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

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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.

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...
connectivity, its sensitivity to within-subject exacerbation of pain is unknown. In the present study, we assessed the effect of experimen-
tal 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 pain-
less 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 
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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 
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 previ-
ously published [54]. All participants in the study provided written 
informed consent in accordance with the Human Research Commit-
tee 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 disco-
genic 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, 6 6-minute pulsed ASL scans were performed, 
before and after 12 clinical maneuvers (“clinical maneuvers” vis-
its) 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 determi-
nching the degree of change in pain within an experimental session.

For both patients and controls, heat pain stimuli were also indi-
vidually 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 maneu-
vers 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 maneu-
vers 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 Sys-
tem (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 x 1 x 1.33 mm) was also ac-
quired 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 Func-
tional MRI of the Brain’s [FMRIB’s] Software Library, http:// 
www.fmrib.ox.ac.uk/fsl) and Freesurfer (http://www.surfer.nmr. 
mg.h.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 Registration 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 concate-
nated 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 dif-
ferent 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 esti-
mation. 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 individ-
ual 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 compo-
ients. 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 
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
the latter, we first calculated DMN connectivity “change maps” (post-pre maneuvers) by subtracting parameter estimate maps for the premaneuvers scan from the maps corresponding to the postmaneuvers scan, for each subject. We also summed the associated variance images. These were entered into a regression model with regressor of interest being change in pain (post-pre maneuvers pain ratings). In order to test if significant clusters from this change-score regression were influenced by baseline connectivity or pain, we performed a regions of interest (ROI)-based multiple linear regression analysis, which allowed us to include both baseline pain and connectivity values as regressors of no interest. Finally, we evaluated the predictive capacity of baseline DMN connectivity, using a regression model with change in pain as regressor of interest, and baseline pain as regressor of no interest. Follow-up ROI-based multiple linear regression further allowed us to correct the imaging results for baseline pain, average pain rating reported during the maneuvers, and duration of pain. For ROI analyses, connectivity values \((z\) stats\) were averaged across all voxels from clusters of interest.

The group-level analyses were performed using FLAME (FMRIB’s Local Analysis of Mixed Effects) stage 1, with a voxel-wise cluster forming threshold of \(Z = 2.3\) and a (corrected) cluster significance threshold of \(P = 0.05\). Finally, as the DMN–insula connectivity was found to be higher than in controls in patients with a different chronic pain condition (fibromyalgia) [32], and also to correlate with clinical pain in that study as well as this one (see below), the baseline DMN connectivity maps were also compared across groups with a direct search restricted to the insula. This analysis was performed with an uncorrected threshold of \(P < 0.005\) and a minimum cluster size of 5 voxels, a procedure previously used in several imaging studies [38,46].

3. Results

Following probabilistic independent component analysis on the concatenated ASL data, we were able to identify the majority of RSNs reported in previous blood oxygen level-dependent (BOLD) fMRI resting state studies, including the default mode, medial...
and lateral visual, salience, right and left frontoparietal control, and dorsal attention networks (Fig. 1). We confirmed that the component identified as the DMN by the goodness-of-fit tests included brain areas previously noted as “core regions” of the DMN [11]: medial prefrontal cortex, posterior cingulate cortex/precuneus, inferior parietal lobule, and lateral temporal cortex.

Fig. 2. Default mode network (DMN) connectivity is altered in chronic low back pain (cLBP) patients. Pregenual anterior cingulate cortex (PgACC), left inferior parietal lobule (L IPL) and R insula are more connected to DMN in cLBP than in controls at baseline (A, left column; B). In patients, DMN–pgACC connectivity is negatively correlated with clinical pain at baseline (B, right column) and is disrupted after the maneuvers (A, top row; C). After the maneuvers, all patients exhibited a reduction in DMN-pgACC connectivity, except for the 3 single patients (empty circles) who did not report an increase in pain.
Baseline (premaneuvers) DMN connectivity, assessed from resting ASL data using dual regression independent component analysis, was contrasted between patients and healthy controls (Fig. 2, Tables 1 and 2). Whole-brain analyses revealed that, compared to controls, cLBPs patients demonstrated stronger baseline DMN connectivity to the pregenual anterior cingulate cortex (pgACC), a component of the medial prefrontal cortex, as well as to the left inferior parietal lobe (Fig. 2B, left). The strength of DMN–pgACC connectivity within this cluster was negatively correlated with clinical pain at baseline ($r = -0.73$, $P = 0.001$; Fig. 2B, right). Furthermore, a direct search also revealed a stronger DMN–insula connectivity in the patients (Fig. 2B, bottom).

