Pain Catastrophizing is Associated with Dental Pain in a Stressful Context
C.-S. Lin, D.M. Niddam, M.-L. Hsu and J.-C. Hsieh
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What is This?
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ABSTRACT

Pain is associated with anxiety in a dental setting. It has remained unclear how cognitive-affective factors modulate pain and anxiety in a stressful context, such as receiving dental procedures. We hypothesized that both the situational factor (unpredictability about painful stimuli) and the trait factor (pain catastrophizing, i.e., the tendency to interpret pain in a negative orientation) account for dental pain. Fifteen healthy participants were recruited to perform an associative learning task. They were asked to learn the pairing between visual cues and the intensity of incoming painful stimuli delivered at the right upper central incisor. Brain activation associated with pain was recorded by functional magnetic resonance imaging (fMRI). The participants reported increased anxiety and pain in the stressful context, where stimuli intensity was not predicted by the preceding cue. The score of the Pain Catastrophizing Scale was positively correlated with the increased pain modulated by unpredictability. Brain activation at the right posterior hippocampus, a region critically related to associative learning of aversive stimuli and context, was correlated with the individual catastrophizing level. Our findings suggest that both the situational factor (unpredictability) and the trait factor (catastrophizing) influence dental pain, highlighting the role of cognitive-affective factors in pain control of dental patients.

KEY WORDS: anxiety, dental care, functional MRI, hippocampus, pain catastrophizing, pain management.

INTRODUCTION

Pain is modulated by complex cognitive and affective factors (Tracey and Mantyh, 2007). In a clinical setting, highly anxious patients anticipate and perceive worse pain when receiving stressful dental procedures (e.g., root canal treatment or extraction) (Klages et al., 2004; van Wijk and Hoogstraten, 2009), and dental fear leads to avoidance of treatment and poor oral health (Armfield et al., 2007). The etiology of dental pain could be misdiagnosed when patients were highly anxious (Eli, 1993), and patient satisfaction with treatment would decline due to unsuccessful relief of pain and anxiety (Ståhlnacke et al., 2007). Patients’ subjective experience of pain fluctuates in a stressful context of dental pain and dental procedures, yet its psychological and neurological mechanisms are largely unknown.

Feeling uncertain about an imminent threat is stressful (Asmundson et al., 2007). Receiving aversive stimuli with unpredictable occurrence or intensity would evoke sustained anxiety (Shankman et al., 2011). Nociceptive stimuli with unpredictable intensity would be perceived as more painful, even though the physical intensity of stimuli did not change (Ploghaus et al., 2001; Brown et al., 2008). The findings suggest that, on the one hand, the situational factor, such as unpredictability about pain, critically modulates our pain experience (Armfield, 2010). On the other hand, trait factors regarding the cognitive-affective processing of threat may contribute to individual vulnerability to develop anxiety and pain (Asmundson et al., 2007). A critical trait of this kind is pain catastrophizing, the tendency to anticipate pain and interpret experienced pain in a negative orientation (Quartana et al., 2009). This trait can be assessed by the pain catastrophizing scale (PCS) from 3 subcategories: rumination (regarding attentional engagement to pain-related experience), magnification (regarding the tendency to exaggerate pain-related threat), and helplessness (regarding the inability to cope with pain effectively) (Sullivan et al., 1995). People with a higher PCS score showed biased cognitive-affective processing regarding pain-related information (e.g., heightened attentional engagement with the cues predicting incoming pain) (Van Damme et al., 2002, 2004). In the dental setting, patients with higher PCS scores reported more dental anxiety and pain during dental procedures (Sullivan and Neish, 1998, 2000). Therefore, pain catastrophizing may contribute to individual pain experience in a stressful setting, in which the subjects need to learn the dynamic association between pain and the pain-related context. However, the underlying psychological and brain mechanisms remained unclear.

