PAIN® 154 (2013) 24–33

www.elsevier.com/locate/pain

Default mode network connectivity encodes clinical pain: An arterial spin labeling study

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

ARTICLE INFO

Keywords:
Resting state networks
Chronic low back pain
Functional magnetic resonance imaging
Psychophysics
Human

ABSTRACT

Neuroimaging studies have suggested the presence of alterations in the anatomo-functional properties of the brain of patients with chronic pain. However, investigation of the brain circuitry supporting the *perception* of clinical pain presents significant challenges, particularly when using traditional neuroimaging approaches. While potential neuroimaging markers for clinical pain have included resting brain connectivity, these cross-sectional studies have not examined sensitivity to within-subject exacerbation of pain. We used the dual regression probabilistic Independent Component Analysis approach to investigate resting-state connectivity on arterial spin labeling data. Brain connectivity was compared between patients with chronic low back pain (cLBP) and healthy controls, before and after the performance of maneuvers aimed at exacerbating clinical pain levels in the patients. Our analyses identified multiple resting state networks, including the default mode network (DMN). At baseline, patients demonstrated stronger DMN connectivity to the pregenual anterior cingulate cortex (pgACC), left inferior parietal lobule, and right insula (rINS). Patients' baseline clinical pain correlated positively with connectivity strength between the DMN and right insula (DMN–rINS). The performance of calibrated physical maneuvers induced changes in pain, which were paralleled by changes in DMN–rINS connectivity. Maneuvers also disrupted the DMN–pgACC connectivity, which at baseline was anticorrelated with pain. Finally, baseline DMN connectivity predicted maneuver-induced changes in both pain and DMN–rINS connectivity. Our results support the use of arterial spin labeling to evaluate clinical pain, and the use of resting DMN connectivity as a potential neuroimaging biomarker for chronic pain perception.

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1. Introduction

Neuroimaging studies have provided considerable evidence indicating that chronic pain is associated with structural, functional, and neurochemical alterations distributed across multiple brain networks [49]. In spite of such progress, the identification of neural measures underlying the perception of clinical pain itself presents methodological hurdles. Unlike experimental pain (eg, exogenous heat stimulus applied to the skin), clinical pain (eg, endogenous pain in a patient suffering from low back pain) is difficult to elicit in a controlled manner. This fact makes it challenging to probe its neural correlates using classical "two-state subtraction" (ie, block- and event-related) neuroimaging designs [3]. Hence, alternative functional magnetic resonance imaging (fMRI) approaches have been adopted. For instance, our recent studies have reported an association between clinical pain intensity at the time of the scan and patterns of intrinsic brain connectivity [31,32]. While the observation that brain activity or connectivity covaries with clinical pain is intriguing, correlational analyses alone, in the absence of any concomitant experimental manipulation, do not allow us to conclusively determine whether these patterns are specific to the perception of clinical pain. Thus, the current approaches limit an understanding of the mechanistic relationships between brain function and chronic pain perception. Specifically, while potential neuroimaging markers for clinical pain have included resting brain

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http://dx.doi.org/10.1016/j.pain.2012.07.029

connectivity, its sensitivity to within-subject exacerbation of pain is unknown. In the present study, we assessed the effect of experimental exacerbation of clinical pain on connectivity of the default mode network (DMN) [11,39]. Our study builds on the growing evidence supporting altered brain processing within the DMN in chronic pain patients [5–7,13,32,48].

Patients with chronic low back pain (cLBP) and healthy controls were imaged with arterial spin labeling (ASL) *at rest* (ie, absent any stimulation during scanning) before and after a series of physical maneuvers aimed to exacerbate clinical pain in patients, but painless in controls [54]. While all patients received the same sequence of individually tailored maneuvers, the magnitude of change in clinical pain (from baseline) at the postmaneuver scan varied significantly across patients. As our recent studies have linked clinical pain intensity and resting DMN connectivity to insula [31,32], we hypothesized that within-subject experimentally induced *changes* in clinical pain would be associated with proportional *changes* in DMN-insula connectivity. Furthermore, the activity of DMN regions increases whenever a subject's attention is focused introspectively [11], is modulated by the behavioral relevance of a stimulus [17,45], and has been found to predict behavior in a variety of tasks [26,28,40]. Therefore, we also hypothesized that baseline DMN connectivity would predict the amount of pain change reported by patients following maneuvers.

2. Materials and methods

2.1. General procedures

We evaluated brain connectivity using resting ASL data acquired from both cLBP patients and healthy controls in a previously published study [54]. In that study, ASL was the imaging technique of choice because we wanted to quantify pain-induced regional cerebral blood flow (rCBF) changes in cLBP patients.

