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Article in Pain · May 2016
Impact Factor: 5.21 · DOI: 10.1097/j.pain.0000000000000606

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Perturbed connectivity of the amygdala and its subregions with
the central executive and default mode networks in chronic
pain

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Abstract

Maladaptive responses to pain-related distress, such as pain catastrophizing, amplify the impairments associated with chronic pain. Many of these aspects of chronic pain are similar to affective distress in clinical anxiety disorders. In light of the role of the amygdala in pain and affective distress, disruption of amygdalar functional connectivity in anxiety states, and its implication in the response to noxious stimuli, we investigated amygdala functional connectivity in 17 patients with chronic low back pain and 17 healthy comparison subjects, with respect to normal targets of amygdala subregions (basolateral versus centromedial nuclei), as well as connectivity to large-scale cognitive-emotional networks, including the default mode network (DMN), central executive network (CEN) and salience network (SN). We found that patients with chronic pain had exaggerated and abnormal amygdala connectivity with CEN, which was most exaggerated in patients with the greatest pain catastrophizing. We also found that the normally basolateral-predominant amygdala connectivity to the DMN was blunted in chronic pain patients. Our results therefore highlight the importance of the amygdala and its network-level interaction with large-scale cognitive/affective cortical networks in chronic pain, and help link the neurobiological mechanisms of cognitive theories for pain with other clinical states of affective distress.

Keywords: amygdala; chronic pain; pain catastrophizing; functional connectivity
**Introduction**

Chronic pain affects 100 million Americans with annual costs exceeding $500M [49]. Low back pain is the most common chronic pain condition [31] with increasing prevalence, treatment and associated expenditures [48] and disability [40]. Psychological distress is frequently associated with chronic pain [18], and implicates an interaction between sensory perception, cognition and emotion [13]. Negative emotional states directly modulate pain experience [11, 38], which in turn biases affective-motivational systems and elicits unpleasant feelings [42, 45]. Chronic pain additionally has a secondary emotional component, which is mediated by cognitive factors such as one’s beliefs, attitudes and thoughts about the consequences of persistent pain on one’s work and life [44, 63], an example of which is catastrophizing [60]. Such responses predict poor outcomes [54], and may maintain or worsen the illness [64].

One brain region that may account for the emotional component of pain is the amygdala – a structure itself composed of several major subregions. Experimentally-induced pain in chronic pain patients increases activation in the basolateral amygdala (BLA) [56], the major sensory input region of the amygdala. Additionally, the centromedial amygdala (CMA), which provides much of the descending output of the amygdala, also receives ascending nociceptive information [9]. Recent resting-state functional magnetic resonance imaging (fMRI) studies have found that the BLA and CMA have dissociable patterns of functional connectivity in humans [24, 50]. Moreover, the amygdala may promote dysfunctional cognitive/emotional reactions such as pain catastrophizing through interactions with other networks implicated in a range of cognitive and emotional functions, which have been shown to be perturbed in chronic pain [7, 14, 41, 61]. Namely, the fronto-parietal “central executive network” (CEN), the dorsal anterior cingulate-anterior insula “salience network” (SN) and the medial prefrontal-medial parietal “default mode network” (DMN).

The CEN responds broadly to cognitive and emotional stimuli and is involved in attention selection [16] and working memory modulation [39]. The DMN activates when processing self-referential information and social and emotional inference of others [12]. The SN tracks affective and pain-related sensations [17], maintains a stable cognitive set [20], and mediates interactions between emotion and cognitive control [37]. Of note, amygdala-CEN connectivity is abnormally increased and amygdala-SN connectivity is decreased in patients with generalized anxiety disorder [24, 46] – another clinical population featuring emotional distress mediated by dysfunctional cognitions [1].

We therefore hypothesized that amygdala connectivity will be perturbed in chronic pain patients to its subregion-selective targets as well as to the major...
cognitive/emotional networks (i.e. CEN, SN, and DMN), and that this will relate to patients’ maladaptive pain-related cognitions (i.e. pain catastrophizing).

