the mild and moderate pain stimuli was increased by 0.5J while keeping both stimuli above the pain threshold. Data from each participant were evaluated for performance. Criteria for inclusion in data analysis was a correct trial rate and the balanced accuracy (0.5*(Hit Rate+Correct Rejection Rate)) greater than 0.7 (70%) during the first block of the CPT.[29] If participants performed above chance, but below inclusion criteria, they were contacted to repeat the

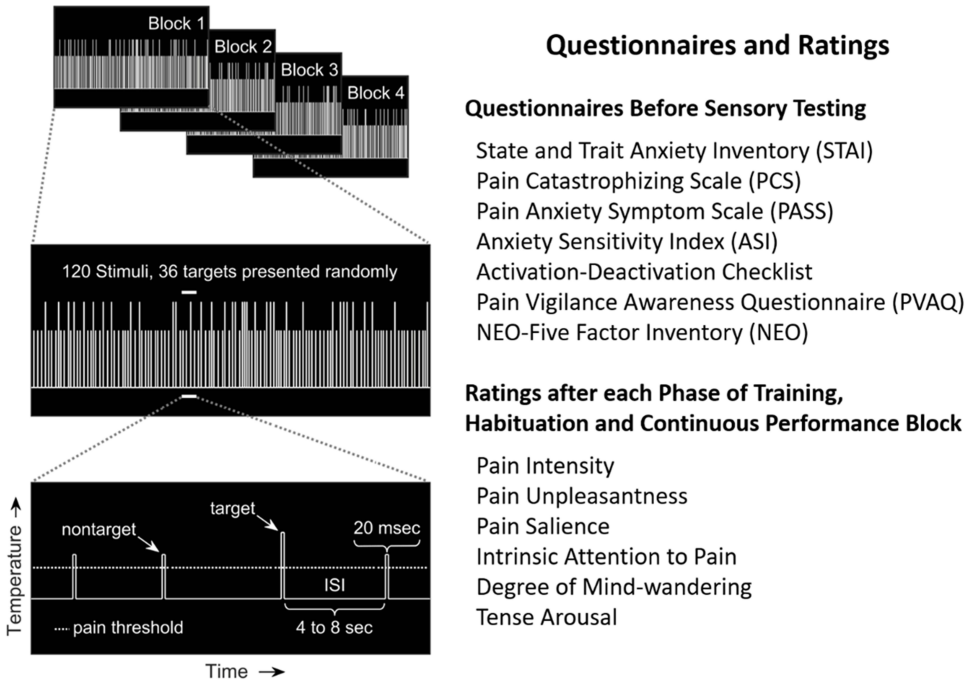

Figure 1 Participants completed four blocks of the continuous performance task with painful stimuli (CPTpain). Each block consisted of 120 stimuli, 36 of which were targets, (high intensity) stimuli distributed randomly within four sub-blocks. All stimuli were 20 ms laser pulses with a random interstimulus interval (ISI) between 4 and 9 s. The dotted line in the lower panel is the threshold temperature for pain, as established for participants individually.

session once and their data was included if their performance met inclusion criteria. Six participants (3 F) were excluded from the 24 first enrolled based on failure to distinguish between mildly and moderately painful stimuli as in our previously published protocol.[13] Participants excluded at this point in the protocol did not participate in any subsequent part of the protocol. After the final successfully discriminated series of stimuli, participants rated pain intensity, pain unpleasantness, salience of the stimuli, degree of mind-wandering, and tense arousal.

Next, participants experienced two 2.5-minute series of stimuli to control for possible effects of habituation. Mild and moderate painful laser stimuli alternated with a 5 s interstimulus interval for a total of 30 total stimuli. Participants were instructed:

> For this next test, the skin will rapidly increase in temperature several times. You will answer some questions about the sequence of stimuli and then we will repeat the sequence. Please put on the headphones now.

After each 2.5-minute series of stimuli, participants rated pain intensity, pain unpleasantness, salience of the stimuli, intrinsic attention to pain, degree of mind-wandering, and tense arousal.[13,30,31] Tense arousal was measured using the tense arousal (TA) subscale of the Activation-Deactivation Checklist.[31] Participants were instructed to "Please use the rating scale next to each word to describe your feelings at this moment". Five adjectives (Jittery, Intense, Clutched-up, Tense, and Fearful) were rated using a 4-point Likert scale anchored at 1 (definitely do not feel) and 4 (definitely feel). During the habituation blocks, participants were not required to differentiate between the two stimulus types and did not have access to the mouse button.