We hypothesized that individual variation in pain catastrophizing would account for participants’ exacerbated pain experience in the stressful context regarding dental pain (e.g., receiving painful pulpal stimulation). We adopted...
an associative learning paradigm to compare the self-reported pain intensity and pain-related anxiety in the condition where stimulating intensity was predictable vs. unpredictable (Ploghaus et al., 2001). We hypothesized that the PCS score predicts pain exacerbation by increased unpredictability, but not pain evoked by increased stimulating intensity. We reasoned that catastrophizers experience such unpredictably-modulated pain because they tended to associate pain with the stressful context in negative orientation (e.g., through ruminating and magnifying pain-related information). We hypothesized that such a biased cognitive/affective processing of pain relates to functions of the hippocampus, a brain region critically related to acquisition of the association between aversive stimuli and the context (Fanselow and Dong, 2010; Goosens, 2011). To test the working hypothesis, we applied functional magnetic resonance imaging (fMRI) to investigate the correlation between hippocampal activation and the PCS score, when the participants received painful pulpal stimulation in a stressful context.

MATERIALS & METHODS

Participants

Sixteen healthy participants (seven men and nine women) were recruited from the public through an advertisement. One male subject was excluded because he did not follow experimental instructions, leaving 15 participants (mean age ± standard deviation [SD] = 26.3 ± 11.2 yrs). All participants were right-handed and had no history of neurological or psychiatric disease or chronic pain. Oral examination was performed to confirm that the stimulation site (the right upper central incisor) was intact. Written informed consent was obtained from participants. The study was approved by the Institutional Ethics Committee of Taipei Veterans General Hospital and conducted in accordance with the Declaration of Helsinki.

Psychological Assessment

Prior to the experiment, participants completed the Pain Catastrophizing Scale (PCS) (Sullivan et al., 1995), which consists of the subscale of rumination, magnification, and helplessness, and 3 assessments regarding the general and dental-specific traits about the cognitive-affective aspects of pain: Beck’s Depression Inventory (BDI; Beck et al., 1961), the Modified Dental Anxiety Scale (MDAS; Humphris et al., 1995), and the revised Dental Belief Survey (DBS; Milgrom et al., 1995). After the experiment, participants completed the short-form McGill pain questionnaire (MPQ; Melzack, 1987), a tool that quantified the pain they experienced during the experiment.

Experimental Design and Procedure

The experiment consisted of a behavioral task and fMRI scanning, which measures the blood-oxygen-level-dependent (BOLD) effect associated with the task-related brain activation. The behavioral task was modified from the associative learning paradigm (Ploghaus et al., 2001) (see Fig. 1A for detailed description of the paradigm). Briefly, the participants received electrical stimuli that evoked high and low levels of pain on their upper right central incisor (Brügger et al., 2012). The physical intensity of the stimuli (mA) was calibrated at the beginning of the experiment and fixed throughout the experiment. Details on the tooth stimulation paradigm can be found in the Appendix Methods under “Electrical Stimulation”. In a trial, a stimulus would be delivered in 1 of the 2 conditions (with different levels of stress): (i) a predictable condition, in which the participant would always receive a low-intensity stimulus; and (ii) an unpredictable condition, in which the participant would receive either a low- or a high-intensity stimulus.
In each trial, the stimulus was preceded by a visual cue, and the participants were asked to associate the cue and the following stimuli intensity (e.g., to differentiate if a cue was predictive or unpredictive to intensity). The participants thus encountered 1 of the 3 conditions in each trial: (1) low-intensity predictable (LI-P), (2) low-intensity unpredictable (LI-UnP), and (3) high-intensity unpredictable (HI-UnP). The participants received fMRI scanning concurrently when performing the behavioral task and rated the intensity of perceived stimulus, in each trial, after receiving the stimulus (Fig. 1A).