Materials and Methods

Subjects and clinical details. The study was comprised of 3 groups: (1) 17 patients (14 females, 3 males) with chronic low back pain recruited from the community (diagnosed by JH), (2) 17 healthy controls (14 females, 3 males) matched for age, gender and education to the chronic pain group and recruited by advertisement, and (3) a healthy control group that was used only to determine region of interest targets for amygdala subregions (see Table 1 for demographics). For the first two groups, all subjects gave their written, informed consent. Stanford University’s institutional review board approved the study. The cLBP participants had experienced non-specific cLBP for an average of 8.9 years (SE=1.9, Minimum=0.5 years, Maximum=26 years). Their average pain severity was 6/10(SE=0.4, Minimum=3/10, Maximum=10/10) during past month, and was 5.7/10(SE=0.5, Minimum=2/10, Maximum=10/10) for past few days. They were without serious spinal pathology, radicular pain, comorbid pain syndromes, use of opioids, thyroid medication, antiepileptic or antidepressant medication, substance abuse, Diagnostic and Statistical Manual of Mental Disorders Axis I psychiatric disorders (determined through the MINI diagnostic interview) [55], or ongoing legal or disability claims and their first language was English. Thus, patients were a particularly homogenous sample, wherein conclusions would not be confounded by co-occurring psychiatric disorders, use of any psychotropic medications, or use of significant opioid or antineuropathic pain medication.

Prior to their scan, all participants were given the Trait form of State-Trait Anxiety Inventory (STAI-T) [58], Beck Depression Inventory (BDI-II) [8] and the Beck Anxiety Inventory (BAI) [4]. Additionally, cLBP participants completed the Pain Catastrophizing Scale (PCS) [60] in order to further characterize the psychological correlates of the functional connectivity abnormalities in this group. The PCS consists of 13 items that are rated for frequency on a 5-point Likert scale (0=not at all, 4=all the time). The PCS is comprised of 3 subscales: rumination (4 items; sample item: “I keep thinking about how badly I want the pain to stop”), helplessness (6 items; sample item: “It’s terrible and I think it’s never going to get any better”) and magnification (3 items; sample item: “I wonder whether something serious may happen”). The PCS is widely used in pain research and has good psychometric properties [60]. For the latter control group we used an independent age-matched sample group of 36 healthy subjects from the Nathan Kline Institute (NKI) dataset made freely accessible online (http://fcon_1000.projects.nitrc.org/indi/pro/nki.html) by the 1000 Connectome database [10]. All individuals in the NKI sample have been given semi-structured diagnostic psychiatric interviews.
Data Acquisition. Imaging acquisition was performed on a GE 3T MRI system (GE Healthcare, Milwaukee, Wisconsin). Participants were told to keep their eyes closed, remain still and try not to fall asleep during the resting state scan. At the beginning of the scan, a magnetic fieldmap was acquired automatically by the pulse sequence. Six minutes of functional data were collected using a gradient echo, spiral-pulse sequence (repetition time, 2000 milliseconds; echo time, 30 milliseconds; flip angle, 77°; voxel size, 3.43 mm). Whole-brain coverage was obtained with 30 interleaved slices and 5mm slice thickness. A T1-weighted spoiled grass gradient-recalled inverted recovery 3-dimensional MRI sequence (repetition time, 9.516 milliseconds; echo time, 2.896 milliseconds; flip angle,15°; field of view, 22 cm; 124 axial slice; voxel size, 0.86 × 0.86 × 1.50 mm) was used for acquiring high resolution structural images for preprocessing. Anatomical data were acquired in the same scan session with resting state data. The NKI sample was acquired using SIEMENS 3T MR (MAGNETOM TrioTim syngo). The resting state scan lasted for 10 minutes, and the scanning parameters were: repetition time, 2500 milliseconds; echo time, 30 milliseconds; flip angle, 80°; interleaved; slices, 38; slice thickness, 3mm; voxel size, 3.0 mm.

