Disrupted amygdala connectivity in chronic back pain reflects spontaneous pain perception

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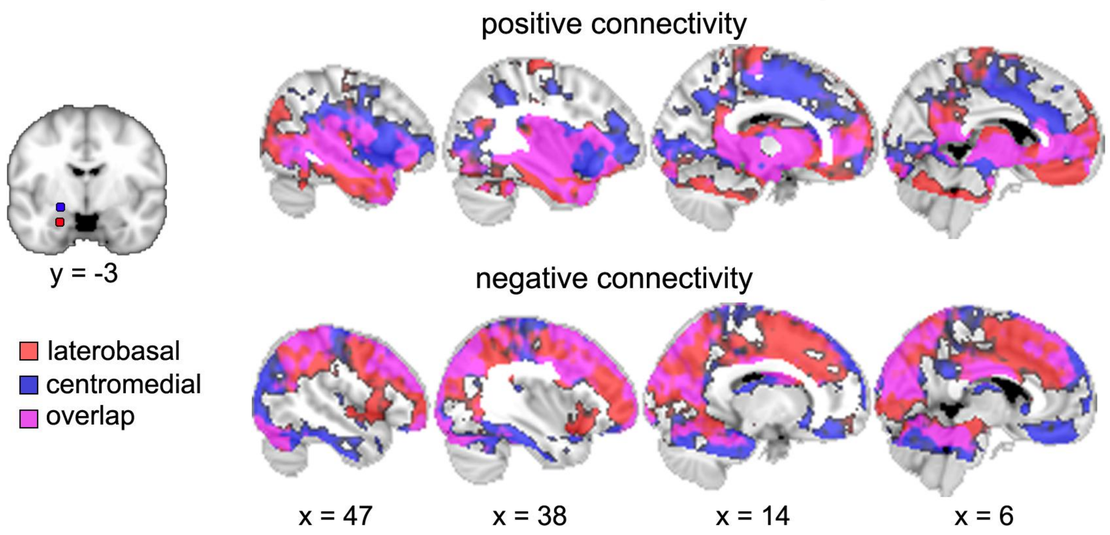
INTRODUCTION

- Chronic, spontaneous back pain (CBP) is known to engage brain systems involved in affective processing. Yet, how the amygdala – whose role in affect is well known -- contributes to pain processing is unknown.
- Here we examine the connectivity of 2 distinct nuclei of the amygdala – laterobasal (LB) and centromedial (CM), and study how it is related to evoked, and spontaneous pain during resting and task conditions.
- Further, we determine how nuclei connectivity is related to the development of chronic pain and immediate pain perception in subacute back pain (SBP) patients who have had back pain for less than 6 weeks.
- We find that disrupted BL connectivity in CBP correlates to spontaneous pain during rest, but not during task.
- We further demonstrate that BL connectivity is predictive of transition to chronic pain from a subacute state over 1 year, and that each nuclei is distinctly related changes in pain over a range of seconds.