Statistical Analysis

Behavioral Data

To investigate our behavioral hypothesis regarding the role of pain catastrophizing, for each participant, we first quantified the degree of increased pain ratings (ΔP) modulated by (i) increased unpredictability (i.e., ΔP unpredictability) and (ii) increased nociceptive intensity (i.e., ΔP intensity), respectively:

(i) \[ \Delta P_{\text{unpredictability}} = \frac{\text{Pain}_{\text{LI-UnP}} - \text{Pain}_{\text{LI-P}}}{\text{Pain}_{\text{LI-P}}} \]

(ii) \[ \Delta P_{\text{intensity}} = \frac{\text{Pain}_{\text{HI-UnP}} - \text{Pain}_{\text{LI-UnP}}}{\text{Pain}_{\text{LI-UnP}}} \]

Next, we performed stepwise multiple-regression analysis, across all participants, by taking ΔP unpredictability and ΔP intensity, respectively, as the dependent variable, with the participants’ age and the assessment scores from PCS, MDAS, DBI, MPQ, and BDI as the predictors. We expected the PCS score to be significantly positively correlated with ΔP unpredictability but not with ΔP intensity with all the other variables being controlled.

Functional MRI Data

The acquired imaging data were pre-processed and analyzed with SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). Details on imaging data processing can be found in the Appendix Methods under “Imaging Data Acquisition and Processing”. To test our imaging hypothesis regarding the role of the hippocampus, we performed region-of-interest (ROI) analysis, focusing on the hippocampal activation in the contrast image (the LI-UnP condition compared with the LI-P condition). We selected the anterior and posterior hippocampus as the ROIs and confined the regression analysis to only the voxels within the ROI (Poldrack, 2007). We also performed whole-brain exploratory analysis by searching in the whole brain for regions in which activation positively correlated with the PCS score. The whole-brain analysis was performed separately for the 3 baseline images and the contrast image. Details on the imaging statistical analysis can be found in the Appendix Methods under “Imaging Data Analysis” and “ROI Definition”.

RESULTS

Behavioral Results

The participants rated increased pain and pain-related anxiety in the unpredictable condition compared with the predictable condition. Multiple-regression analysis revealed the PCS total score as the only variable significantly correlated with ΔP unpredictability (\( t = 3.75, p = 0.002, \) zero-order \( r = 0.72 \)) (Fig. 2A). In contrast, the PCS total score was not correlated with ΔP intensity (Fig. 2A) (see Appendix Table for results of psychological assessment). Notably, the score of each of the 3 PCS subscales (rumination, magnification, and helplessness) was positively correlated with ΔP unpredictability. The finding confirmed our behavioral hypothesis that pain catastrophizing predicted the increased pain modulated by unpredictability; in contrast, it did not predict the increased pain modulated by increased nociceptive intensity. Individual variations in increased anxiety did not significantly correlate with the increased pain (\( p = 0.37 \)) or the PCS total score (\( p = 0.98 \)). The findings suggest that the changing anxiety per se did not account for the changing pain experience. Details on the behavioral results can be found in the Appendix Results under “Behavioral Results”.

Functional MRI Results

ROI Analysis

For the contrast image (LI-UnP > LI-P), within the pre-defined ROIs, we found brain activation positively correlated with PCS scores at the right posterior hippocampus ((x, y, z) = [32, -32, -6], \( Z = 2.83, \) SVC-corrected \( p = 0.048, \) corrected for family-wise error) (Fig. 2B). The results confirmed our imaging hypothesis that the hippocampal activation is associated with catastrophizing in the stressful context modulated by unpredictability.

Whole-brain Analysis

For the contrast image, within the whole brain, we found brain activation positively correlated with PCS scores only at the posterior hippocampus (Table, A; Fig. 2C). For images of the respective baseline conditions, the PCS-related activation was found in the hippocampus for the conditions LI-UnP and HI-UnP (Table, C and D), but not in the condition LI-P (Table, B). The findings suggested that the coupling between hippocampal activation and PCS scores was specific to the stressful context.

DISCUSSION

Increased Pain is Modulated by Both Context and Trait Factors

Exaggeration or magnification of pain of dental patients has been widely documented (Klagge et al., 2004; van Wijk and Hoogstraten, 2009). Yet the psychological mechanisms of such a phenomenon remained unexplored. The trait view focused on the influence of personality factors, such as dental anxiety, depression, or neuroticism, on the worst pain experience in a dental setting. The situational (or contextual) view, in contrast, focused on the situational factors specific to the context regarding dental pain and its treatment, such as uncontrollability, unpredictability, or dangerousness (Armfield, 2006). It is noteworthy that these 2 lines of theoretical views are not mutually exclusive: The cognitive-affective factors may create a threatening...
or stressful context where individuals are prone to feel about pain, and their predisposing traits predict how bad the pain would be. In this integrative model, both situational factors and trait factors shape our pain experience (Fig. 3).