Data Preprocessing. The first 8 volumes of resting-state data were discarded for all subjects to account for signal equilibration effects. A linear shim correction was used to reconstruct each slice using the acquired magnetic fieldmap[27]. Preprocessing steps were implemented using FSL 5.0 (http://fsl.fmrib.ox.ac.uk/) as follows: (1) structural images were segmented and spatially transformed to standard stereotaxic space in the Montreal Neurologic Institute coordinate system [25] with nonlinear normalization using standard settings for FNIRT tool; (2) functional images for each subject were registered to their structural images and corrected for motion with affine registration using MCFLIRT tool. All participants had movement within 3mm translation and 3 deg of rotation; (3) functional images were spatially smoothed (6mm full-width half-maximum gaussian kernel) and temporally band-pass filtered (0.008-0.1 Hz). The same preprocessing steps were applied to the NKI sample.

Functional Connectivity Analyses. The amygdala subregional seed regions of interest (ROIs) used for connectivity analyses were the basolateral (BLA) and centromedial nuclei (CMA). These were constructed from probabilistic cytoarchitectonic maps by including voxels whose probability to be assigned to BLA or CMA is no less than 40% compared with other amygdala subregions or surrounding medial temporal cortex [21,22] and were identical to those used in our prior analyses [24](see figure 1a). For each seed ROI, a BOLD time course was extracted from band-pass filtered resting-state data and then was correlated with the time courses from all other brain voxels using a first level fixed-effect GLM model, regressing out signal from ventricular regions and white matter as well as six motion parameters. The correlation maps consisted of voxels whose values represented their degree of connectivity with the seed ROIs. These values were then
converted to z-scores by a Fisher’s z transform, producing z-score maps with a normalized distribution [32]. Average functional connectivity with the BLA or CMA seed for right and left hemispheres were extracted from individual z-score maps for brain regions with high degrees of correlation with amygdala seeds as well as regions representing large-scale brain networks. The extracted functional connectivity measures were then analyzed using SPSS 19.0 (SPSS IBM, New York, USA). Normative target ROIs for amygdala subregions were derived from the independent control sample as described below in the results. Large-scale networks were obtained from thresholded ICA maps from an independent sample of our previous study, yielding ~1000 voxel regions of interest [15]. As shown in Figure 1b, the CEN was composed of clusters in the right lateral prefrontal cortex (rLPFC; Brodmann’s area(BA): 6/8/9/46; number of voxels: 994), right lateral posterior parietal cortex (rLPPC; BA: 7/39/40; number of voxels: 1009), left lateral prefrontal cortex (lLPFC; BA:9/10/45/46/47; number of voxels: 1001) and left lateral posterior parietal cortex (lLPPC; BA:7/19/39/40; number of voxels:991) ; the SN consisted of clusters in the dorsal anterior cingulate cortex (dACC; BA:24/32/6; number of voxels:999) and fronto-insular cortices (FIC; BA:13/44/45/47; number of voxels:996); and the DMN included the medial prefrontal cortex (mPFC; BA:9/10/11/32; number of voxels:999) and posterior cingulate cortex (PCC; BA: 23/29/30/31; number of voxels:1009). Group-level voxel-wise analyses were performed in SPM8 (http://www.fil.ion.ucl.ac.uk/spm/) using z-score maps from the individual functional connectivity analyses, with a flexible factorial ANOVA model.

Correlation Analyses. For patients with cLBP, Pearson’s correlation was used for correlating individual extracted average amygdala functional connectivity with affect/pain scales, including STAI_T, BAI, BDI-II and PCS, in SPSS.

Head motion analyses. Head motion was measured in terms of mean motion, number of movement and mean rotation. Mean motion was the mean absolute displacement (displacement=\sqrt{x^2+y^2+z^2}) where x, y, z represent translation parameters in the left/right, anterior/posterior, and superior/inferior directions respectively) of each volume compared to its previous volume. Number of movement was calculated as the number of relative displacements larger than 0.1mm. Mean rotation was estimated by averaging the absolute value of Euler angle (Euler angle=\arccos((\cos(\phi)\cos(\theta)+\cos(\phi)\cos(\psi)+\cos(\theta)\cos(\psi)+\sin(\phi)\sin(\theta)\sin(\psi)-1)/2, where \phi, \theta and \psi are the rotation parameters along three axes [19].