Experimental maneuvers, aimed at exacerbating clinical back pain in cLBPs patients, on average significantly increased pain in these patients ($P = 0.005$). Patients who reported clinical pain increase ($n = 13; \Delta = 2.5 \pm 1.9$, on a scale of 0–20) exhibited a reduction in resting DMN connectivity to the medial prefrontal cortex, including pgACC, whereas controls, for whom the maneuvers were painless, instead demonstrated an increase. The interaction between TIME (post- vs premaneuvers) and GROUP (cLBPs vs controls) (Fig. 2C, left) revealed a statistically significant cluster within a near-identical region that demonstrated stronger DMN–pgACC connectivity at baseline (Fig. 2B, left). An examination of the individual connectivity change scores (Fig. 2C, right) revealed that while no healthy controls demonstrated decreasing DMN–pgACC connectivity, cLBPs patients demonstrated decrease in DMN–pgACC connectivity following physical maneuvers in all but 3 patients (empty circles). Intriguingly, these 3 patients were the only ones who actually reported a slight decrease, rather than an increase, in clinical pain at the end of the maneuvers (see below for more detail).

In order to determine whether DMN connectivity covaried with clinical pain intensity in cLBPs patients in regions other than the pgACC, we performed a whole-brain regression analysis on the
Table 2
Unpaired (cLBP vs controls) and paired (post-pre maneuvers) t-tests.

<table>
<thead>
<tr>
<th>Cluster size (# voxels)</th>
<th>Cluster P-value</th>
<th>Peak z Score</th>
<th>x (mm)</th>
<th>y (mm)</th>
<th>z (mm)</th>
<th>Anatomical location</th>
</tr>
</thead>
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<tr>
<td><strong>cLBP &gt; Controls, baseline DMN connectivity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>576</td>
<td>0.00152</td>
<td>4.19</td>
<td>–4</td>
<td>40</td>
<td>16</td>
<td>Medial prefrontal cortex (pregenual anterior cingulate cortex)</td>
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<tr>
<td>335</td>
<td>0.0384</td>
<td>3.74</td>
<td>–38</td>
<td>–56</td>
<td>28</td>
<td>L Inferior parietal lobule</td>
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<tr>
<td>29</td>
<td>n/a</td>
<td>3.72</td>
<td>36</td>
<td>–18</td>
<td>2</td>
<td>R Insula*</td>
</tr>
<tr>
<td><strong>cLBP (only patients experiencing pain increase), postmaneuvers &gt; baseline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>398</td>
<td>0.00428</td>
<td>4.23</td>
<td>–14</td>
<td>46</td>
<td>–4</td>
<td>Medial prefrontal cortex (pregenual anterior cingulate cortex)</td>
</tr>
<tr>
<td><strong>Controls &gt; cLBP, postmaneuvers &gt; baseline</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>319</td>
<td>0.0166</td>
<td>4.22</td>
<td>4</td>
<td>40</td>
<td>12</td>
<td>Medial prefrontal cortex (pregenual anterior cingulate cortex)</td>
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<tr>
<td>288</td>
<td>0.029</td>
<td>3.96</td>
<td>–14</td>
<td>44</td>
<td>–2</td>
<td>Medial prefrontal cortex (pregenual anterior cingulate cortex)</td>
</tr>
<tr>
<td>263</td>
<td>0.046</td>
<td>3.77</td>
<td>16</td>
<td>60</td>
<td>2</td>
<td>Frontal pole</td>
</tr>
</tbody>
</table>

cLBP, chronic low back pain; DMN, default mode network; R, right; L, left.
* Direct (uncorrected) search.