Full details of patients' characterization, stimulation protocol, scanning parameters, and psychophysical results have been previously published [54]. All participants in the study provided written informed consent in accordance with the Human Research Committee of the Massachusetts General Hospital. Briefly, we studied 16 patients with chronic low back and radicular pain (mean [95% confidence interval (CI)]: age = 47.4 years [CI 40–54.8]; pain duration = 6.24 years [CI 3.9–11.8]; baseline pain [0–20] = 6.4 [CI 2.8–5.9]; Oswestry Disability Index score = 35.8 [CI 30–41.6]; Pain Catastrophizing Scale score = 36 [CI 27.8–42.1]; % female = 69; % with neuropathic pain = 44), and 16 age- and gender-matched pain-free healthy controls (age = 46.7 years [CI 40.1–53.2], % female = 69). None of the patients were being treated with opioid medications. Inclusion criteria for cLBP patients included a discogenic component to their pain, as determined by study physician (A.D.W.), with the use of history, physical examination, and review of a lumbar MRI. All subjects participated in 2 imaging visits. During both imaging visits, 2 6-minute pulsed ASL scans were performed, before and after 12 clinical maneuvers ("clinical maneuvers" visit) or 12 heat pain stimuli ("heat pain" visit). The maneuvers (eg, straight leg raise or pelvic tilt) were individually tailored to elicit a pain rating of ~10–11 ("moderate") or ~14–15 ("strong") on a 0–20 numerical rating scale in patients, but were painless in the controls. Ratings were expressed on the Gracely Box Scale [22], which is a ratio scale particularly suited and sensitive to determining the degree of change in pain within an experimental session.

For both patients and controls, heat pain stimuli were also individually tailored to elicit a "moderate" or a "strong" pain sensation. While the ASL data from the heat pain visit were included in the independent component analysis (see below) in order to provide a more solid estimation of the DMN, these were not included in any other step of the analysis because, unlike the clinical maneuvers session, the heat pain session, A) did not produce a clinically significant increase in patients' pain (19.4%, vs 34.3% in the clinical maneuvers visit [54]); and B) exhibited lower dynamic range in pain scores at baseline (0–9/20, vs 1–15/20 in the clinical maneuvers visit), thus limiting our inference power in all analyses.

2.2. Imaging acquisition and analyses

ASL time series were acquired on a 3T Siemens TIM Trio MRI System (Siemens Medical, Erlangen, Germany), equipped with a 32-channel head coil, and using a PICORE-Q2TIPS sequence [30] TR/TE/TI1/TI2 = 3000/13/700/1700 ms, voxel size = 3.515 * 3.515 * 6.25 mm, number of slices = 16). A high resolution MPRAGE scan (TR/TE = 2300/3.39 ms, voxel size 1 * 1 * 1.33 mm) was also acquired to optimize spatial normalization to the MNI152 standard space.

ASL data preprocessing and analyses were performed using a combination of packages including FSL (Oxford Centre for Functional MRI of the Brain's [FMRIB's] Software Library, http://www.fmrib.ox.ac.uk/fsl) and Freesurfer (http://www.surfer.nmr.mgh.harvard.edu/). The first tag-control pair was discarded to allow the MR signal to reach steady-state equilibrium. The remaining volumes were skull-stripped using BET (Brain Extraction Tool) and motion-corrected using MCFLIRT (Motion Correction using FMRIB's Linear Image Regression Tool). Perfusion-weighted time series were obtained by pair-wise subtraction of adjacent tag and control images [1]. These time series were then registered to their respective Freesurfer-reconstructed high resolution anatomical volume using BBREGISTER [23], and then to the MNI152 standard space using FLIRT. The spatially normalized perfusion-weighted time series were finally high-pass filtered (cutoff = 0.008 Hz) and spatially smoothed (full width at half maximum = 5 mm).

All the preprocessed ASL data obtained (for all subjects and for both visits) were concatenated to create a single 4D dataset. A probabilistic independent component analysis [8] was performed using MELODIC (Multivariate Exploratory Linear Optimized Decomposition into Independent Components) on this concatenated 4D dataset in order to identify the resting state networks (RSNs). In order to select the parameter set that yielded the most reliable estimation of RSNs, this analysis was performed with different numbers of components (25, 40, or 50), using only the clinical maneuvers visit data or both visits' data, and with or without low-pass filtering. Using goodness-of-fit tests [16] with previously defined templates generously provided by Beckmann et al. [8], we established that using 25 components on the low-pass filtered data from both imaging sessions yielded the most consistent RSN estimation. The subject-specific temporal dynamics and associated spatial maps of the DMN were calculated for both pre- and post-maneuver scans using the dual regression approach [20,58]. In this technique, group-level spatial maps were used as a set of spatial regressors in a general linear model (GLM) to identify the individual subjects' time course associated with each group-level map. These time courses were then variance normalized, and used as a set of temporal regressors in a GLM, to find subject-specific maps associated with the different group-level independent components. In this GLM, explanatory variables also included time courses from ventricles and white matter (but not global signal) as covariates of no interest. The dual regression technique is widely used, and has moderate-to-high test-retest reliability [58]. Subject-specific DMN maps were compared across groups as well as across time points (post-pre maneuvers) using unpaired and paired *t*-tests, respectively. We also evaluated the association between connectivity and pain intensity, as well as changes in both. For the former, we performed a regression analysis with baseline DMN connectivity and baseline pain as regressor of interest. For

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