Mean motion, number of movement and mean rotation were compared between patients with cLBP and healthy controls using t tests and were correlated with functional connectivity estimates within each group using SPSS.

Results

Connectivity of amygdalar subregions to their expected targets
We first defined target mask ROIs for the subregion-specific connectivity maps of the BLA and CMA using the independent NKI sample by contrasting BLA- to CMA-seeded maps in an ANOVA. Target ROIs for the BLA (compared with CMA) and CMA (compared with BLA) were determined by thresholding the statistical maps at \( q < 0.05 \) FDR corrected. Consistent with prior work, the BLA was more strongly connected with a number of cortical regions, encompassing primary and secondary sensory cortices, mPFC, ventromedial prefrontal cortex (vmPFC), precuneus and PCC, as well as with the thalamus, pons and cerebellum; the CMA was more associated with subcortical connectivity, including the striatum, midbrain and cerebellum, as well as with the insula and dorsal anterior cingulate cortex (see Figure 1c; [24]). We also did a one sample t-tests on the BLA and CMA connectivity, separately, to explore the source of the connectivity difference (see Supplemental Figure, available online at http://links.lww.com/PAIN/A272).

To test whether amygdalar subregional connectivity with their typical targets was altered in cLBP, average connectivity of both the BLA and CMA-target ROIs were extracted from bilateral BLA and CMA-seeded connectivity analyses (separated for amygdala subregions and hemisphere) for patients with cLBP and healthy controls. For healthy controls, a 2×2×2 ANOVA (target ROI × amygdala subregion × hemisphere of amygdala subregion) confirmed that the BLA and CMA connected differentially to their expected targets (determined from the independent NKI dataset maps; target ROI × amygdala subregion interaction, \( F(1,16)=5.765, p<0.001, \eta^2=0.78 \)), with no interaction by hemisphere (\( F(1,16)=0.762, p=0.396 \)). Next, we conducted a between-group mixed 2×2×2×2 ANOVA (group× target ROI × amygdala subregion × hemisphere of amygdala subregion) to test for group differences in subregional connectivity, but found that subregional connectivity to amygdala targets was not significantly perturbed in patients with cLBP (group × target ROI × amygdala subregion interaction, \( F(1,32)=1.915, p=0.176 \)).

Connectivity of the amygdala to large-scale cognitive-emotional networks

Next, we extracted bilateral average BLA and CMA-seeded connectivity to core nodes of the CEN, SN and DMN for patients with cLBP and healthy controls, and conducted an omnibus 3×2×2×2 ANOVA, with large-scale network, amygdala subregion and hemisphere of amygdala subregion as within-subject factors and group as a between-subjects factor. We found a group effect for amygdala subregional connectivity (group × network × amygdala subregion interaction, \( F(2,64)=3.850, p=0.026, \text{partial } \eta^2=0.107 \)), with no interaction with amygdala seed hemisphere (amygdala hemisphere × group× network × amygdala subregion interaction, \( F(2,64)=0.175, p=0.840 \)). We then decomposed this effect by performing 2×2×2 ANOVAs (group × amygdala subregion × amygdala hemisphere) separately for the CEN, SN and DMN to examine group difference in amygdala subregional connectivity separately to each of the large-scale networks examined.
Central executive network: The 2x2x2 ANOVA (group x amygdala subregion x amygdala hemisphere) for amygdala connectivity to the CEN revealed a main effect of group (F(1,32)=10.915, p=0.003, partial η²=0.24), not moderated by interaction with amygdalar subregion (group x amygdala subregion interaction, F(1,32)=0.008, p=0.929) or amygdala seed hemisphere (group x amygdala hemisphere, F(1,32)=0.040, p=0.842). As shown in figure 2a, this was driven by greater amygdala-CEN connectivity, across subregions, in patients with cLBP relative to controls. When breaking down the CEN into individual regions of interest, we found no interaction of group with region of the CEN in a 2x2x2x2 ANOVA (CEN region x group x amygdala subregion x amygdala hemisphere; F(1,32)=2.120, p=0.103; figure 2b). To visualize the group main effect, we performed a voxelwise group contrast collapsing across amygdala subregion and amygdala seed hemisphere. The right LPPC, right LPFC, left LPFC and left LPPC within the CEN showed especially strong amygdala connectivity in patients with cLBP compared to healthy controls (see Figure 2c, p<0.05, voxel-wise small volume correction). This further supported our ROI analysis result that, in patients with cLBP, increased amygdala connectivity with CEN occurs across amygdalar subregions and to all regions of the CEN – in other words, there is a change in network-level connectivity between the amygdala and CEN in patients.

