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Disrupted functional connectivity of the periaqueductal gray in chronic low back pain

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ABSTRACT

Chronic low back pain is a common neurological disorder. The periaqueductal gray (PAG) plays a key role in the descending modulation of pain. In this study, we investigated brain resting state PAG functional connectivity (FC) differences between patients with chronic low back pain (cLBP) in low pain or high pain condition and matched healthy controls (HCs). PAG seed based functional connectivity (FC) analysis of the functional MR imaging data was performed to investigate the difference among the connectivity maps in the cLBP in the low or high pain condition and HC groups as well as within the cLBP at differing endogenous back pain intensities. Results showed that FC between the PAG and the ventral medial prefrontal cortex (vmPFC)/rostral anterior cingulate cortex (rACC) increased in cLBP patients compared to matched controls. In addition, we also found significant negative correlations between pain ratings and PAG–vmPFC/rACC FC in cLBP patients after pain-inducing maneuver. The duration of cLBP was negatively correlated with PAG–insula and PAG–amygdala FC before pain-inducing maneuver in the patient group. These findings are in line with the impairments of the descending pain modulation reported in patients with cLBP. Our results provide evidence showing that cLBP patients have abnormal FC in PAG centered pain modulation network during rest.

1. Introduction

Chronic low back pain (cLBP) is one of the most common reasons for all physician visits in the USA and is a leading contributor to job-related disability and missed work (Chou and Shekelle, 2010; Hart et al., 1995). The etiology of cLBP is heterogeneous (Ehrlich, 2003). Non-specific cLBP, which represents the majority of cLBP patients, is characterized by a lack of recognizable pathology (Chou et al., 2007; Ehrlich, 2003; Savigny et al., 2009). Although cLBP is a serious health concern, treatment for cLBP has achieved limited success (Bogduk, 2004). Increasing evidence suggests a crucial role of central nervous system plasticity in the development and maintenance of non-specific cLBP. To develop more effective treatments, it is crucial to understand the underlying neurobiology of cLBP in the brain.

A prevailing theory in the pathogenesis of chronic pain is that the nociceptive afferents become sensitized in such a way that the signaling of these nociceptive afferents increases perceived pain disproportionately to the pain stimulus (Coderre et al., 1993). This process is facilitated by a dysfunction of the descending pain modulatory circuits (Woolf and Doubell, 1994; Zimmermann, 2001). The periaqueductal gray (PAG) is a key region involved in endogenous pain inhibition (Fields, 2004). Previous studies have shown that PAG stimulation can significantly inhibit behavioral responses to noxious stimuli in both animals (Mayer et al., 1971; Reynolds, 1969) and humans (Baskin et al., 1986; Hosobuchi et al., 1977). Recent studies have shown that the functional connectivity fluctuations and structural connectivity between the PAG and the ventral medial prefrontal cortex (vmPFC)/rostral anterior cingulate cortex (rACC) predicted mind wandering away from pain, i.e., spontaneous disengagement of attention from pain (Kucyi et al., 2013). The structural connectivity between these two regions also predicted individual difference in placebo analgesia (Stein et al., 2012). It is now believed that the brainstem (PAG) receives direct projections from regions within the limbic forebrain such as the anterior cingulate cortex (ACC) and limbic-related areas such as the insula and amygdala and modulates pain by descending modulation of the spinal cord neurons (Brooks and Tracey, 2005; Fields, 2004; Heinricher et al., 2009; Ploner et al., 2010; Tracey and Mantyh, 2007). A recent study has shown that the PAG is functionally connected to the vmPFC/rACC, insula and amygdala during resting state (Kong et al., 2010b).

The insula is a key region in pain process (Bernard et al., 1992; Chudler et al., 1993; Craig, 2002; Craig et al., 2000; Kong et al., 2013a; Kong et al., 2006; Schneider and Lidsky, 1981; Wiech et al., 2005). A

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previous study suggested that prestimulus functional connectivity between the insula and pain-modulatory brain regions (e.g., PAG) differed between physically identical trials that were rated as painful and trials perceived as non-painful (Ploner et al., 2010). The amygdala has a central role in regulating emotional responses during acute and persistent pain (Martikainen et al., 2013; Neugebauer et al., 2004). Given the close anatomical connectivity between the PAG–insula–amygdala and their role in pain perception and modulation (Ploner et al., 2010), it is possible that alterations in these pathways may also contribute to the development or maintenance of chronic pain. Recent neuroimaging studies have shown that cLBP is associated with alterations in resting state brain activity (Apkarian et al., 2009; Apkarian et al., 2004; Baliki et al., 2011; Baliki et al., 2006; Kobayashi et al., 2009; Tagliazucchi et al., 2010; Wasan et al., 2011). However, the role of the PAG and the associated networks detected by resting state fMRI in cLBP is still unclear. In the present study, we investigated PAG centered brain resting state functional connectivity (FC) differences between cLBP patients and matched HCs and FC differences when cLBP patients experienced different levels of pain intensity. We hypothesized that cLBP would be associated with abnormal FC between the PAG and other brain regions including the vmPFC, insula, and amygdala, given the close link between these regions and their role in pain modulation.

