

C.-S. Lin^{1†*}, D.M. Niddam^{1,2,3†},
M.-L. Hsu⁴, and J.-C. Hsieh^{1,3}

¹Integrated Brain Research Unit, Department of Medical Research & Education, Taipei Veterans General Hospital, Taipei, Taiwan; ²Brain Research Center, Department of Research and Development, National Yang-Ming University, Taiwan; ³Institute of Brain Science, National Yang-Ming University, Taipei, Taiwan; and ⁴Department of Dentistry, National Yang-Ming University, Taiwan; †authors contributing equally to this work; *corresponding author, winzcs1@gmail.com

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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 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.

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Pain Catastrophizing is Associated with Dental Pain in a Stressful Context

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 (Ståhltnacke *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: *ruminat*ion (regarding attentional engagement to pain-related experience), *magnifica*tion (regarding the tendency to exaggerate pain-related threat), and *helpless*ness (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 exacerbated by increased unpredictability, but not pain evoked by increased stimulating intensity. We reasoned that catastrophizers experience such unpredictable-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 \pm standard deviation [SD] = 26.3 \pm 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

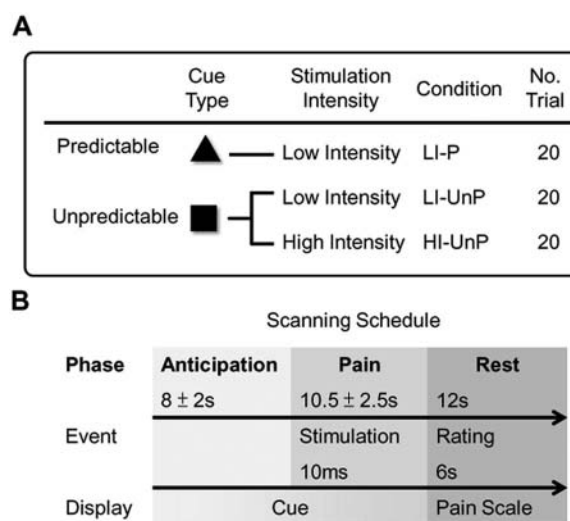


Figure 1. Experimental design and scanning protocol. **(A)** Experimental design. Each trial consisted of an *anticipatory* phase followed by a *pain* phase and ended with a *rest* phase. The anticipatory phase was initiated by 1 of 2 types of visual cues, which differed in predictability of the pain intensity of the impending stimulus and thus induced different levels of anticipatory anxiety. The high-predictability cue (P) was always followed by a single low-intensity painful stimulus (LI). The low-predictability cue (UnP) was followed by either a low-intensity (as above) or high-intensity (HI) painful stimulus. Overall, each of the cue-intensity events (LI-P, LI-UnP, and HI-UnP) was presented in equal numbers (20 trials) throughout the experiment. Participants were instructed that 2 types of cues would be displayed during functional scanning, and that attention should be paid to the cue-intensity association. Two sessions were performed, with 30 event-cycles *per* session and a five-minute rest between 2 sessions. Two fixed sequences were generated in which stimuli were randomly presented. The order of sequences with respect to sessions was counterbalanced across participants. **(B)** Scanning protocol. The visual cue was displayed throughout the anticipatory phase (mean duration = 8 sec) and pain phase (mean duration = 10.5 sec), with a 10-msec electrical pulpal stimulus. After the stimulus was delivered, the visual cue was replaced by a visual-analog scale (VAS) for the following rest phase (mean duration = 12 sec). In this phase, participants were required to rate the pain intensity of the stimulus just received via an online response box. The discrete 11-point pain intensity scale with verbal anchors used for psychophysical calibration and stimulus evaluation during functional scanning ranged from 0 (no pain) to 10 (intolerable pain). After scanning, participants rated pain-related anxiety based on a 0- to 5-point scale, in which '0' represented 'no anxiety about the impending pain' and '5' represented 'extreme anxiety about the impending pain'.