Default mode network: The patients with cLBP showed altered differential amygdala subregional connectivity to the DMN (group x amygdala subregion interaction, F(1,32)=5.108, p=0.031, partial η²=0.14), with no moderation by amygdala hemisphere (amygdala hemisphere x group x amygdala subregion interaction, F(1,32)=0.042, p=0.839) (see Figure 2a). This effect was driven by differential BLA/CMA connectivity with the DMN in healthy controls (F(1,16)=10.365, p=0.005, partial η²=0.39), such that DMN connectivity was stronger to the BLA than the CMA. This connectivity difference between amygdalar subregions was not found in patients with cLBP (F(1,16)=0.018, p=0.896). The lack of distinction between amygdala subregional connectivity in patients with cLBP was consistent for the two core nodes of the DMN, the mPFC and the PCC, suggesting that differential amygdalar subregional connectivity is perturbed across the DMN (for patients with cLBP: FmPFC(1,16)=0.033, p=0.859; FpPFC(1,16)=0.005, p=0.943; for healthy controls: FmPFC(1,16)=9.430, p=0.007, partial η²=0.37; FpPFC(1,16)=8.590, p=0.01, partial η²=0.35). Thus, amygdalar connectivity to the DMN was perturbed in a different manner than for amygdala-CEN connectivity, such that the subregional specificity of amygdala-DMN connectivity was blunted in patients, rather than wholesale level of connectivity.

Salience network: There was no main effect of group (group main effect, F(1,32)=0.171, p=0.682) or group by amygdalar subregion interaction for amygdala-SN connectivity (group x amygdala subregion interaction, F(1,32)=0.787, p=0.381).

Relationship of perturbed amygdalar connectivity to head motion
No significant difference between healthy controls and patients with cLBP was found for the three head motion estimates: mean motion ($t = -1.502$, $p = 0.143$), number of movement ($t = -0.758$, $p = 0.454$), and mean rotation ($t = -1.578$, $p = 0.124$). Also, amygdala subregional connectivity with CEN and difference between BLA-DMN and CMA-DMN connectivity did not significantly correlate with these head motion estimates within and across both groups.

**Relationship of perturbed amygdalar connectivity to pain catastrophizing**

To further explore behavioral/symptom correlates of the cLBP patient abnormalities, we extracted amygdala-CEN connectivity values collapsing across amygdala subregions and hemisphere from patients and correlated these extracted average values with affect/pain scales, including STAI_T, BAI, BDI-II and PCS. The results showed that exaggerated amygdala connectivity with the CEN in patients with cLBP was positively associated with total scores from the Pain Catastrophizing Scale (PCS; $r = 0.622$, $p = 0.008$). Breaking the PCS into subscales, we found positive correlations between increased amygdala–CEN connectivity and rumination ($r = 0.621$, $p = 0.008$) and also with helplessness ($r = 0.612$, $p = 0.009$). There was no significant correlation for magnification scores of PCS ($r = 0.108$, $p = 0.681$). We also found a positive relationship between increased amygdala–CEN connectivity and pain intensity during past few days ($r = 0.542$, $p = 0.025$) (see Figure 3). After controlling for pain intensity during past few days, amygdala connectivity remained significantly correlated with total ($r = 0.603$, $p = 0.013$), rumination subscale ($r = 0.058$, $p = 0.025$) and helplessness subscale ($r = 0.604$, $p = 0.013$) scores of the PCS. There was no significant association between reported pain intensity with the PCS or subscales. We also examined amygdalar connectivity relationships with anxiety and depression symptoms, in order to determine whether our findings in chronic pain patients may secondarily reflect elevated anxiety symptoms (noting also that through our experimental design, no patient met criteria for a psychiatric disorder and that anxiety and depression levels were below clinical levels). We found, moreover, no relationship between amygdala-CEN connectivity and anxiety/depression symptoms (BDI: $r = -0.310$, $p = 0.243$; BAI: $r = -0.002$, $p = 0.994$). Finally, we explored the association between blunted subregional differentiation between BLA-DMN and CMA-DMN connectivity by correlating BLA-DMN connectivity, CMA-DMN connectivity and the subtraction of BLA-DMN and CMA-DMN connectivity with the pain and affective scales above, and found no significant brain-symptom relationships.

