



# Identifying brain nociceptive information transmission in patients with chronic somatic pain

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## Abstract

**Introduction:** Recent advances regarding mechanisms of chronic pain emphasize the role of corticolimbic circuitry in predicting risk for chronic pain, independently from the site of injury-related parameters. These results compel revisiting the role of peripheral nociceptive signaling in chronic pain. We address this issue by examining what information brain circuitry transmits regarding the intensity of chronic pain and how this information may be related to a common comorbidity, depression.

**Objectives:** To identify what information brain circuitry transmits regarding intensity of chronic somatic pain.

**Methods:** Resting-state functional magnetic resonance imaging was used in a large group of patients with chronic pain ( $n = 40$  chronic back pain and  $n = 44$  osteoarthritis patients), and in comparison with healthy subjects ( $n = 88$ ). We used a graph theoretical measure, degree count, to investigate voxelwise information sharing/transmission in the brain. Degree count, a functional connectivity-based measure, identifies the number of voxels functionally connected to every given voxel. Subdividing the chronic pain cohort into discovery, replication, and also for the overall group, we show that only degree counts of diencephalic voxels centered in the ventral-lateral thalamus reflected intensity of chronic pain, independently of depression.

**Results:** Pain intensity was reliably associated with degree count of the thalamus, which was correlated negatively with components of the default mode network and positively with the periaqueductal gray (in contrast to healthy controls). Depression scores were not reliably associated with regional degree count.

**Conclusion:** Collectively, the results suggest that, across 2 types of chronic pain, nociceptive-specific information is relayed through the spinothalamic pathway to the lateral thalamus, potentiated by pronociceptive descending modulation, and interrupting cortical cognitive processes.

**Keywords:** Chronic back pain, Osteoarthritis, Functional connectivity, Graph theory, Thalamus, Default mode network, Nociception, Depression

## 1. Introduction

Recent human neuroimaging studies and complimentary rodent model experiments provide accumulating evidence

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that brain anatomical and functional properties provide risk for development of chronic pain and reorganize the brain into a chronic pain state. Specifically, functional and anatomical properties of the corticolimbic circuitry (comprising medial prefrontal cortex (mPFC), accumbens, amygdala, and hippocampus) commonly associated with motivated behavior, emotional learning, and memory<sup>18,35,44,52</sup> seems to account for a large portion of the risk for chronic pain, without the need of incorporating injury-related parameters such as duration and intensity of pain experienced.<sup>49</sup> The latter evidence builds on earlier observations showing that functional connectivity between mPFC and accumbens,<sup>7</sup> as well as white matter structural abnormalities<sup>34</sup> predicts who will eventually develop chronic back pain (CBP) based on brain parameters collected at a time when subjects are not differentiated regarding the duration or intensity of their pain. In addition, rodent neuropathic pain model studies now indicate that accumbens shell activity both amplifies and diminishes tactile allodynia,<sup>40</sup> and mPFC stimulation can relieve tactile allodynia.<sup>30</sup> These observations raise the critical question as to the role of nociceptive activity, which undoubtedly provides the initial signal of tissue injury, in chronic pain. In fact, the classical and

still currently highly viable competing hypothesis is that peripheral injury-related reorganization of afferents, increased excitability of dorsal root ganglion cells and ensuing spinal cord reorganization (central sensitization) is the primary determinant of the transition to chronic pain. Ample rodent peripheral injury studies are consistent with the latter hypothesis,<sup>29,54</sup> and this position is best articulated by recent evidence that peripheral nerve blocks yield total or major relief from phantom limb pain and neuropathic pain.<sup>24,50</sup> In this study, we directly address the question regarding what information brain circuitry transmits and/or shares regarding intensity of chronic pain with the rest of the brain.