Fig. 3. Connectivity strength between right insula and default mode network (DMN–rINS) correlates with clinical pain. Clinical pain correlated with DMN–rINS connectivity at baseline (A). Maneuvers-induced changes in pain correlated with changes in DMN–rINS connectivity (B). These analyses identified clusters overlapping over the right mid-insula (C). The r values displayed in the scatter plots were computed from data extracted from significant clusters in the whole brain regression analyses, and are reported here for illustrative purposes.
baseline DMN connectivity maps. The regressor of interest was clinical pain intensity. We found a single statistically significant cluster localized to the right mid-insula, extending slightly towards the adjacent putamen (Fig. 3A; Table 3). As expected given the significant, negative relationship between DMN–pgACC connectivity and pain, baseline DMN–rINS connectivity was also negatively correlated with DMN–pgACC connectivity in patients ($r = -0.60, P = 0.014$). However, a partial correlation analysis between baseline pain, DMN–rINS, and DMN–pgACC connectivity revealed that when controlling for baseline pain, DMN–rINS and DMN–pgACC were no longer associated ($r = 0.06, P = 0.83$). This suggests that the correlation between these connectivity patterns is significantly associated with the presence of ongoing clinical pain. Indeed, resting DMN–rINS and DMN–pgACC were not correlated in pain-free controls ($r = 0.04, P = 0.896$), further supporting this interpretation.

In order to assess whether within-session, maneuver-induced changes in mechanical low back pain were associated with changes in DMN connectivity, a second whole-brain regression analysis was performed on the within-session (post-pre maneuvers) DMN connectivity “change maps,” using change score in clinical pain (post-pre maneuvers) as regressor. This analysis yielded another single cluster (Fig. 3B; Table 3) on the right mid-insula, overlapping (Fig. 3C) with the insular component of the cluster observed in the baseline regression analysis. In order to ensure that the relationship between change in pain and change in connectivity was not driven by a significant correlation between baseline and change scores (suggesting, for example, a regression to the mean), we performed a follow-up ROI-based regression analysis using change in DMN–rINS connectivity as the dependent variable, change in pain as the independent variable, and including both baseline clinical pain and cluster connectivity as covariates of no interest. This analysis confirmed that, even after controlling for the strong relationship between baseline and change scores, changes in pain were still significantly ($P = 0.001$) associated with changes in DMN–insula connectivity.

In order to determine whether baseline DMN connectivity predicted changes in clinical pain, we performed another whole-brain regression analysis on the baseline DMN connectivity maps, using pain change scores (post-pre maneuvers) as regressor of interest, and baseline pain ratings as covariates of no interest. Indeed, baseline connectivity between DMN and posterior cingulate/retrosplenial regions of the DMN and the rest of the DMN reported the most severe pain increase after the maneuvers. rINS, right insula; IPL, inferior parietal lobule; PCC, posterior cingulate cortex; RSp, retrosplenial cortex; LTC, lateral temporal cortex.

**Table 3**

<table>
<thead>
<tr>
<th>Cluster size (# voxels)</th>
<th>Cluster P-value</th>
<th>Peak z Score</th>
<th>x (mm)</th>
<th>y (mm)</th>
<th>z (mm)</th>
<th>Anatomical location</th>
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<tr>
<td>cLBP, DMN connectivity vs pain at baseline</td>
<td>254</td>
<td>0.0412</td>
<td>3.8</td>
<td>32</td>
<td>6</td>
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<tr>
<td></td>
<td>254</td>
<td>0.0199</td>
<td>3.42</td>
<td>40</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>cLBP, change in DMN connectivity vs change in pain (post-maneuvers minus baseline)</td>
<td>254</td>
<td>0.0199</td>
<td>3.38</td>
<td>48</td>
<td>14</td>
<td>0</td>
</tr>
</tbody>
</table>

DMN, default mode network; cLBP, chronic low back pain; R, right.

**Fig. 4.** Default mode network (DMN) baseline connectivity predicts sensitization to the clinical maneuvers. Patients exhibiting the strongest connectivity between posterior regions of the DMN and the rest of the DMN reported the most severe pain increase after the maneuvers. rINS, right insula; IPL, inferior parietal lobule; PCC, posterior cingulate cortex; RSp, retrosplenial cortex; LTC, lateral temporal cortex.
nial cortex (PCC/RSp), right inferior parietal lobule (IPL), and left IPL extending into the lateral temporal cortex (LTC), predicted increasing pain following the maneuvers (Fig. 4; Table 4). The predictive value of these baseline DMN connectivity patterns was statistically significant even when correcting for baseline pain, average pain rating reported during the maneuvers, and duration of pain in multiple regression analyses (PCC: b = 1.76, P < 0.010; left IPL/LTC: b = 1.56, P < 0.001; right IPL: b = 2.36, P < 0.001). As expected given the above-mentioned observation that DMN-insula connectivity encoded intensity of clinical pain, we further observed that baseline DMN connectivity within these regions also predicted maneuvers-induced changes in DMN-insula (although, after correcting for baseline DMN-insula connectivity, baseline pain and average pain reporting during the brief maneuvers, only the right IPL results met strict criteria for statistical significance; P = 0.026; left IPL/LTC: P = 0.09; PCC: P = 0.09).