METHODS

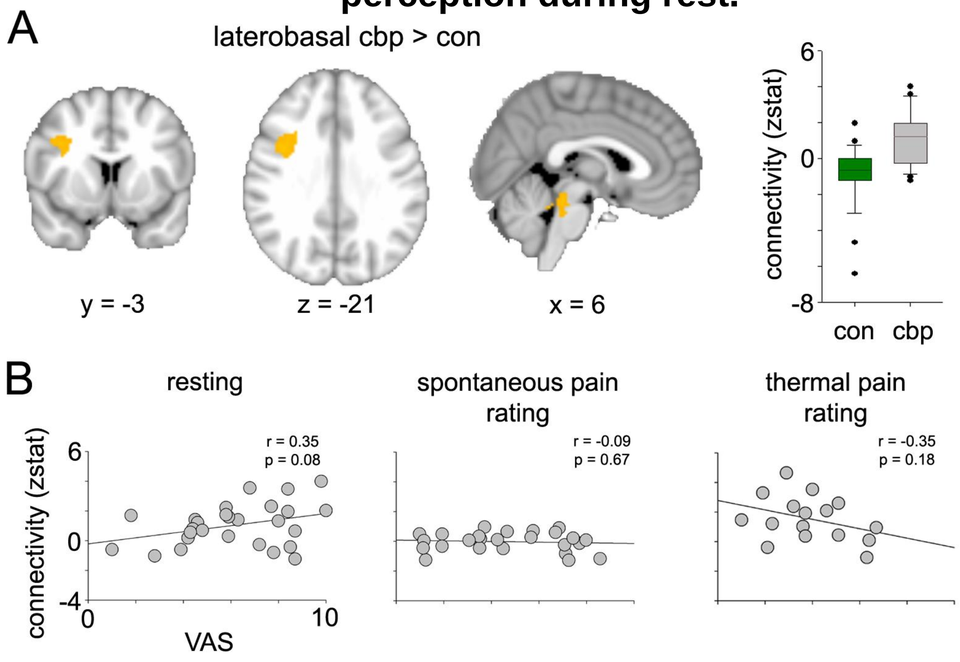
- CBP (N = 33, 12 females, 47± 9 y.o.) and SBP (N = 43, 21 females, 42 ± 10 y.o.) patients were scanned during, spontaneous pain rating, and/or thermal-evoked pain rating. Control (CON) subjects (N = 27, 12 females, 47 ± 9 y.o.) were scanned during rest and thermal-evoked pain rating.
- Whole –brain functional MR data was acquired with a 3T Siemens TIM Trio whole-body scanner with echo-planar imaging (EPI) capability using an 8-channel head coil TR = 2.5 sec, echo time TE = 30 ms. Most scans lasted 10 minutes, acquiring 244 volumes, while half of the resting scans were 12 minutes with 305 volumes. Images were preprocessed with FSL and included skull extraction, slice timing correction, bulk head motion correction, spatial smoothing, and a high-pass temporal filter (150 sec).
- Average time-series of the BOLD signal was extracted with a 6x6x6mm seed at left and right LB and CM nuclei, as determined by the standard Jeulich brain atlas. Connectivity during rest for each nuclei was determined using FSL FEAT (panel 1), and compared between CON vs CBP. Regional significant differences in connectivity during rest were then correlated to pain perception during resting, pain rating, and thermally-evoked pain scans (panel 2).
- Connectivity was also compared between subgroups of SBP patients whose pain would either persist (SBPp, N = 28) or recover (SBPr, N = 15) 1 year later, using a clinically relevant 30% pain decrease threshold. Receiver-operator curve (ROC) analysis was performed to determine how well amygdala connectivity predicts pain chronicity (panel 3).
- To relate LB and CM BOLD activity to online pain perception, z-scored BOLD time series were thresholded at 1 standard deviation to determine relevant BOLD signal peaks. Changes in pain perception were calculated by averaging pain ratings within multiple time windows before and after these peaks (panel 4).

1 Laterobasal and centromedial amygdala exhibit distinct functional connectivity



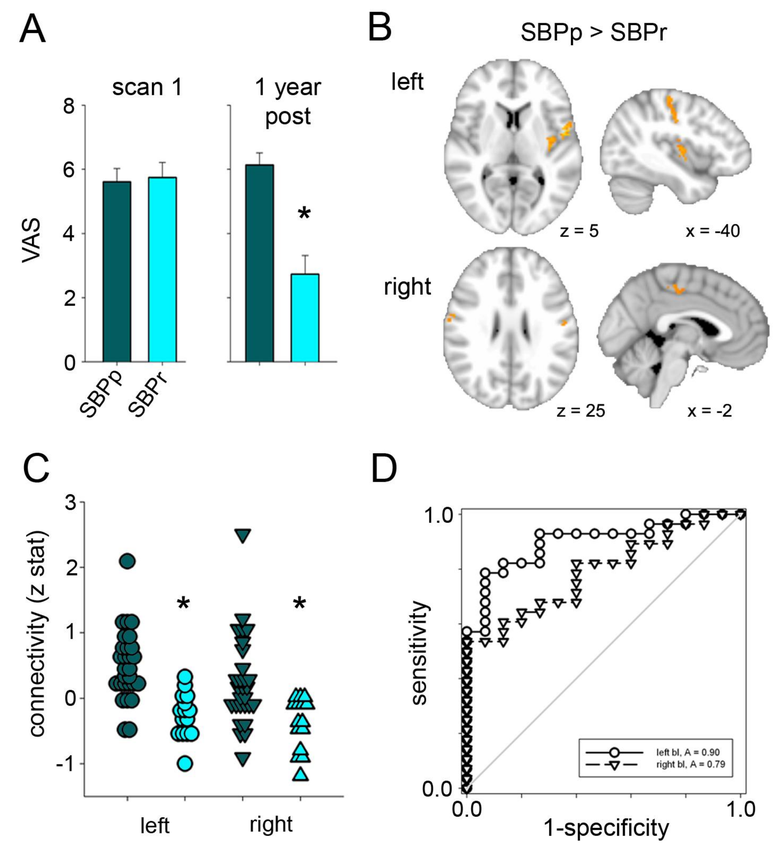
Functional connectivity was determined using a general linear model of the BOLD time series extracted from the LB and CM nuclei of the amygdala. Here we show the group average z-stat connectivity map for CON subjects, generated using ordinary least-sqares on subject z-stat maps. Maps are thresholded at zero (i.e. positive connectivity > 0) to demonstrate the distinct connectivity of the 2 nuclei.