Our findings support such an integrative model regarding pain experience exacerbated in a stressful dental setting. We have demonstrated that PCS scores predicted the increased pain in the unpredictable vs. predictable context, where the participants also felt increased anxiety. Notably, PCS scores did not predict the increased pain modulated by stimuli intensity. The finding suggested that pain catastrophizing modulates pain experience via modulating the cognitive-affective aspects, rather than the sensory aspects, regarding stimuli. Our findings are in line with the cognitive model of dental fear (Armfield, 2006; Armfield et al., 2007), which highlights the role of contextual features, such as unpredictability, in shaping anxiety. Because the heightened pain-related stress was induced by an associative learning paradigm, the finding highlights the cognitive theory of pain catastrophizing, which proposed that pain catastrophizing can be characterized by biased information-processing regarding threat (e.g., increased attention biases to pain information) (Van Damme et al., 2002, 2004; Quartana et al., 2009).

Hippocampal Activation Reflects Individual Variations of Pain Catastrophizing in a Stressful Context

We found that the hippocampus activation was associated with increased PCS scores. The coupling between hippocampal activation and PCS was found only in the stressful context when pain was unpredictable. An interesting finding in our results was that only the posterior part of the hippocampus showed significant correlation with PCS scores. The hippocampus is a functionally heterogeneous region. The anterior part is predominantly associated with anxiety and fear, whereas the posterior hippocampus plays a key role in context-modulated fear conditioning (i.e., associating an aversive stimulus with the context of stimulation) (Fanselow and Dong, 2010; Goosens, 2011). Therefore, while the anterior hippocampus reflects the degree of anxiety induced by a threat (McHugh et al., 2004), the posterior hippocampus reflects how an individual acquires the threat-context association. Its activation may therefore indicate biased...
information-processing about a threat in a stressful context, and reflect the vulnerability in which one perceives pain-related anxiety (when anticipating the threat to come). In line with our finding, a recent study has revealed a functional segregation regarding anxiety in the hippocampus. While anterior hippocampal activation is associated with state anxiety (i.e., the anxiety about a particular situation or activity), posterior hippocampal activation is associated with trait anxiety (i.e., the proneness to experience anxiety across various contexts and events) (Satpute et al., 2012). Further discussion on the low-intensity predictable conditions can be found in the Appendix Discussion.

**Clinical Significance**

Our behavioral and neuro-imaging findings highlight the role of cognitive-affective factors for pain control in dental patients. Until now, a systematic approach for managing highly anxious dental patients and alleviating their pain has not been fully established. Based on our behavioral and neurological findings, we suggest that:

1. Manipulating the predictability of pain is crucial to the relief of pain-related anxiety. This issue can be particularly important during complicated dental treatment (e.g., implant surgery or root canal treatment), when the patients feel uncertain about the effect of a dental procedure.

2. It is crucial to assess trait pain catastrophizing for highly anxious dental patients, especially when they are scheduled to undergo very stressful procedures. For dentists, to understand such a pain-related 'cognitive profile' of patients would contribute to a customized strategy for pain control.

3. Dental patients would not just passively receive a painful stimulus, but would also actively associate their experienced

### Table. Summary of Imaging Findings

**A** Significant Brain Activation in the Contrast Image

<table>
<thead>
<tr>
<th>Brain Region</th>
<th>BA</th>
<th>Side</th>
<th>Cluster Size</th>
<th>Z Score</th>
<th>p value</th>
<th>x</th>
<th>y</th>
<th>z</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hippocampus</td>
<td>37</td>
<td>R</td>
<td>58</td>
<td>3.01</td>
<td>0.001</td>
<td>34</td>
<td>-46</td>
<td>-6</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>37</td>
<td>R</td>
<td>2.83</td>
<td>0.002</td>
<td></td>
<td>32</td>
<td>-32</td>
<td>-6</td>
</tr>
</tbody>
</table>