Finally, participants performed the continuous performance task with painful stimuli (CPTpain), which was composed of 4 blocks of 120 laser stimuli made up of 36 target (moderate pain) and 84 nontarget (mild pain) laser stimuli with a randomized interstimulus interval of 4 to 9.[13,32] Within each block, target and nontarget stimuli were fully randomized in four subblocks. After each of the 4 blocks, participants rated pain intensity, pain unpleasantness, salience of the stimuli, degree of mind-wandering, and tense arousal. For this section of the study, participants were instructed:

> For this next test, the skin will rapidly increase in temperature several times. Please press the button on the response pad as soon as you detect the more intense stimulus. Please be as accurate as you can but press the button as quickly as you are able to. You will answer some questions about the sequence of stimuli, and we will repeat the sequence. Please press the button only once after each stimulus. Please put on the headphones and stare at the crosshairs.

Psychological Questionnaires

To identify psychological factors that may contribute to sensory perception and task performance during vigilance to pain, participants completed self-report questionnaires over a one-hour period before the sensory testing. These included: PCS: Pain Catastrophizing Scale,[33] PASS: Pain Anxiety Symptom Scale,[34] ASI: Anxiety Sensitivity Index,[35] STAI: State and Trait Anxiety Inventory,[36] Activation-Deactivation Checklist,[31] and the NEO Five Factor Inventory.[37,38] STAI State Anxiety and tense arousal from the Activation-Deactivation Checklist were also assessed immediately after the participant completed the CPTpain task.

Statistical Analysis

All statistical analyses were conducted using R version 3.6.3. Data from all variables were assessed for normality using the Shapiro–Wilk test. Data were analyzed after Z-transformation to scale and standardize each variable. All variables were evaluated for the presence of outliers, defined as values more than three median absolute deviations from the median.[39] No outliers were detected.

We tested for a vigilance decrement over time using a linear mixed model (LMM), with the factor of time represented by the four blocks in the protocol.[40] In the LMM, each outcome variable (eg, number of hits or false alarms per block, average hit or average false alarm response time per block), was modeled as a within-participant factor of time with participant as a random effect. The effect of time was explicitly modeled by comparing block 1 to blocks 2, 3 and 4, as in Dunnett's method, with the covariance structure of the model assuming compound symmetry. This has the effect of reducing the number of possible pairwise comparisons and is warranted by extensive prior literature examining the

vigilance decrement in other sensory modalities.[41] We previously reported the superiority of this model compared to a simple repeated-measures analysis of variance (RM-ANOVA) model assuming compound symmetry, a model including an autoregressive correlation structure for time, and a model for each test.[32] All post hoc comparisons across time were corrected for multiple comparisons with a normed multivariate t correction.[42]

We report F-stat values for the fixed effects derived from LMMs using the ANOVA function in Rbase and p-values derived using corrected degrees of freedom from the Kenward–Roger correction.[43–45] All bivariate correlations were tested using the ppcor package in R.[46] Because we evaluated many variables at each task block, over time on task, we corrected for the repeated-measures correlation with a *t*-test using the effective degrees of freedom. For figures, we used the R package ggscatter to create bivariate scatterplots with corresponding 95% confidence curves for relationships of interest. We used a paired *t*-test to assess changes in state anxiety and tense arousal between before and after the CPT with painful laser stimuli. We calculated correlation values for all simple and partial correlations while controlling separately for age and sex (See Supplemental Tables 1 and 2).

Results

Stimulus Characteristics and Perception

The mean laser energy that produced mild pain (nontarget) was 12.0 Joules (SD=0.72; range = 10.5J to 13J), while the mean laser energy to produce moderate pain (target) was 13.9J (SD=0.73; range = 12.5J to 15J). The mean pain intensity reported in response to mild pain (nontarget) was 2.6 out of 10 (SD=1.1; range = 0.9 to 4.6), while that reported in response to moderate pain (target) was 4.5 (SD=1.8; range = 1.8 to 8.1). Before the habituation protocol, there were 19 mostly painful laser stimuli during laser energy selection, then 20 painful stimuli during each training and verification period.

When using the LMM to compare the first block to CPTpain blocks 2, 3, and 4, there was no significant change in pain intensity ratings ($F_{3,50}$=0.39; p=0.76), pain unpleasantness ratings ($F_{3,50}$=0.27; p=0.85), or salience ratings ($F_{3,50}$ =2.03; p=0.12). Also, during habituation trials, there were no significant reductions in pain intensity ratings ($t_{paired,17}$ =0.00; p=1.00), pain unpleasantness ratings ($t_{paired,17}$=0.27; p=0.79), or salience ratings ($t_{paired,17}$=−0.33; p=0.75). These results support the absence of sensitization or habituation in pain intensity, pain unpleasantness and salience during painful laser stimulation. In addition, the change in pain intensity ratings (R=−0.37; p=0.13), change in pain unpleasantness ratings (R=−0.085; p=0.74) and change in salience ratings (R=0.30; p=0.22) were not correlated within individuals between the habituation and CPT tasks. These results support that the order of habituation and CPT task during the protocol did not influence stimulus perception across the protocol.