**Discussion**

In this study we examined resting-state connectivity of the amygdala and its subregions in patients with chronic pain. Patients, compared with healthy controls, showed exaggerated amygdalar connectivity with the central executive network (CEN). This network is thought to exert cognitive control through selective attention and working
memory maintenance [20,39]. Normally, the amygdala is only weakly associated with brain regions in the CEN [24,50,52] – a finding we replicated in healthy controls in our study. The importance of this exaggerated connectivity is further amplified by the relationship we found between greater pain catastrophizing and greater amygdala-CEN connectivity. In addition, we found that the normal predominance of BLA connectivity with the DMN relative to the CMA that is observed in healthy participants was absent in patients with chronic pain. Thus, chronic pain is characterized by abnormalities in amygdalar connectivity with two large-scale networks implicated in cognitive/emotional processes.

Consistent with our amygdala-CEN finding, a meta-analysis of experimental pain studies showed that the prefrontal cortex is more activated in patients with chronic pain than in healthy subjects [2]. Abnormal gray matter density in the amygdala and LPFC of people with cLBP has been shown to distinguish patients from healthy controls [62]. Previous work in clinical anxiety has found increased amygdala-CEN connectivity in patients with generalized anxiety disorder and in individuals with elevated childhood anxiety [24,46]. Due to our experimental design, however, the patients with chronic pain in the current study were free of Axis I anxiety or depressive disorders and had no clinically meaningful elevations in depressive (BDI-II) or anxiety (BAI) symptoms. Moreover, while patients with chronic pain had greater BAI scores compared to healthy controls, these subclinical anxiety scores were not associated with exaggerated amygdala-CEN connectivity. Thus, our findings reflect chronic pain-related amygdala-CEN abnormalities, rather than secondarily reflecting anxiety-related processes in these patients. In other words, our findings likely speak to a more generally-relevant disruption in emotion/cognition circuit interactions observed separately across different clinical groups, and which is relevant for understanding chronic pain. Importantly, in the context of chronic pain these are related to aspects of pain catastrophizing rather than more generally affective distress.

Previous work has found positive associations between pain catastrophizing and neural responses in bilateral lateral prefrontal and parietal cortices, as well as the extended amygdala, in patients with fibromyalgia in response to painful stimulation [28]. In healthy subjects, activation of bilateral dorsolateral prefrontal and parietal cortices in response to mild pain has been found to correlate positively with catastrophizing scores [53]. These results are therefore consistent with the relationship we observed in the current study between greater abnormal amygdala-CEN connectivity and greater pain catastrophizing. Importantly, we found here that helplessness and rumination drove the relationship between catastrophizing and exaggerated amygdala-CEN connectivity. A previous study on helplessness showed that perceived uncontrollability of pain stimuli in healthy subjects was associated with activation of the amygdala as well as the lateral prefrontal cortex [51]. The amygdala and lateral prefrontal cortex are also more active...
during anticipation of pain in patients with depression than in healthy controls, and
amygdala activation has also been associated with both the helplessness and rumination
subscales of the pain catastrophizing scale in patients with depression but not in healthy
controls [59].