Chronic pain is a complex experience that habitually leads to multiple morbidities. Depression, anxiety, sleep disturbances, and decision-making abnormalities<sup>2,14</sup> are daily struggles faced by patients with chronic pain which magnify pain severity and diminish quality of life. Perhaps, the most insidious emotional disorder affecting patients with chronic pain is depression, which impacts 30% to 60% of pain populations.<sup>3</sup> This intimate relationship between chronic pain and depression is yet to be fully unraveled. The existing models that aim to explain the relationship between chronic pain and depression are supported by limited clinical and rodent data. Some models, such as the fear-avoidance model of chronic pain, assume that depression is a consequence of pain.<sup>41</sup> This model is clinically appealing because patients with pain frequently present with depression that is focused on the emotional, psychological, social, and financial fallout of their pain. Yet its validity remains uncertain as in our longitudinal study, tracking patients with subacute back pain to either recovery or chronic pain over 1 to 3 years indicates elevated depression at the time of entry into the study but no further change in either group over 3 years.<sup>49</sup> The specificity of information transmission and/or sharing related to pain and depression, and their overlap between pain-processing areas and emotion-processing regions of the brain could bring further insight to our understanding of chronic pain. The secondary aim of this study was to attempt dissociating brain circuitry of depression and pain in patients with chronic pain.

We used functional magnetic resonance imaging (fMRI) to investigate resting state functional connectivity (zero-lag correlation of spontaneous fluctuations of blood oxygen level dependent (BOLD) activity between pairs of voxels or nodes) relevant for CBP and osteoarthritis (OA) and depression. Most of human brain imaging studies of pain addresses the localization of brain activity in relation to the perception. Here, instead we examine voxelwise information transmission and/or information sharing by nodal degree count, defined as the number of voxels (nodes) throughout the brain with functional connections to the specific node (based on

a constant density normalization threshold, see Ref. 8). We hypothesize that the brain regions where degree count reflects magnitude of chronic pain should be distinct from regions reflecting depression. We also hypothesize that the magnitude of chronic pain will preferentially involve somatosensory regions, whereas depression will better engage frontal and/or corticolimbic circuits.

## 2. Methods

This study comprises data gathered from previous studies examining the functional brain relationships to CBP and knee OA.<sup>6,7,48</sup> Here, we analyze whole-brain connectivity as it relates to these patients' chronic pain intensity and depression. The overall approach takes advantage of the fact that we have a large number of patients (CBP and OA) and matched healthy controls. First, we subdivided the chronic-pain-patient data into 2 subgroups with matched characteristics, used one group for identifying brain regions related to pain and/or depression and the second subgroup as a replication. In the third step, we combined all patients together and repeated the analysis for brain regional degree counts being related to pain and depression and tested whether the results were valid for both patient types, OA and CBP. Only brain regions that survived this 3-step discovery/replication procedure were considered significant outcomes. Identified brain regions were then used in seed-based connectivity analyses, comparing between patients and healthy controls, to uncover connectivity differences.

### 2.1. Subjects

The study comprised 84 patients with chronic pain with either CBP or OA. All subjects provided informed consent to procedures approved by the Northwestern University Institutional Review Board. We divided our patient pool into half (random but matched subgroups) to form a discovery group (N = 42) in which voxelwise connectivity was associated with their pain and depression scores, and an independent replication group (N = 42) in which these relationships were reproduced and validated. Our control group of healthy, pain-free subjects (N = 88) were age- and sex-matched. Clinical and demographic data are provided in **Table 1**.

### 2.2. Data acquisition and preprocessing

Functional MRI and T1-weighted anatomical MRI images were acquired for each subject during a single brain imaging session. Standard preprocessing of each subject's fMRI data was performed using FSL 4.1.8 (FMRIB's Software Library, <http://www.fmrib.ox.ac.uk/fsl>). Details of MRI acquisition and

**Table 1**  
Demographics, pain condition, VAS, and BDI scores for discovery and replication groups.

	Combined patients	Discovery	Replication	CBP	OA	Healthy
No. subjects	84	42	42	40	44	88
Age	53.9 ± 8.9	54.2 ± 8.8	53.6 ± 9.5	48.9 ± 8.2	58.5 ± 7.1	44.2 ± 12.6
Gender	42 females (50%)	20 females (47%)	22 females (52%)	15 females (38%)	27 females (61%)	50 females (57%)
Duration	13.9 ± 10.5	12.7 ± 9.9	14.8 ± 11.0	15.5 ± 10.9	12.3 ± 10.0	N/A
VAS	6.7 ± 1.7	6.7 ± 1.8	6.7 ± 1.7	6.6 ± 1.7	6.7 ± 1.7	N/A
BDI	5.4 ± 5.3	5.4 ± 5.1	5.3 ± 5.6	6.3 ± 5.9	4.5 ± 4.5	1.1 ± 0.3

CBP, chronic back pain; OA, osteoarthritis; N/A, not applicable.

preprocessing are in supplementary information (available at <http://links.lww.com/PR9/A2>).