Vigilance Decrement

The vigilance decrement related to painful stimuli is indicated by the decrease in hits over time in a CPT with a painful target (CPTpain). During the CPTpain, hits significantly decreased during time on task across task blocks [$F_{3,51}$=2.91; p=0.043; comparison of block 1 with block 4 was significant (t=2.77; p=0.035); Figure 2A]. In contrast, mean hit RTs to target stimuli did not change by block ($F_{3,51}$=0.31, p=0.82; Figure 2B). Therefore, the most basic element of vigilance, the vigilance performance decrement, was found during CPTpain providing a conceptual replication of our previous results.[32]

False alarms did not significantly change with time on task ($F_{3,51}$=0.33; p=0.80; Figure 2C). Similar to mean hit RTs, mean false alarm RTs to nontarget stimuli did not change by block ($F_{3,51}$=0.16, p=0.93; Figure 2D).

Finally, both state anxiety ($t_{paired,17}$=3.34; p=0.0039) and tense arousal ($t_{paired,17}$=3.20; p=0.0053) significantly increased after the CPTpain when compared to the time immediately before the CPTpain. Importantly, there was no significant change in tense arousal during habituation ($t_{paired,17}$=1.75; p=0.098), though the difference between the change during CPTpain and the absence of the change during habituation was also not significant (($t_{paired,17}$=1.45; p=0.17).

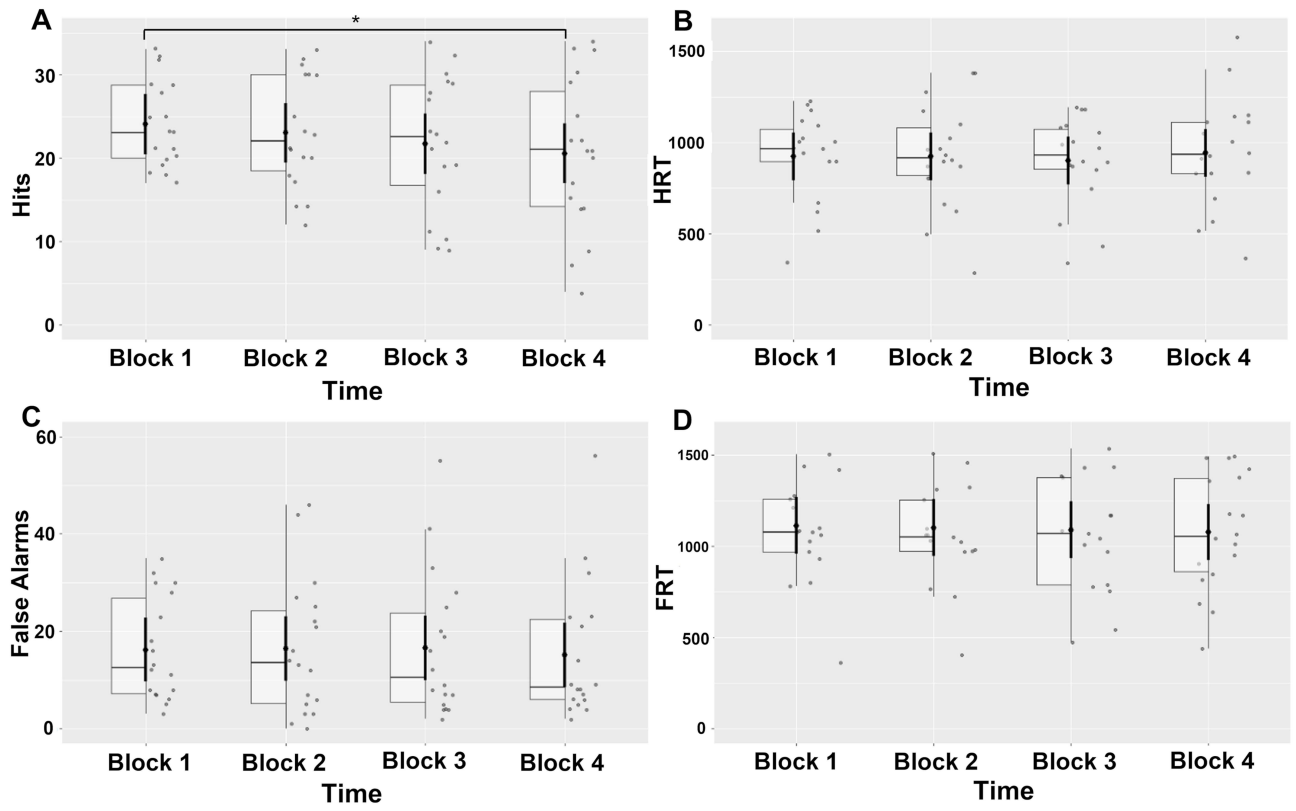

Figure 2 Vigilance metrics over the four blocks of continuous performance task (CPT) with a painful target. (**A**) Hits over time on task. (**B**) Hit reaction time over time on task. (**C**) False alarms over time on task. (**D**) False alarm reaction time over time on task. Bold error bars represent standard error of mean; boxes represent interquartile intervals. * = $p < 0.05$.