2 CBP patients have disrupted connectivity related to pain perception during rest.



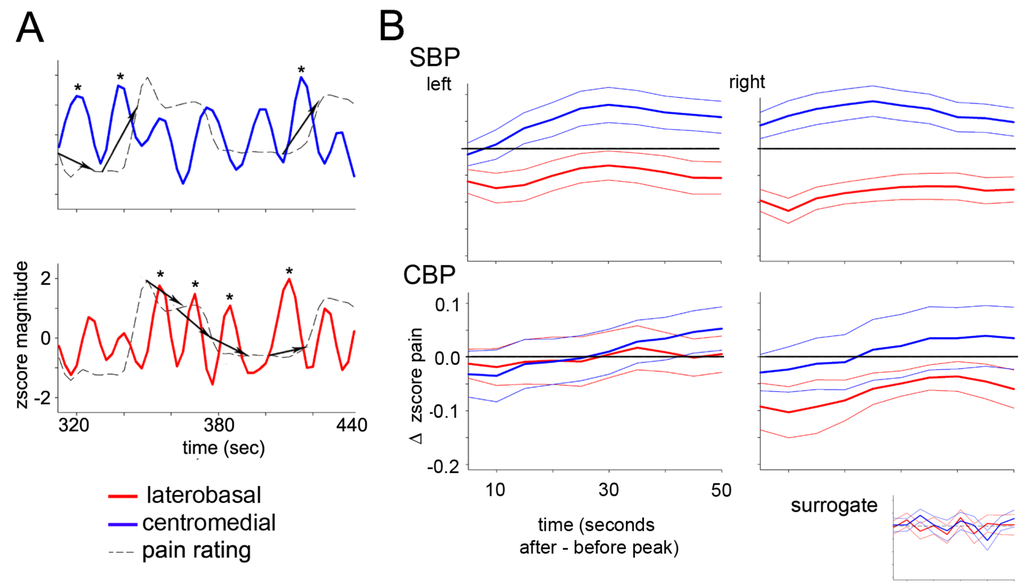
A) CBP patients exhibit increased connectivity from the right BL to middle frontal gyrus and brainstem (z > 3.0, cluster-corrected for multiple comparisons at p < 0.01), corrected for age and sex. B) Mean zstat values were extracted from the above map for CBP subjects, and correlated to pain perception under rest, spontaneous pain rating, and thermal pain rating. Each data point represents a single patient. Only during rest was correlation to pain perception trending significance, suggesting that task-related brain activity may mask amygdala communication related to pain perception.

3 Laterobasal amygdala connectivity is predictive of transition to chronic pain



A) Pain perception was significantly different between groups of SBP patients who experienced at least 30% decrease in their pain 1 year after onset (SBPr, N = 15), compared to those whose pain persisted (SBPp, N = 28). B) BL connectivity was calculated with Fishers z-transform of the Pearson correlation to all voxels in the brain, and thresholded specifically for each subject according to the threshold needed to maintain a global link density of 0.2. Significant differences in connectivity between groups was determined with FSL randomise, and a corrected p < 0.05. SBPp patients exhibited greater connectivity to the insula and sensorimotor cortex. C) We illustrate the same result as in (B) by showing average BL connectivity z-stat values for the map in (B) were significantly increased for SBPp patients. D) ROC analysis demonstrates that left and right BL connectivity to the insula and sensorimotor cortex are predictive of whether patients with new back pain will persist a year later. All * indicate p < 0.01.

4 Laterobasal and centromedial amygdala activity are distinctly related to immediate changes in pain perception



A) Example time series from 1 patient to illustrate the methodology. Relevant BOLD peaks in CM and BL were identified by thresholding the z-scored signal at 1 standard deviation. Changes in pain perception surrounding the peaks were calculated by subtracting the mean pain perception before the peak from that after the peak, for different time windows. Here, the directions of the arrows indicate the change in pain perception over a window of 20 seconds (10 before, 10 after the peak). B) Across most time windows, a peak in CM will be followed by an average increase in pain, while a peak in BL will be followed by an average decrease. However, this distinction is only present in patients with new pain (SBP), and not those with pain that has persisted for many years (CBP), suggesting the role of amygdala in pain perception changes over time. The inset is the result if the BOLD time series of the nuclei are shuffled, signifying the temporal relationship between nuclei peaks and immediate pain perception.

CONCLUSIONS

- Nuclei within the amygdala demonstrate distinct functional connectivity.
- Laterobasal connectivity is disrupted in patients with chronic back pain, and is related to spontaneous pain perception during rest.
- Back pain patients with new pain have laterobasal amygdala connectivity that predicts their recovery a year later.
- Peaks in nuclei activity are distinctly followed by increases or decreases in immediate pain, but only in patients with new pain, suggesting the transformative role of amygdala in pain perception during transition to a chronic state.
- Thus, distinct contributions of nuclei to pain processing may explain the lack of evidence concerning the role of amygdala in pain perception.

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