### 2.3. Degree covariation with pain and depression

To assess functional connectivity, we calculated the degree count of each voxel, which indicates overall how many voxels in the brain share a similar BOLD time course to its own, and is a general measure of coherence. This measurement has been used to study functional brain characteristics of disease,<sup>9</sup> and the algorithms are thoroughly described in the Brain Connectivity Toolbox.<sup>43</sup> Results in the main text are reported using 10% link density; outcomes at other densities are in the supplement.

To determine how a voxel's degree covaried with depression and pain in the patients, degree maps were entered into a group-level general linear model using FSL's Flameo modeling Beck's Depression Inventory (BDI), pain visual analog scale (VAS), and BDI-VAS interaction (BDI\*VAS), correcting for, age, sex, and pain type (CBP or OA). The resulting z-stat maps were thresholded at  $z > 2.3$  and cluster-corrected for multiple comparisons at  $P < 0.05$ . This analysis was performed separately for the discovery and replication groups, additionally by combining both groups.

### 2.4. Replication

Using a linear fit on the data from the discovery group, by which VAS or BDI from every patient was plotted as a function of the mean degree across voxels in a significant cluster, we predicted pain and depression scores in an independent, replication group of 42 patients with chronic pain. We used the following formula to predict for each patient:

$$Y = m \times d + i$$

where  $Y$  is either the predicted VAS or BDI score, and  $d$  is the individual mean degree across voxels, defined by the discovery group's significant cluster. The values  $m$  and  $i$  are the slope and intercept of the linear fit to the discovery group's data, respectively. The strength of the model was calculated based on the Pearson correlation between the predicted and actual BDI and VAS scores in the replication group.

### 2.5. Seed-based connectivity

To specify a peak seed indicating the center of a region most highly relating pain and degree, the group-level pain/degree covariance map was thresholded at  $z > 4.5$  yielding 2 clusters. BOLD time series were averaged for these voxels for each patient and all 88 healthy controls (age:  $44.23 \pm 12.5$  years; 38 men and 50 women), and entered into a general linear model to generate a z-stat map, indicating functional connectivity to the seed, for each participant. Comparison of groups was performed

voxelwise using an unpaired 2-sample  $t$  test, correcting for age and sex. Statistical contrast maps, thresholded at  $z > 2.3$  and cluster-corrected ( $P < 0.05$ ) for multiple corrections, identified brain areas differentially connected to the seeds of interest.

## 3. Results

The aim of the study was to identify across the whole brain, regions where degree count (strength of functional connectivity to the rest of the brain) correlates to pain, depression, and their interaction. Data from a total of 84 patients (40 CBP and 44 OA) were divided into 2 randomly selected group sets, discovery and replication, based on equal distribution of pain and depression scores, age, sex, and duration. Demographics, pain, and depression parameters for patients in the discovery and replication group are listed in **Table 1**. Statistical z-value peak voxels for all maps referred below are in **Table 2** and supplementary table 1 (available at <http://links.lww.com/PR9/A2>).

### 3.1. Discovery group for identifying pain intensity-related brain connectivity

All results are reported as mean  $\pm$  SD, unless otherwise indicated. For patients in the discovery group, mean pain VAS scores were  $6.69 \pm 1.78$ , and mean depression BDI scores were  $5.43 \pm 5.06$ . There was no significant correlation ( $r = 0.16$ ,  $P = 0.29$ ) between pain VAS and BDI (**Fig. 1A**). BDI scores were not normally distributed; however, performing a logarithmic transform on BDI scores did not change any of our overall results and are thus not reported. In addition, the correlation between VAS and log BDI scores remained insignificant ( $r = 0.08$ ,  $P = 0.63$ , supplementary figure 1, available at <http://links.lww.com/PR9/A2>).