4. Discussion

In this study, DMN encoded the intensity of clinical pain both at baseline and in response to maneuvers aimed at exacerbating clinical pain levels, and predicted postmaneuver lingering pain in cLBP patients. Our connectivity analyses used ASL fMRI data, and revealed that greater clinical pain at baseline was associated with greater DMN connectivity with the insula (a region known to be involved in pain processing [2]), and less connectivity with the pgACC (a region involved in pain inhibition [9,36,53]).

Notably, the DMN–rINS result was similar to that reported in our previous study investigating the association between clinical pain and DMN connectivity, but in a different chronic pain population (fibromyalgia) [32]. The observation that a common neuroimaging metric appears to encode clinical pain in different patient populations raises the intriguing possibility that such measures may reflect a general feature of chronic pain. This study, however, does not simply replicate previously published findings in a different patient population. In the present experiment, we did not limit ourselves to examine baseline correlations alone and implemented a paradigm with clinical pain exacerbation in order to test the sensitivity of such metrics to within-subject changes in clinical pain. This approach allowed us to observe that greater change in pain following physical maneuvers was associated with greater change in DMN–rINS. This result complements our observation that reduction in clinical pain induced by a 4-week nonpharmacological intervention in fibromyalgia patients was accompanied by a reduction in DMN–insula connectivity [31]. In sum, our study demonstrated that greater baseline clinical pain in cLBP patients was associated with greater DMN–rINS connectivity, and greater increase in mechanical low back pain following physical maneuvers was associated with greater increase in DMN–rINS connectivity. Altogether, these results support resting DMN–insula connectivity as a state-specific neuroimaging marker for clinical pain. Such association has now, in fact, been reproduced in different patient populations, and linked to within-subject increases and decreases in clinical pain, over both short and long time periods.

The fact that patients exhibited higher DMN–pgACC connectivity at baseline might reflect compensatory mechanisms taking place in preparation for the anticipated maneuver-induced pain increase. This compensatory mechanism would appear to be pain-protective, as the more pgACC connectivity at baseline, the lower the baseline clinical pain. While other subregions of the medial prefrontal cortex have been proposed to have a pain-facilitatory role [42], the pgACC has been extensively associated with antinoceptive functions [9,36,53], likely exerted through its descending projections to the periaqueductal gray matter [52]. Our results further extend these observations by identifying a novel mechanism (pgACC connectivity with the DMN) through which pgACC might produce its pain-protective effects. Baliki and colleagues [7], in a seminal study, observed that DMN dynamics were disrupted in cLBP patients during the performance of a visual task, suggesting that this network is affected by a chronic pain state. Our study extends this finding, and establishes a direct linkage between DMN disruption and perceptual aspects of clinical pain in a chronic pain population.

Despite using individually calibrated maneuvers to elicit similar pain responses in all patients, the amount of change in clinical pain (compared to baseline) reported by patients after the stimulation was quite variable. As the post- vs premaneuver change in pain was predicted by neither the baseline pain nor by the average pain intensity reported during the brief maneuvers themselves, it appears that some patients were more susceptible to developing sustained clinical pain in response to a comparable stimulation paradigm. Since the activity of DMN regions 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], we hypothesized that baseline DMN connectivity would predict pain change following maneuvers. As such, we observed that baseline connectivity between DMN and PCC/RSp, right IPL, and left IPL/LTC predicted increasing pain following the maneuvers (Fig. 4; Table 4).