Our finding extends this amygdalar-LPFC relationship to connectivity dynamics
during the resting state, suggesting that catastrophizing responses may shape neural
functioning and promote persistently abnormal cognitive-emotional interactions that
occur even in the absence of noxious stimulus. Unlike acute pain, which is often only
accompanied by an immediate and transient pain-induced state of negative affect, chronic
pain has secondary effects on cognitive-emotional interactions. These include
anticipating the consequences of persistent pain with regard to one’s long-term well-
being [44]. Pain catastrophizing may be a specific manifestation of a negative cognitive
bias in this appraisal process. Thus, the association we observed between chronic pain
and exaggerated amygdala-CEN connectivity appears to be independent of anxiety, but
parallels findings in anxious patients whose psychological distress is anxiety- instead of
pain-related. In other words, abnormally exaggerated amygdala-CEN connectivity may
represent a shared neural basis driving cognitive/emotional changes and distress
symptoms (e.g. catastrophizing) in anxiety and chronic pain, consistent with overlaps
between the cognitive theories for these disorders.

We also found that the normative pattern of amygdala subregional connectivity
with the DMN is disrupted in patients with chronic pain. In healthy participants, we
found that the DMN is more strongly connected to the BLA than the CMA. The BLA is
the major source of anatomical projections from the amygdala to the mPFC [3,33], and
has a modulatory effect on the mPFC [26,29,30]. Also, mPFC stimulation leads to
activation of BLA neurons [35] and indirectly inhibits CMA neurons through innervating
inhibitory interneurons connecting the BLA and CMA [47]. These amygdala-mPFC
neural interactions, which are thought to be involved in the acquisition and extinction of
learned fear [43], emotion preservation [57] and emotion appraisal [23], might underlie
the normal pattern of amygdala subregional connectivity with the DMN. Our finding that
this normal pattern is absent may thus reflect disturbed amygdala-mPFC interactions in
chronic pain. DMN disruptions, especially in the mPFC, are consistently found in chronic
pain patients during rest or experimental tasks [5–7,61]. Exaggerated mPFC-DMN
connectivity has been associated with pain catastrophizing rumination in chronic pain
patients [34]. Increased DMN-pgACC/mPFC connectivity is also related to self-initiated
compensatory processing for the anticipated increased pain in chronic low back pain
patients[36].

In interpreting these results, it is also important to consider a key strength and
limitation of this study. These patients were specifically selected to have low levels of
anxiety and depression, and none met criteria for a psychiatric disorder. We did so in
order to distinguish between pain-related abnormalities and those related to general affective distress. These patients were also free of psychotropic, opioids, antineuropathic pain medications or non-opioid analgesic medications (e.g. gabapentin and other anticonvulsants used for pain), and hence imaging data are not confounded by concurrent disorder or medication use. As such, these patients are not reflective of many of the chronic pain patients seen in clinical practice, who often have comorbid anxiety or depressive disorders, and are frequently on a variety of medications. Nonetheless, these factors represent important strengths for understanding the neural circuitry of chronic pain from a more mechanistic perspective. In sum, although the amygdala has long been a research focus in affective disorders, its role in chronic pain is understudied – despite the important interplay between affect and pain and broad similarities between clinical anxiety and chronic pain conditions. We found changes in amygdalar connectivity with two large scale networks important in cognitive and emotional operations, the CEN and DMN, and a relationship between abnormal amygdalar connectivity and pain-related affective distress (i.e. pain catastrophizing). Together, these data argue for an important role for the amygdala and its network-level interactions in chronic pain, and help inform a broader understanding of the relationship between chronic pain and other states of affective distress.

Acknowledgements

This study was funded by an International Association for the Study of Pain International Collaborative Research Grant 2008-9 to Julia Hush, an NIH P01 AT006651, K24 DA029262 and the Redlich Pain Research Endowment to Sean Mackey, and the Sierra-Pacific Mental Illness Research Education and Clinical Center (MIRECC) for Amit Etkin.

Conflict of Interest Statement

None of the authors have any financial relationships that may lead to a conflict of interest.