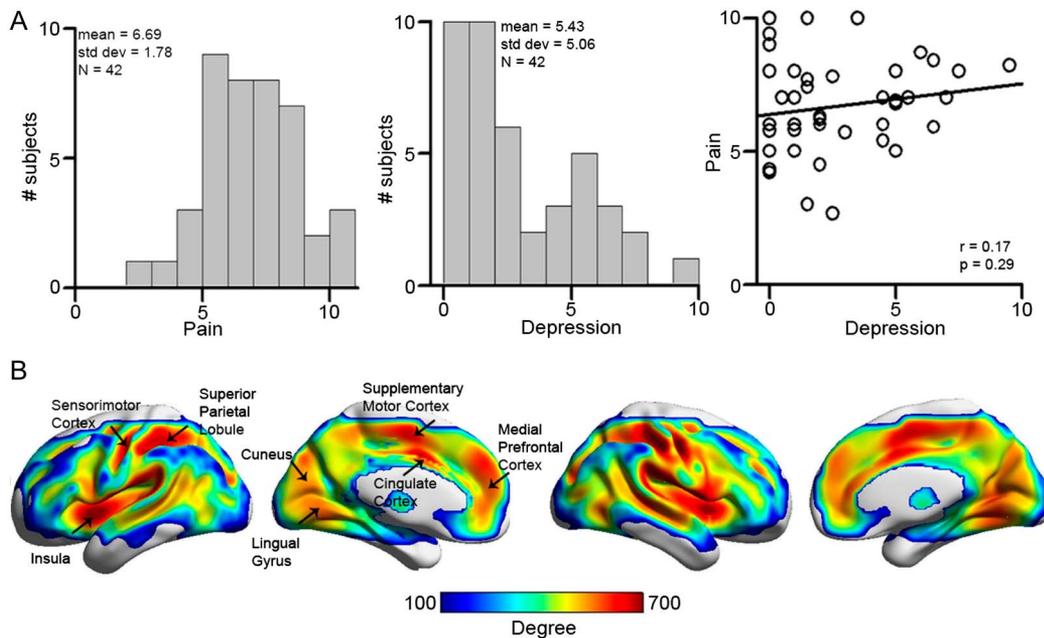
Threshold correlation values for generating degree maps at 10% link density were  $r = 0.30 \pm 0.04$  and increased with lower link densities (supplementary figure 2A, available at <http://links.lww.com/PR9/A2>). The group-averaged degree map at 10% link density is shown in **Figure 1B**. This map summarizes the mean number of brain voxels with which any given brain location is functionally connected. The map illustrates higher degree (more than 500 connections) in primary sensory, motor, visual, frontoparietal, and default mode networks (DMN) and relatively lower degree in subcortical and limbic areas (less than 200 connections).

To identify brain regions related to pain intensity, we performed a voxelwise correlation analysis between individual patient degree maps and corresponding pain scores ( $z$ -stat  $> 2.3$ , cluster-corrected for multiple comparisons  $P < 0.05$ ). Significant clusters were present in sensory areas, such as bilateral thalamus and posterior insula (**Fig. 2A**). Increasing the threshold of this map to  $z > 4.5$  resulted in a few voxels

**Table 2**

Peak voxel coordinates and corresponding z-stat values for maps shown in each figure.

	Peak voxel coordinates			Peak z-value	Cluster size, mm <sup>3</sup>	Avg. z-value
	x	y	z			
Figure 2A	12	-18	0	4.95	15,336	2.62
Figure 3B (red)	-4	-46	-26	3.60	10,072	2.67
Figure 3B (blue)	34	-64	46	4.20	34,408	2.70



**Figure 1.** Depression and pain are not correlated in our patient group. (A) Distribution of VAS and BDI scores across all patients in the discovery group (CBP N = 20, OA N = 22) (left and middle panels), and their correlation (right panel) ( $r = 0.167$ ,  $N = 42$ ). (B) Group-average spatial distribution of connectivity degree (number of functional connections at each node). Blue represents relatively fewer connections; red indicates more connections. CBP, chronic back pain; OA, osteoarthritis.

localized to the medial–dorsal thalamus (**Fig. 2B**). Posthoc correlation of the average degree in the identified region (**Fig. 2A**) and pain intensity was  $r = 0.55$  ( $P < 0.001$ , link density = 10%) (**Fig. 2C**). These results remained consistent at a range of link densities (supplementary figure 2A, available at <http://links.lww.com/PR9/A2>); thus, our remaining results are reported at 10% link density, unless otherwise indicated.