2. Materials and methods

We briefly describe the experimental procedures below. Please also see a previous published study (Kong et al., 2013b) for more details on the experimental procedure. The data have been used in this previous publication (Kong et al., 2013b), but the analytic methods used here do not overlap. In that study, we compared structure and function difference between the cLBP and controls using structural imaging data with morphometric analysis and resting state MRI data with degree centrality (DC) analysis (Kong et al., 2013b). Degree centrality is a measure of local network connectivity and identifies the most connected nodes by counting the number of direct connections to all other nodes (Buckner et al., 2009). There is no overlap on the results between the previous paper and the current paper.

2.1. Participants

Eighteen cLBP patients and 18 healthy controls, matched for age and gender, completed the study (see Table 1 for demographic details). The Institutional Review Board at Massachusetts General Hospital approved the study and all subjects gave written informed consent. All participants received compensation for their participation.

All subjects were clinically diagnosed with nonspecific cLBP with a duration of at least 6 months by a clinical evaluation, including the use of X-ray/MRI reports, when available. Only those patients meeting the Quebec Low Back Pain Task Force classification criteria for Class I or II (axial LBP with possible occasional radiation to the thigh, and no sensory or motor complaints) were enrolled (Werneke and Hart, 2004). Subjects were classified as having non-specific back pain (i.e., patients with specific diagnoses, non-spinal etiology, or radicular symptoms were not included in the study). Subjects were also excluded if they reported major systemic diseases or history of head injury or coma. cLBP patients were asked to rate their current pain using a visual analog scale (0 no pain, 10 maximum imaginable pain), both before and after the resting state fMRI scan. Endogenous back pain intensity during the resting state was defined as the average pain rating before and after the scan. The Brief Pain Inventory (BPI) was used to assess the severity of pain (the sensory dimension) and the impact of pain on daily feelings and functions (the reactive dimension) in the preceding week, i.e., a week before the experiment date (Cleeland and Ryan, 1994; Tan et al., 2004). Depressive symptoms were assessed using the Beck Depression Inventory (BDI-II) for all participants (Beck et al., 1961). All questionnaires were administered immediately prior to brain scanning. Healthy controls, matched for gender, age and race, were recruited in the community. All HC subjects were screened to ensure that they did not have back pain.

2.2. Clinical maneuvers

After the first resting state scan, cLBP patients were taken out of the scanner to perform exercises for a period lasting up to 10 min to exacerbate their endogenous lower back pain (see Fig. 1A). These exercises were tailored to each patient based on their report of which movements exacerbated their pain. The exercises determined to exacerbate low back pain included a set of slow movements such as sit-ups, lumbar flexion/extension, and lumbar rotation, where the subject rotated his or her body from side to side at a self-selected speed. During the screening, all subjects were asked to confirm that they could perform these exercises. If at the end of the first resting state scan the patient's cLBP pain rating was too strong (≥7 in 0–10 scale) and the patient was reluctant to perform exercises to enhance their pain experience, they were

Table 1
Demographics and clinical characteristics for cLBP patients and controls.

Patients									Controls			
ID	Gender	Age	Race	BDI	Duration (years)	Pain intensity (Low pain)	Pain intensity (High pain)	BPI (avg)	Gender	Age	Race	BDI
1	F	48	White	13	3	4.5	3.5	7	F	47	White	0
2	M	41	Asian	8	4	5	6.5	6	M	37	Asian	10
3	F	49	Black	30	8	6.5	8.75	6	F	50	Black	4
4	F	47	Hisp.	7	3	10	9.5	10	F	49	Black	0
5	F	23	White	1	10	3	6	3	F	26	White	11
6	M	27	White	0	10	4	6.5	3	M	30	White	0
7	F	23	White	4	3	2	6	3	F	23	White	3
8	M	38	White	0	2	4.5	6	4	M	39	White	7
9	M	25	Multi.	0	5	4.5	7	3	M	27	White	0
10	F	44	White	9	12	2.25	6	4	F	45	White	0
11	M	30	Multi.	5	10	2	5.5	9	M	34	White	4
12	F	31	Black	1	2	5.5	8.5	6	F	32	Black	3
13	F	47	Black	3	5	0	9.5	8	F	47	Black	0
14	F	46	Black	9	3	3	8.5	6	F	46	Black	3
15	F	46	White	8	10	3	6.5	5	F	47	White	0
16	F	34	Black	10	3	7	8.5	8	F	34	White	2
17	M	26	White	0	1.5	0.5	3	2	M	27	White	0
18	F	25	Asian	9	0.5	1	4	2	F	28	Asian	9

BDI = Beck Depression Inventory; BPI = Brief Pain Inventory; Pain Intensity = Average self-reported pain rating before and after resting state fMRI scanning. Multi. = Multiple; Hisp. = Hispanic; SE = standard error.