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 unpredictable 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.*, $\Delta P_{\text{unpredictability}}$) and (ii) increased nociceptive intensity (*i.e.*, $\Delta P_{\text{intensity}}$), respectively:

$$(i) \quad \Delta P_{\text{unpredictability}} = (\text{Pain}_{\text{LI-UnP}} - \text{Pain}_{\text{LI-P}}) / \text{Pain}_{\text{LI-P}}$$

$$(ii) \quad \Delta P_{\text{intensity}} = (\text{Pain}_{\text{HI-UnP}} - \text{Pain}_{\text{LI-UnP}}) / \text{Pain}_{\text{LI-UnP}}$$

Next, we performed stepwise multiple-regression analysis, across all participants, by taking $\Delta P_{\text{unpredictability}}$ and $\Delta P_{\text{intensity}}$, 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 $\Delta P_{\text{unpredictability}}$ but not with $\Delta P_{\text{intensity}}$, 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 $\Delta P_{\text{unpredictability}}$ ($t = 3.75$, $p = 0.002$, zero-order $r = 0.72$) (Fig. 2A). In contrast, the PCS total score was not correlated with $\Delta P_{\text{intensity}}$ (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 $\Delta P_{\text{unpredictability}}$. 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 (Klages *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; Goossens, 2011). Therefore, while the anterior