### 3.2. Replication group for pain intensity–related brain connectivity

An equally large independent replication data set (matched for patient type, age, sex, pain intensity, pain duration, and depression) yielded similar results relating connectivity and pain intensity. The distribution of pain intensity ( $6.69 \pm 1.69$ ) and depression scores ( $5.33 \pm 5.55$ ) across all patients in the replication group and the lack of correlation between the 2 ( $r = -0.04$ ,  $P = 0.82$ ) are consistent with the discovery group. Degree maps correlated to pain intensity were also similar between discovery and replication groups. Posthoc correlation of the average degree in the identified region and pain intensity were highly significant ( $r = 0.92$ ,  $P < 0.001$ ) (supplementary figure 3, available at <http://links.lww.com/PR9/A2>).

We used a model based on the linear fit between pain intensity and average degree in clusters identified in the discovery group (**Fig. 2A**) to predict pain in the replication group. Predicted pain correlated highly with observed pain ( $r = 0.60$ ,  $P < 0.001$ ) (**Fig. 2D**) and was consistent across link density thresholds (supplementary figure 2B), indicating that connectivity of this thalamic region is a robust predictor of subjective pain rating. Our overall findings remained consistent after switching discovery and replication groups, with almost identical mapping of pain to degree in the thalamus (supplementary figure 4A), and highly significant correlations between predicted and observed pain (supplementary figure 4B). And finally, as expected, combining both groups yielded similar

degree maps (supplementary figure 6A) and correlations to pain (supplementary figures 6B and C). Because our overall results were robust to grouping, our remaining analyses were performed on the combined set of patients. Supplemental files are available at <http://links.lww.com/PR9/A2>.

### 3.3. Depression-related brain connectivity

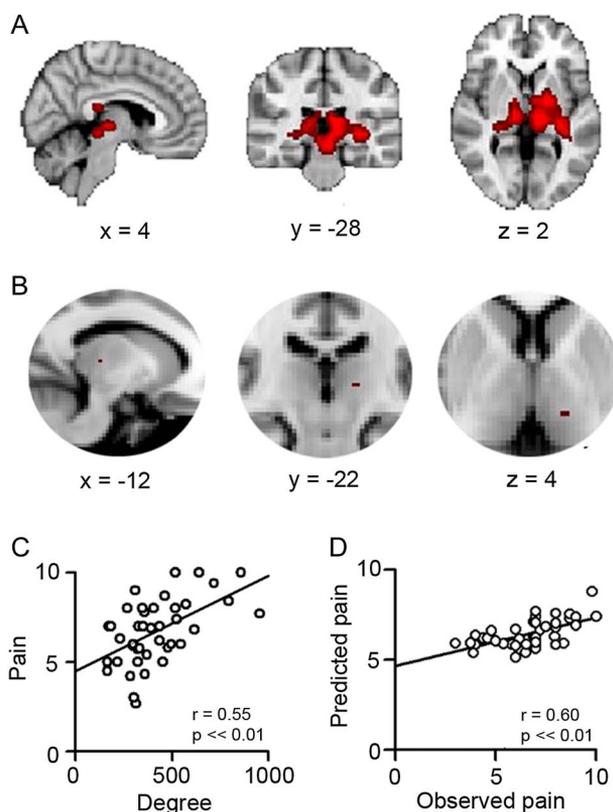
In the discovery group, depression scores covaried positively with degree in the mPFC and medial orbitofrontal cortex ( $z$ -stat  $> 2.3$ , cluster-corrected for multiple comparisons  $P < 0.05$ ) and negatively with degree in the bilateral temporal–parietal junction ( $z$ -stat  $> 2.3$ , cluster-corrected for multiple comparisons  $P < 0.05$ ) (supplementary figures 5A and B). There were no significant results for the BDI\*VAS interaction.

In the same manner as the pain-related analysis, we used a model based on the linear fit between depression and average degree in significant clusters in the discovery group to predict depression in the replication group. Correlations between observed and predicted depression were not significant (supplementary figure 5C).

Finally, to ensure that depression was not related to degree in the thalamus, we performed a posthoc correlation between the average degree in the pain–degree correlation map from the combined group analysis (see supplementary figure 6B) and all patients' depression scores. The correlation was not significant ( $r = 0.05$ ,  $P = 0.63$ ) (supplementary figure 6C). Overall, because we found no reliable brain signal related to depression in these patients, we performed remaining analyses on pain intensity.