Tense Arousal, Pain Intensity and Unpleasantness

During CPT with painful laser stimuli, tense arousal positively correlated with salience (R=0.380; t-stat=2.96; p=0.0046), but not pain intensity (R=−0.0084; t-stat=−0.061; p=0.952) or pain unpleasantness (R=0.189; t-stat=1.40; p=0.172) (Figure 3A; Supplemental Table 1) – a distinctly different pattern than we observed with the thermode. As pain intensity, pain unpleasantness and salience are often highly correlated with each other, we tested a 4-variable partial correlation model relating tense arousal, pain intensity, pain unpleasantness and salience during CPT with painful laser stimuli. Within this partial correlation model, tense arousal was positively correlated with salience (R=0.433; t-stat=3.47; p=0.0011), negatively correlated with pain intensity (R=−0.385; t-stat=−3.01; p=0.0040) and not significantly correlated with pain unpleasantness (R=0.138; t-stat=1.00; p=0.321).

During the habituation task, in a partial correlation model including tense arousal, pain intensity, pain unpleasantness and salience, tense arousal trended toward being negatively correlated with pain intensity (R=−0.426; t-stat=−1.883; p=0.078), but not correlated with pain unpleasantness (R=0.298; t-stat=1.25; p=0.229) or salience (R=0.292; t-stat=1.22; p=0.240). In bivariate correlations tense arousal was not significantly correlated with pain intensity (R=−0.019; t-stat=0.077; p=0.940), pain unpleasantness (R=0.283; t-stat=1.18; p=0.259), or salience (R=0.284; t-stat=1.18; p=0.254).

To examine the interrelationships of pain intensity, pain unpleasantness and salience across the CPT, as well as the change within the CPT, and to compare this to interrelationships during the habituation period, we used bivariate. For ratings during the CPTpain, we tested bivariate correlations among pain intensity, pain unpleasantness and salience, pain intensity was positively correlated with pain unpleasantness (R=0.839; t-stat=11.12; p<0.0001) and salience (R=0.767; t-stat=8.63; p<0.0001), while pain unpleasantness was positively correlated with salience (R=0.684; t-stat=6.76; p<0.0001) (Figure 3B).

Next, for changes in ratings during CPTpain, we tested bivariate correlation among change in pain intensity, change in pain unpleasantness and change in salience. During the CPT with painful laser stimuli, change in pain unpleasantness