**B** Significant Brain Activation in the Low-intensity Predictable (LI-P) Condition

<table>
<thead>
<tr>
<th>Brain Region</th>
<th>BA</th>
<th>Side</th>
<th>Cluster Size</th>
<th>Z Score</th>
<th>p value</th>
<th>x</th>
<th>y</th>
<th>z</th>
</tr>
</thead>
<tbody>
<tr>
<td>S2/posterior insula</td>
<td>13</td>
<td>L</td>
<td>267</td>
<td>4.33</td>
<td>&lt; 0.001</td>
<td>-36</td>
<td>-28</td>
<td>18</td>
</tr>
<tr>
<td>Superior temporal gyrus</td>
<td>22</td>
<td>L</td>
<td>386</td>
<td>3.79</td>
<td>&lt; 0.001</td>
<td>-48</td>
<td>-8</td>
<td>-6</td>
</tr>
<tr>
<td>Temporal pole</td>
<td>21</td>
<td>L</td>
<td></td>
<td>3.72</td>
<td>&lt; 0.001</td>
<td>-46</td>
<td>8</td>
<td>-18</td>
</tr>
<tr>
<td>Putamen</td>
<td></td>
<td></td>
<td></td>
<td>2.97</td>
<td>0.001</td>
<td>-26</td>
<td>12</td>
<td>-10</td>
</tr>
<tr>
<td>Anterior insula</td>
<td>13</td>
<td>R</td>
<td>102</td>
<td>3.48</td>
<td>&lt; 0.001</td>
<td>34</td>
<td>12</td>
<td>-14</td>
</tr>
<tr>
<td>Anterior cingulate cortex</td>
<td>32</td>
<td>R</td>
<td>49</td>
<td>3.36</td>
<td>&lt; 0.001</td>
<td>2</td>
<td>46</td>
<td>6</td>
</tr>
<tr>
<td>Precuneus</td>
<td>7</td>
<td>L</td>
<td>39</td>
<td>3.21</td>
<td>0.001</td>
<td>-14</td>
<td>-72</td>
<td>32</td>
</tr>
<tr>
<td>M1</td>
<td>4</td>
<td>L</td>
<td>26</td>
<td>3.03</td>
<td>0.001</td>
<td>-4</td>
<td>-30</td>
<td>50</td>
</tr>
</tbody>
</table>

**C** Significant Brain Activation in the Low-intensity Unpredictable (LI-UnP) Condition

<table>
<thead>
<tr>
<th>Brain Region</th>
<th>BA</th>
<th>Side</th>
<th>Cluster Size</th>
<th>Z Score</th>
<th>p value</th>
<th>x</th>
<th>y</th>
<th>z</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hippocampus</td>
<td>37</td>
<td>R</td>
<td>372</td>
<td>2.88</td>
<td>0.002</td>
<td>32</td>
<td>-42</td>
<td>-2</td>
</tr>
</tbody>
</table>

**D** Significant Brain Activation in the High-intensity Unpredictable (HI-UnP) Condition

<table>
<thead>
<tr>
<th>Brain Region</th>
<th>BA</th>
<th>Side</th>
<th>Cluster Size</th>
<th>Z Score</th>
<th>p value</th>
<th>x</th>
<th>y</th>
<th>z</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hippocampus</td>
<td>37</td>
<td>R</td>
<td>54</td>
<td>4.02</td>
<td>&lt; 0.001</td>
<td>32</td>
<td>-40</td>
<td>-2</td>
</tr>
</tbody>
</table>

BA, Brodmann area; S2, Secondary somatosensory cortex; M1, primary motor cortex. All p values reported are uncorrected for multiple comparison. Cluster size is measured by the number of voxels.
pain with the context wherein they received the stimulus. The patients with a higher pain catastrophizing score may be more prone to learn an association between the context and pain from a negative orientation and form traumatic memory regarding pain. The neurobiological evidence related to pain catastrophizing during dental pain would highlight the influence of biopsychosocial factors on oral health (Marcenes et al., 1993).

ACKNOWLEDGMENTS

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