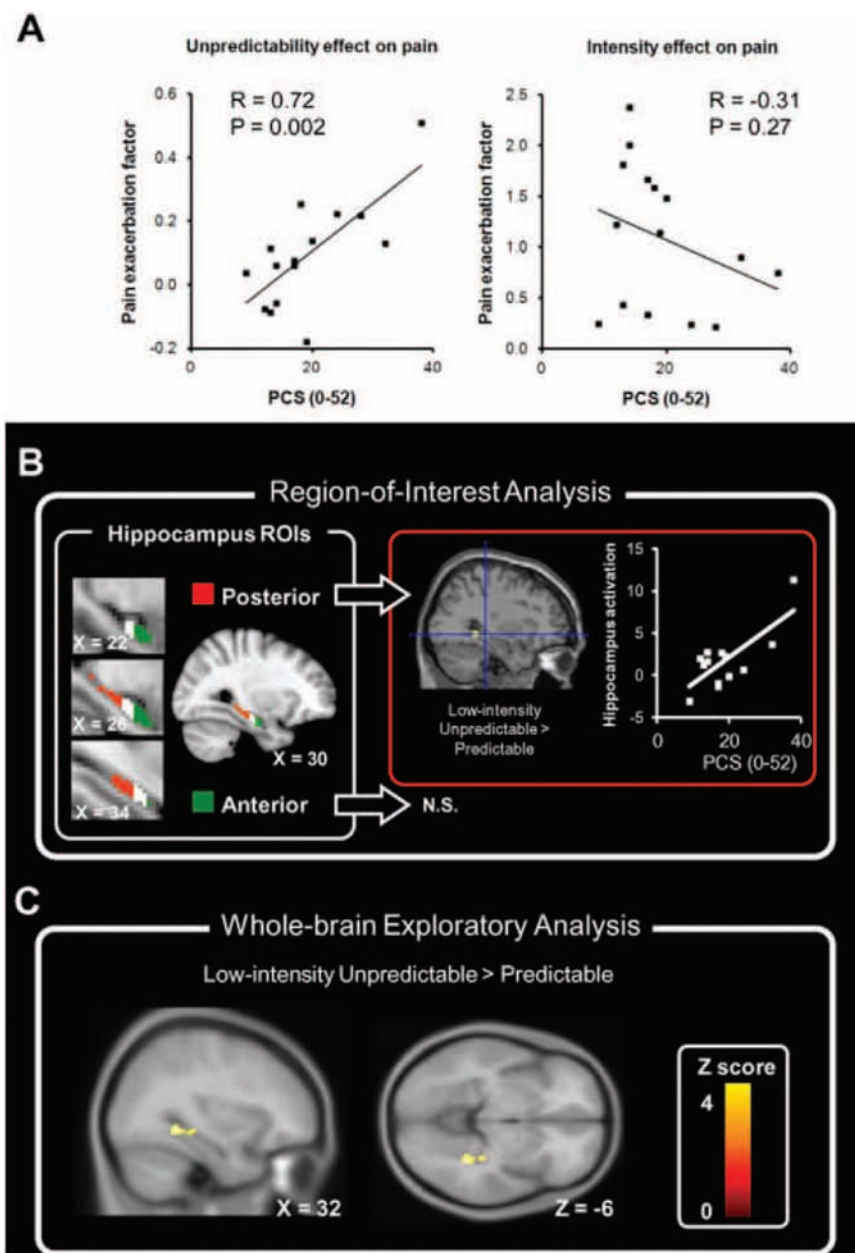


Figure 2. Summary of main results. (A) Behavioral results. The score of the Pain Catastrophizing Scale predicted the exacerbated pain modulated by increased unpredictability (left panel) but not that modulated by increased nociceptive intensity (right panel). (B) ROI analysis. The posterior (red) and anterior (green) hippocampus each occupied 1/3 of the hippocampus ROI (see Appendix for ROI definition), and ROI analysis was performed for the anterior and posterior hippocampus (left panel). The PCS score was positively correlated with brain activation in the contrast image in the posterior hippocampus (framed with a red border), but not the anterior hippocampus (N.S.), of the right hemisphere (right panel). (C) Whole-brain analysis. Brain regions with activation positively correlated with PCS were found at the right hippocampus in the contrast (LI-UnP > LI-P), consistent with the finding from the above ROI analysis. The color bar indicates the Z score from a voxel-wise comparison of brain activation between the 2 conditions.

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

Table. Summary of Imaging Findings**(A)** Significant Brain Activation in the Contrast Image

Low-intensity Unpredictable > Predictable (LI-UnP > LI-P) Condition

Brain Region	BA	Side	Cluster Size	Z Score	p value	MNI Coordinates		
						x	y	z
Hippocampus	37	R	58	3.01	0.001	34	-46	-6
Hippocampus	37	R		2.83	0.002	32	-32	-6

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

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

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

Brain Region	BA	Side	Cluster Size	Z Score	p value	MNI Coordinates		
						x	y	z
Hippocampus	37	R	372	2.88	0.002	32	-42	-2

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

Brain Region	BA	Side	Cluster Size	Z Score	p value	MNI Coordinates		
						x	y	z
Hippocampus	37	R	54	4.02	< 0.001	32	-40	-2

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.

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

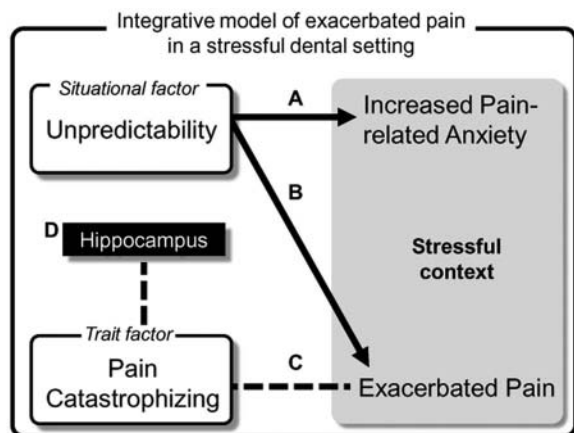


Figure 3. A proposed cognitive-affective model regarding exacerbated pain in a stressful context. Increased unpredictability, a situational factor, evokes both heightened pain-related anxiety (A) and increased pain (B), resulting in a stressful context (shaded by gray). The individual variation in the degree of magnified pain is predicted by the trait factor, pain catastrophizing (C). Note that the change of anxiety *per se* does not predict the change of pain. Participants with higher pain catastrophizing showed increased hippocampal activation, which is associated with memory and learning of aversive stimuli (D). The current model highlights that both the stressful context (modulated by unpredictability) and the catastrophizing trait are critical to pain experience in a stressful dental setting.

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).

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