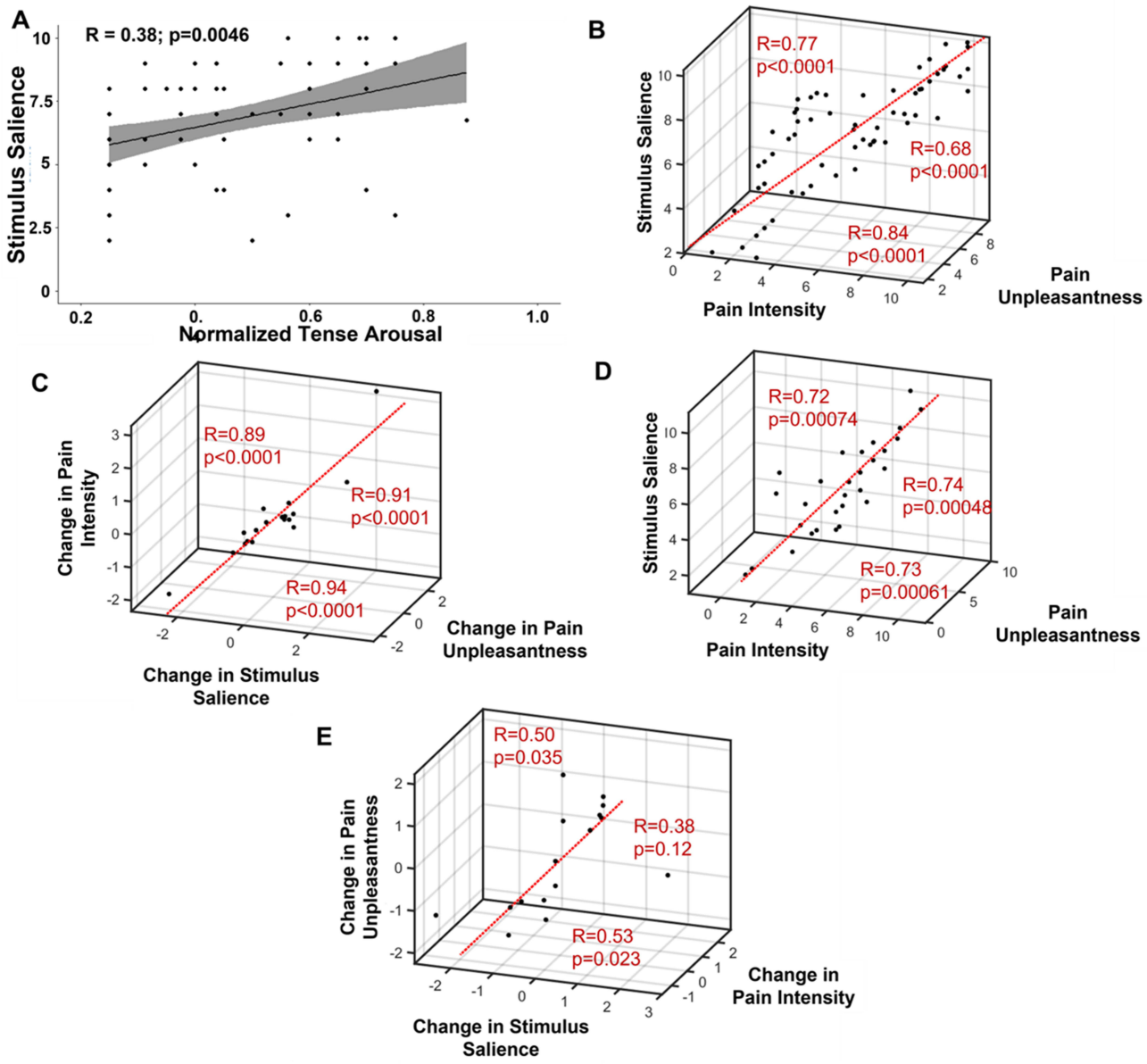

Figure 3 Pearson correlations between (**A**) salience and tense arousal during the continuous performance task with painful stimuli (CPTpain). Pearson correlations among (**B**) salience, pain intensity and pain unpleasantness and (**C**) change in salience, change in pain intensity, and change in pain unpleasantness during the continuous performance task with painful stimuli (CPTpain). Pearson correlations among (**D**) salience, pain intensity and pain unpleasantness and (**E**) change in salience, change in pain intensity, and change in pain unpleasantness during the habituation phase. In part A, the gray area indicates the 95% confidence interval.

and change in salience (R=0.938; t-stat=10.78; p<0.0001) and change in pain intensity (R=0.908; t-stat=8.69; p<0.0001) were positively correlated, while change in pain intensity and change in salience were also significantly positively correlated (R=0.886; t-stat=7.64; p<0.0001) (Figure 3C).

To compare the CPTpain results with ratings taken during the habituation phase of the paradigm, we tested a separate set of bivariate correlations among pain intensity, pain unpleasantness and salience during the painful laser habituation. Consistent with extensive prior literature, pain intensity was positively correlated with pain unpleasantness (R=0.729; t-stat=4.26; p=0.00061) and salience (R=0.721; t-stat=4.16; p=0.00074), while pain unpleasantness was positively correlated with salience (R=0.738; t-stat=4.37; p=0.00048) (Figure 3D).

Finally, during painful laser habituation, change in salience positively correlated with change in pain unpleasantness (R=0.498; t-stat=2.30; p=0.035) and with the change in pain intensity (R=0.534; t-stat=2.52; p=0.023), but the change in pain intensity and change in pain unpleasantness were not significantly correlated (R=0.378; t-stat=1.635; p=0.122) (Figure 3E).

Together these results suggest a tighter coupling of pain intensity, pain unpleasantness and salience during the CPTpain when compared to the habituation task. To test this prediction, we evaluated the differences in bivariate correlation coefficients between phases of our paradigm, comparing habituation to CPTpain. The differences between the habituation phase and CPTpain phase in the correlation coefficients among pain intensity, pain unpleasantness and salience were not significant (PI vs PU: ΔR=0.11; t-stat=0.44; p=0.66; PI vs salience: ΔR=0.046; t-stat=0.18; p=0.86; PU vs salience: ΔR=−0.054; t-stat=−0.22; p=0.83). In contrast, differences between the habituation phase and CPTpain phase in the correlation coefficients among change in pain intensity and change in pain unpleasantness were significant, while the difference between change in pain intensity and change in salience and between change in pain unpleasantness and change in salience were not significant (ΔPI vs ΔPU: ΔR=0.53; t-stat=2.50; p=0.024; ΔPI vs Δsalience: ΔR=0.35; t-stat=1.50; p=0.15; ΔPU vs Δsalience: ΔR=0.44; t-stat=1.96; p=0.068). The results in this section were not significantly affected by controlling for age or sex (Supplemental Table 1).