References


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Figure Captions

Figure 1 a. Seed regions of interest of amygdala subregions; BLA indicates basolateral amygdala; CMA, centromedial amygdala. b. Regions of interest of large-scale networks; CEN indicates fronto-parietal “central executive network”; DMN, medial prefrontal-medial parietal “default mode network”; SN, dorsal anterior cingulate-anterior insula “salience network”. c. Regions of Interest of expected targets for amygdala subregions resulting from a voxelwise one-way ANOVA contrasting the basolateral amygdala (BLA) and the centromedial amygdala (CMA) for the independent NKI sample (FDR q<.05). Hot color indicates regions have greater connectivity with BLA than CMA, and cool color shows regions connected more with CMA than BLA. Occ indicates occipital cortex; PPC, posterior parietal cortex; vmPFC/OFC, ventromedial prefrontal cortex/orbitofrontal cortex; FG, fusiform gyrus; M1/S1, primary somatosensory and motor cortices; STG/MTG, superior temporal gyrus/middle temporal gyrus; SFG/MFG, superior frontal gyrus/middle frontal gyrus; dACC, dorsal anterior cingulate cortex; and VTA/SN, ventral tegmental area/substantia nigra.

Figure 2 a. Connectivity of basolateral amygdala (BLA) or the centromedial amygdala (CMA), on right or left hemisphere, with the large-scale networks in patients with cLBP and healthy controls. b. Connectivity of BLA or the CMA, on right or left hemisphere, with the core nodes within CEN in patients with cLBP and healthy controls. c. A voxelwise ANOVA (group×amygdala seed×hemisphere of amygdala seed) showed the voxels within CEN with significant stronger amygdala connectivity in patients with cLBP, compared with healthy controls (p<0.05, FDR-corrected). Bars, mean values; Error bar, standard error of the mean; rBLA, right basolateral amygdala; IBLA: left basolateral amygdala; rCMA, right centromedial amygdala, ICMA, left centromedial amygdala.

Figure 3. Significant correlations between amygdala connectivity strength (z score) and Pain Catastrophizing Scale and pain intensity during past few days.
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<th>patients with eLBP(P) (N=17)</th>
<th>Healthy controls(HC) (N=17)</th>
<th>NKI sample (N=36)</th>
<th>P vs. HC Comparisons</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age(SE)</strong></td>
<td>37.4(2.5)</td>
<td>33.9(2.4)</td>
<td>34.5(1.7)</td>
<td>p=0.33</td>
</tr>
<tr>
<td><strong>Female(%)</strong></td>
<td>14(82%)</td>
<td>14(82%)</td>
<td>19(67%)</td>
<td>p&gt;0.99</td>
</tr>
<tr>
<td><strong>Right-handed(%)</strong></td>
<td>17(100%)</td>
<td>17(100%)</td>
<td>38(100%)</td>
<td>p&gt;0.99</td>
</tr>
<tr>
<td><strong>Education(year)</strong></td>
<td>15.2(0.6)</td>
<td>16.2(0.3)</td>
<td>NA</td>
<td>p=0.11</td>
</tr>
<tr>
<td><strong>STAI_T</strong></td>
<td>32.9(2.3)</td>
<td>30.1(1.5)</td>
<td>NA</td>
<td>p=0.30</td>
</tr>
<tr>
<td><strong>BAI</strong></td>
<td>7.3(1.8)</td>
<td>2.4(0.7)</td>
<td>NA</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td><strong>BDI-II</strong></td>
<td>5.9(1.3)</td>
<td>4.5(1.0)</td>
<td>NA</td>
<td>p=0.41</td>
</tr>
<tr>
<td><strong>PCS_total</strong></td>
<td>15.7(2.1)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>PCS_rumination</strong></td>
<td>6.7(1.0)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>PCS_helplessness</strong></td>
<td>6.1(1.1)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>PCS_magnification</strong></td>
<td>2.8(0.4)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

STAI-T, Trait form of the State-Trait Anxiety Inventory; BAI, Beck Anxiety Inventory; BDI-II, Beck Depression Inventory II; SF-MPQ, Short-Form McGill Pain Questionnaire; PCS, Pain Catastrophizing Scale; NKI: Nathan Kline Institute
Pain Catastrophizing Scale Total Score

Connectivity, Z score

R=0.622
P=0.008*

Pain Catastrophizing Scale Rumination Score

Connectivity, Z score

R=0.621
P=0.008*

Pain Catastrophizing Scale Helplessness score

Connectivity, Z score

R=0.612
P=0.009*

Pain Intensity during Past Few days

Connectivity, Z score

R=0.542
P=0.025*