### 3.4. Degree and pain intensity according to the patient type

The combined group of all patients yielded a degree map in which the thalamus correlated most highly to pain ratings (see supplementary figure 6B). Using this same map, we found it correlated highly to the pain ratings of CBP ( $r = 0.66$ ,  $P < 0.001$ )



**Figure 2.** Functional connectivity degree in the thalamus predicts subjective pain. (A) Functional connectivity degree in the thalamus correlated most strongly to pain in our discovery group. Maps are thresholded at  $z > 2.3$  and cluster-corrected for multiple comparisons at  $P < 0.05$ . (B) Higher thresholding of the  $z$ -stat correlation maps ( $z > 4.5$ ) shown in A demonstrates that the highest correlations between connectivity degree and VAS are located in the thalamus. (C) Posthoc correlation between average degree within the map in A and pain is highly significant. (D) Pain scores in the replication group were predicted based on the relationship between pain and degree in the discovery group (as shown in panel C).

and of OA ( $r = 0.41$ ,  $P < 0.001$ ) patients, separately as well. The correlation remained highly significant at different link densities (supplementary figure 6D). Because our results consistently indicated that degree of the thalamus correlated highly to pain ratings, regardless of the patient type, remaining analyses were performed on both CBP and OA, combined. Furthermore, our results were robust to motion correction using a previously described scrubbing procedure,<sup>38</sup> as correlation between average degree in the thalamus and pain remained highly significant ( $r = 0.49$ ,  $P < 0.001$ ) (supplementary figure 8).

### 3.5. Seed-based thalamic functional connectivity

To specify how functional connectivity in the thalamus of patients with pain differed from a pain-free, healthy population, we compared seed-based connectivity maps between patients and healthy controls. Our seed region was specified by applying a high statistical threshold ( $z > 4.5$ ) to the pain–degree correlation map (see supplementary figure 6B), indicating the voxels most highly associated with pain, and yielded 2 small clusters in the bilateral thalamus (**Fig. 3A**). Functional connectivity to this region was compared between our patients and 88 age- and sex-matched controls using a voxelwise 2-sample  $t$  test. Patients with pain exhibited greater positive connectivity

to the periaqueductal gray (patients =  $0.82 \pm 0.252$  [mean  $\pm$  SE], healthy =  $-0.50 \pm 0.264$ ) and greater negative connectivity to cortical regions within DMN and dorsal attention networks (DAN) (patients =  $-0.61 \pm 1.40$ , healthy =  $0.27 \pm 0.093$ ) (**Fig. 3B, C**), which are associated with high-level cognitive and evaluative function (supplementary figure 8).

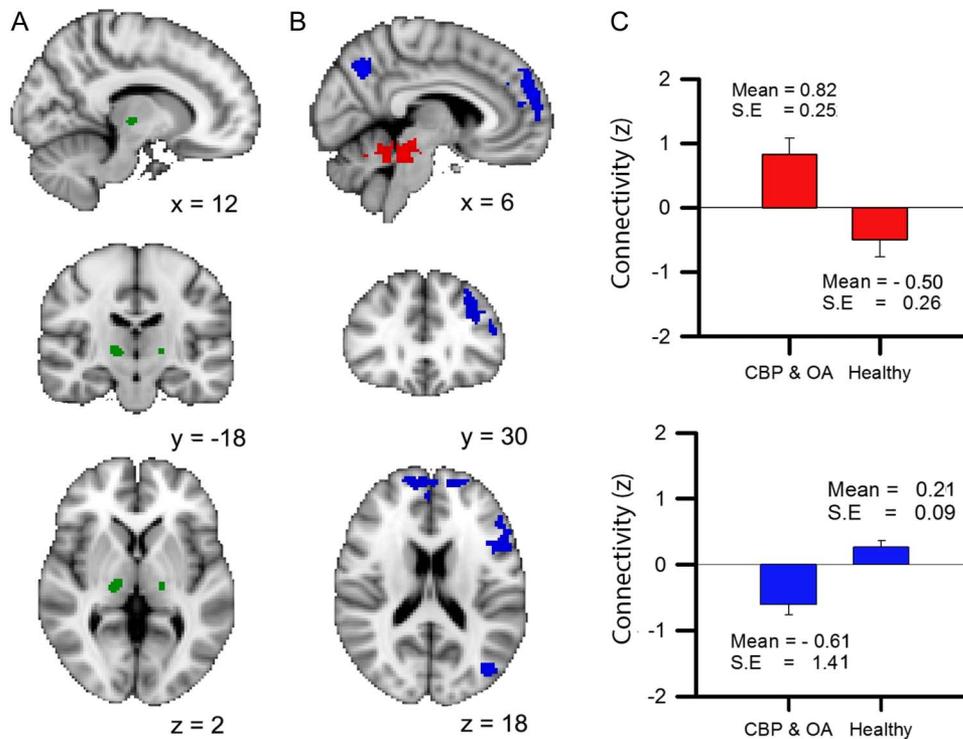
### 3.6. Thalamic structural connectivity