Influence of Anxiety and Neuroticism on Tense Arousal

During CPT with painful laser stimuli, tense arousal positively correlated with state anxiety (R=0.268; t-stat=2.01; p=0.050) and neuroticism (R=0.353; t-stat=2.72; p=0.0088) but not trait anxiety (R=0.132; t-stat=0.96; p=0.341) (Figure 4A; Supplemental Table 2). As state anxiety, trait anxiety and neuroticism are highly correlated, we tested the 4-variable partial correlation model including tense arousal, state and trait anxiety as well as neuroticism. Within the

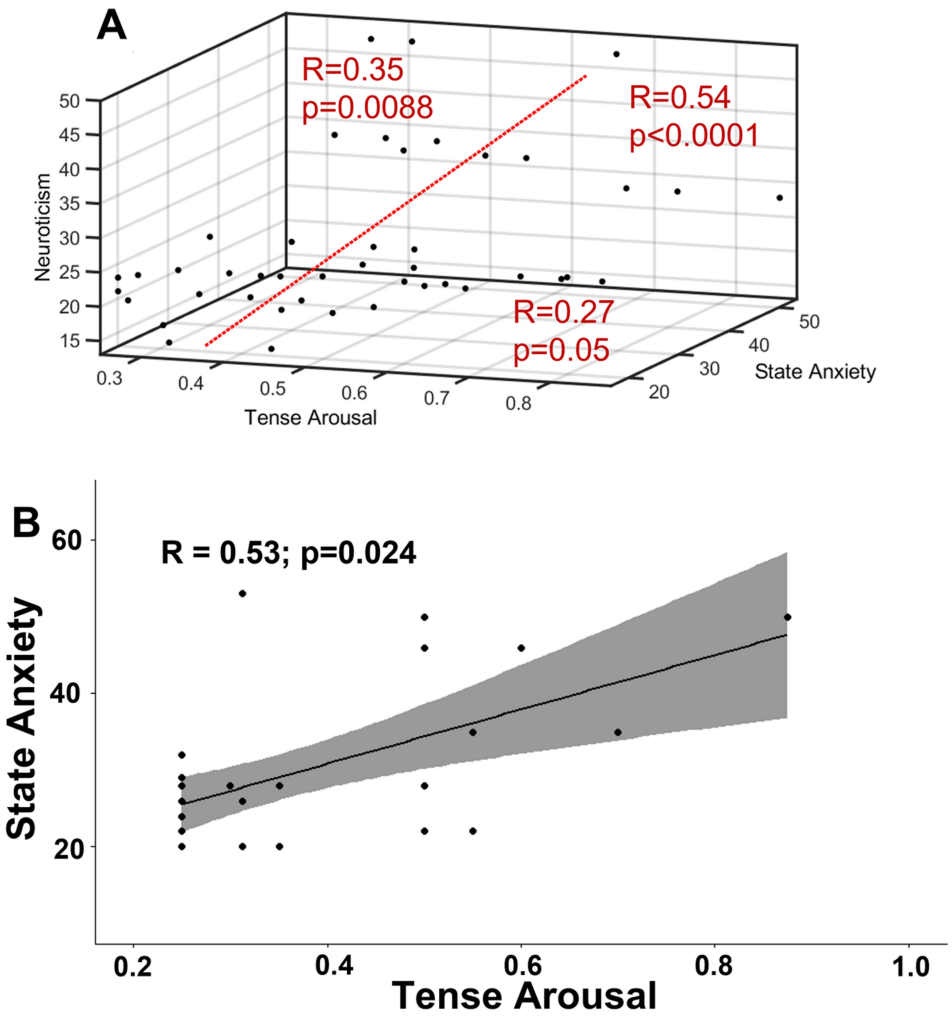

Figure 4 Pearson correlations among (**A**) neuroticism, state anxiety and tense arousal during the continuous performance task with painful stimuli (CPTpain). Pearson correlations between (**B**) tense arousal and state anxiety during the habituation phase. In part B, the gray area indicates the 95% confidence interval.

partial correlation model, tense arousal was positively correlated with neuroticism (R=0.291; t-stat=2.20; p=0.033), but not with state anxiety (R=0.134; t-stat=0.997; p=0.333) or trait anxiety (R=−0.142; t-stat=1.04; p=0.305).