Prestimulus brain activity/connectivity and sensitivity to stimuli or task performance have been the object of investigation in several studies [4,14,21,24,47,55]. In the field of pain, recent studies on healthy volunteers receiving experimental pain stimuli have found that baseline activity of the anterior cingulate cortex and the insula predicted higher pain sensitivity in response to a subsequently presented experimental stimulus [10,38], whereas the baseline activity of the periaqueductal gray and the functional connectivity between this midbrain region and the insula predicted lower pain sensitivity [38]. The present results significantly extend these findings, by providing evidence that a different neuroimaging metric, specifically, resting DMN connectivity, can predict susceptibility to lingering clinical pain. Notably, our study on prediction of clinical pain did not identify regions common to the studies investigating prediction of experimental pain, possibly indicating that entirely different neurobiological underpinning may mediate...
hypothesized to experimental and clinical pain. While at this time the mechanisms by which increased DMN connectivity predicts stronger clinical pain exacerbations eludes a clear explanation, it is tempting to speculate that stronger connectivity within the DMN, a network thought to be involved in introspection and self-oriented cognition [11], might reflect hyper-attention to clinical pain. Attentional focus, in fact, has been widely shown to affect pain perception [29,41,50], and hyper-attention to pain has been discussed as a potential aberrant mechanism in chronic pain, including low back pain, patients [15]. Furthermore, the fact that DMN connectivity has also been implicated in negative affect [44] suggests that affective processing may also play a role in promoting lingering pain after the stimulation period.

ASL has been recently applied to evaluate pain processing [25,33–35,43,54,56]. While a handful of studies have recently demonstrated that connectivity analyses can be successfully employed on ASL data [12,18,19,37,51,57], to the best of our knowledge, no such study has been published in the field of pain. Several features of the ASL technique confer potential advantages over BOLD [1], which might be beneficial in connectivity analyses. First, while the BOLD signal exhibits increasing noise at low frequencies, the power spectrum of the ASL signal is flat. This suggests that the estimation of DMN connectivity, which demonstrates peak power at relatively low frequencies (0.008–0.1 Hz), should be less affected by low frequency drifts, likely of nonneural origin, when estimation is made from ASL data. Second, whereas BOLD is dominated by venous signal, ASL is primarily sensitive to signal changes localized at the level of the capillary bed, and therefore evaluates activity more closely co-localized with neuronal and synaptic physiology. The unique possibility to perform functional connectivity analyses as well as to quantify regional cerebral blood flow from the same dataset demonstrates that ASL can be a very powerful and versatile technique for the investigation of brain correlates to chronic pain and other disorders of the central nervous system.

When comparing our ASL-based connectivity results with clinical pain-induced changes in rCBF previously reported [54], we noted that nearby medial prefrontal cortex (MPFC) and insula sub-regions were implicated in both analyses. For instance, pain-inducing maneuvers reduced DMN-MPFC connectivity and increased MPFC rCBF. While these results may seem at odds, they are not, as MPFC activation during clinical pain, a phenomenon also observed in other chronic pain populations [6,42], might be the mechanism responsible for altered resting-state connectivity (an analogous interaction between functional connectivity and activation was observed by our laboratory for primary sensorimotor cortex [27]). While connectivity analyses revealed baseline differences between patients and controls, rCBF analyses did not [54]. Therefore, the observed group differences in connectivity appear to be at least partially independent from and complementary to the results of our rCBF analyses. Future studies will need to specifically dissect the mechanisms underlying the ostensibly complex relationship between connectivity changes and activation induced by pain.

Several limitations should be taken into consideration when interpreting the results from our study. First, the brain coverage of our ASL analyses did not include caudal structures such as the brainstem and the cerebellum. As such, in the present experiment we could not investigate the activity of other regions that are crucial for pain processing and/or modulation. Future studies will be performed focusing on such regions. Furthermore, while every attempt was made to individually calibrate the clinical maneuvers, patients exhibited variability in their responses to the maneuvers. Although it could be argued that such variability might in part explain the differences in lingering pain observed at the end of the stimulation period, our results show that baseline DMN connectivity predicted lingering pain even after correcting for the pain reported after the maneuvers (as well as the baseline pain and pain duration).

In conclusion, we show that resting DMN connectivity encodes the severity of clinical pain, is sensitive to within-subject exacerbation of such pain, and can predict lingering clinical pain. In the future, studies will need to investigate the clinical implications of these observations, for instance, by evaluating whether DMN connectivity can be used as a tool to predict which sub-clinical or acute pain patients go on to develop chronic pain.

Conflict of interest statement

The authors of the article declare that they have no competing financial interests.

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