During painful laser habituation, tense arousal positively correlated with state anxiety (R=0.529; t-stat=2.50; p=0.024), but not neuroticism (R=0.401; t-stat=1.751; p=0.099) or trait anxiety (R=0.154; t-stat=0.626; p=0.541) (Figure 4B). In the 4-variable partial correlation model, there was a trend for a positive correlation between tense arousal and state anxiety (R=0.459; t-stat=2.06; p=0.056), but no relationship with trait anxiety (R=−0.262; t-stat=−1.09; p=0.294) or neuroticism (R=0.266; t-stat=1.10; p=0.286). The results in this section were not significantly affected by controlling for age or sex (Supplemental Table 2).

Discussion

In the current report, we extend our results characterizing experimental vigilance to painful stimuli with comparatively slow thermal stimuli[13,32] to a CPT with painful rapid laser stimuli (CPTpain). Specifically, we found a vigilance decrement in hits during time on task. There was no change in false alarms, HRT, or FRT. These findings contrasted with our previous results with 1.5s thermal stimuli where there was a vigilance decrement in both false alarms and hits during time on task.[13,32] In the current report, using painful laser stimuli, we replicated our finding of a positive relationship of tense arousal with state anxiety during the CPTpain. Consistent with the negative valence and threat associated with painful stimuli that are associated with actual or potential tissue damage by the IASP criteria,[47] we found both tense arousal and state anxiety were greater after the CPTpain than before.

During the CPT with painful thermal stimuli delivered by a thermode we previously showed tense arousal positively correlated with pain intensity and pain unpleasantness, but not salience consistent with the relationship between tense arousal and negative valence.[13] During phasic painful stimulation, participants typically report pain intensity, pain unpleasantness and salience ratings that are closely correlated with each other.[48] Significant psychological manipulations such as meditation or induction of negative moods uncouple these relationships.[49,50]

While pain intensity and pain unpleasantness were not positively correlated with tense arousal during the CPTpain, as they were previously with painful thermal stimuli delivered with the thermode,[13] salience was positively related to tense arousal. Differential peripheral afferent nerve fiber recruitment by thermal stimuli from laser compared to thermode, touch inhibition of certain qualities of pain by the thermode and differences in spatial summation may explain these differences between the experimental results.[51–57] The touch inhibition associated with the thermode may be tonic when the thermode remains in place during a multiple stimuli task, or phasic as in our prior study when the thermode is moved from place to place on the skin.[13] Finally, we found that pain intensity, pain unpleasantness and salience were positively correlated with each other throughout the CPTpain and during the habituation task. Furthermore, while the change in pain intensity, change in pain unpleasantness, and change in salience were all positively correlated during the CPTpain, there was no positive correlation between change in pain intensity and change in pain unpleasantness during habituation. This suggests these variables are tightly associated when participants attend closely to stimuli during the CPTpain. This contrasts with the habituation task, where participants are free to think of external stimuli or internal thoughts. This may weaken the link between pain intensity and pain unpleasantness, as reported in recent meditation studies.[50,58–60]

We have now reported a vigilance decrement in hits with thermal stimuli delivered by both thermode and laser. While we found a decrement in hits and false alarms during time on task with the 1.5 s plateau painful thermal stimulus, we only found a decrement in hits with the painful laser stimulus.[13] This difference in the form of vigilance decrement is similar to that found in visual vigilance tasks when varying the discriminability of visual stimuli.[14] The more discriminable a stimulus, the more easily participants can tell successive stimuli apart from one another in terms of magnitude. In a task with more difficult to discriminate stimuli, time on task is associated with a decrease in hits without a change or with a decrease in false alarms. In contrast, an easier task with more discriminable stimuli causes a vigilance decrement in hits and increment in false alarms.[61] The initial discriminability of successive thermal stimuli delivered by the thermode was 0.93±0.006 (mean±SEM), whereas the initial discriminability in the laser vigilance task was 0.83 ±0.016.[32] The effect of change in type of vigilance decrement is generally ascribed to high event rate tasks (≥30 - per minute). However, as the system transmitting painful thermal stimuli is dominated by slow conduction velocity primary afferents, we may expect a lower rate of stimuli to saturate the sensory channel for painful stimuli.[62,63] Our

experimental design reflects this fact; at 15 stimuli per minute there is minimal interaction between successive painful stimuli. More rapid rates of painful stimuli presentation have traditionally led to sensitization.[64] Hence, the vigilance decrement we see with thermal stimuli delivered by the laser may be due to sensory channel saturation and not simply high event rate. Careful experiments are required to elucidate this possibility.

During the CPT with painful thermal stimuli delivered by a thermode we previously found tense arousal positively correlated with state anxiety, trait anxiety, and neuroticism.[13] During CPT with painful laser stimuli, we found that tense arousal positively correlated with state anxiety and neuroticism but was not related trait anxiety. This largely replicates the results found with painful thermal stimuli delivered by thermode, and fully replicates our previously reported partial correlation results.[13]

Both tense arousal and state anxiety increased significantly during the CPT pain. During the pre-task period, tense arousal may reflect anxiety related to anticipation of the experimental task. However, tense arousal levels were relatively low at pre-task baseline. Furthermore, the tense arousal and state anxiety reported by the participants during the CPTpain, were positively associated with each other. The relevance of our CPTpain method to potential mechanisms underlying the psychological drivers of pain severity are made clear by the interaction between state anxiety and acute pain. An association of tense arousal with headache intensity in headache has been identified and longitudinal findings in patients suffering from chronic pain have demonstrated a temporally dependent role of anxiety and depression in the exacerbation of chronic pain.[5,65] A recent longitudinal study found baseline anxiety in patients with musculoskeletal pain predicted pain severity twelve months later.[66] More specific to state anxiety, a recent systematic meta-analysis found that while pre-surgery state anxiety predicts the development post-surgical pain, trait anxiety was only a weak predictor of chronic post-surgery pain spanning multiple procedures and patient groups.[67,68] Furthermore, pre-procedural state anxiety predicts the expectation and experience of post-procedural pain following third molar extraction.[69,70] In studies of prolonged acute pain such as capsaicin exposure or cold pressor task, state anxiety is associated with pain intensity, tolerance and intensity of capsaicin-induced mechanical hyperalgesia.[71,72] Further studies with a control task, such as CPT with warm or vibratory stimuli, should examine whether these changes in state anxiety or tense arousal are potentially related specifically to painful stimuli or are common due to task difficulty.

In the current study, we found that changes in pain intensity, unpleasantness and salience were highly positively correlated during the CPTpain. Positive correlations among change in pain intensity and change in salience, as well as change in pain unpleasantness and change in salience over time on task during habituation were lower. In the case of change in pain intensity versus change in pain unpleasantness were not significant. These findings are consistent with participants maintaining their attention on the sensory characteristics of the painful stimuli, especially when performing the CPTpain. Given that participants seem to be maintaining attention on the sensory characteristics of the painful stimuli, this may be related to each participant's intrinsic attention to pain.[73] This contention requires further research.

Human factors research clearly indicates that performance in a CPT protocol is influenced by attention as well as arousal, reflecting a state of physiological readiness.[74–76] Well-established biopsychological models divide arousal into components including tense and energetic arousal.[31,77–79] Negative valence is the factor that may distinguish fearful, unpleasant tense arousal from energetic arousal.[16,80] In fact, energetic and tense arousal often co-vary except in the presence of pain[81] or with time on task in a CPT.[41,82] Over time, energetic arousal undergoes a progressive and reproducible decrease,[41,83] while there is an increase in tense arousal[74,84] and scores in sustained performance tasks.[85,86] Tense arousal is related to clinical pain, which suggests that high tense arousal and intrinsic attention to pain may identify patients at risk for chronic pain.[81,87]

Previous reports have implicated disinhibition of the dorsolateral prefrontal cortex from the amygdala during threat-related hypervigilance, which regulates attentional processes related to nonthreatening visual stimuli in a train of threatening stimuli.[88] Prefrontal structures, such as the left dorsolateral prefrontal cortex, are activated during both experimental vigilance and in participants with high levels of trait anxiety during conflict processing. Accordingly, decreased volumes of these structures are found in phobias, panic disorders, and chronic pain.[89–92] These overlapping anatomical and behavioral effects suggest that vigilance in chronic pain and anxiety disorders may share common features, consistent with an underlying mechanism mediating the relationships among tense arousal, pain unpleasantness, and trait and state anxiety during vigilance to pain. While our present findings provide further support to the body of

evidence on experimental vigilance to pain, our study has some limitations. Primarily, our sample size is relatively small for behavioral findings. However, mitigating against this weakness is that many findings support previously reported results in a different cohort experiencing a similar experimental protocol.[13] Furthermore, given the intensive data collection session, common in vigilance studies, rater fatigue may have exacerbated the effects of sustained attention.

Conclusion

We have found support for our previous findings that vigilance to painful stimuli during a CPT with a painful stimulus is characterized by a vigilance decrement in hits. Furthermore, we found additional support that state anxiety positively correlates with tense arousal. During our task pain intensity, unpleasantness and salience ratings were tightly intertwined, and their relationships and changes over time were more related to each other during vigilance to painful laser stimuli during time on task compared to the habituation phase. Performing the CPTpain task was associated with enhanced tense arousal and state anxiety.

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Disclosure

The authors report no conflicts of interest in this work.

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