The relationship between pain and connectivity in our patients robustly mapped to a specific cluster of voxels within the thalamus, which, depending on its proximity to specific thalamic nuclei, has important implications in determining the role of nociceptive input in pain processing. To determine the associated thalamic nuclei, we mapped it to the Oxford thalamic connectivity atlas,<sup>11</sup> which is a probabilistic atlas of thalamic regions segmented according to their white matter connectivity to cortical areas (**Fig. 4A**). The clusters overlapped ventral posterior, ventral lateral, and ventral anterior nuclei, indicating structural connectivity to somatosensory, premotor, and primary motor regions (**Fig. 4B**).

## 4. Discussion

The main result of this study is the demonstration that magnitude of chronic pain, across CBP and OA, is represented by the degree count of the thalamus. Consistently with earlier results,<sup>49</sup> depression was not directly related to magnitude of chronic pain, and although it was related to frontal cortex degree counts in the discovery group, this result could not be replicated, implying that in fact depression was of too low a magnitude (hence also too variable or noisy resulting in false-positive maps) to be consistently mapped to brain functional connectivity in this chronic pain group. The peak location of the degree count reflecting magnitude of chronic pain bilaterally mapped to the ventral lateral thalamus, suggesting that the chronic pain magnitude is best captured by connectivity of thalamic regions that receive spinothalamic projections. The whole-brain contrast for these thalamic nodes, between the patients and healthy controls, indicated decreased functional connectivity between multiple cortical regions and increased connectivity with periaqueductal gray (PAG) in the patients. The decreased cortical connectivity could be generally interpreted as a diminution of cognitive control over spinothalamic inputs. However, reversal of the relationship between the thalamic nodes and PAG, from anticorrelation to a positive correlation, suggests a shift in information processing between descending modulatory pathways and the spinothalamic system from competition to coactivation.

At first sight, thalamic degree count being related to the magnitude of chronic pain seems contradictory to our earlier reports where we show brain activity related to subjectivity of chronic pain (a similar measure to the magnitude of pain used in the current analysis) localized to the mPFC and amygdala.<sup>5,25</sup> It is therefore important to emphasize the type of brain information measure used in this study relative to earlier reports. The most common analysis of brain BOLD signal simply identifies voxelwise BOLD response (shape and size) in relation to a task (general linear model-type analyses). Instead, here we extracted the extent to which any given brain voxel shares its local activity with the rest of the brain. A measure that reflects the brain network connectivity properties, which in turn undoubtedly would influence BOLD activity (yet with a complex interplay between the network properties and the specific representational access of a given perception or task to the network). What is remarkable is our observation that even at the



**Figure 3.** Functional connectivity of the thalamus is disrupted in patients with pain. (A) The correlation map between degree and pain in the combined group analysis was thresholded at  $z > 4.5$ , and the remaining voxels (shown in green) were used as seeds to determine functional connectivity to the thalamus. (B) Results of a 2-group unpaired  $t$  test, comparing functional connectivity between patients and healthy controls ( $z > 2.3$ , cluster-corrected for multiple comparisons at  $P < 0.05$ ). Red indicates voxels that had greater positive connectivity to the thalamus in patients, blue indicates greater positive connectivity in healthy controls. (C) The average  $z$ -stat values from the map shown in B and SE for each group. CBP, chronic back pain; OA, osteoarthritis.

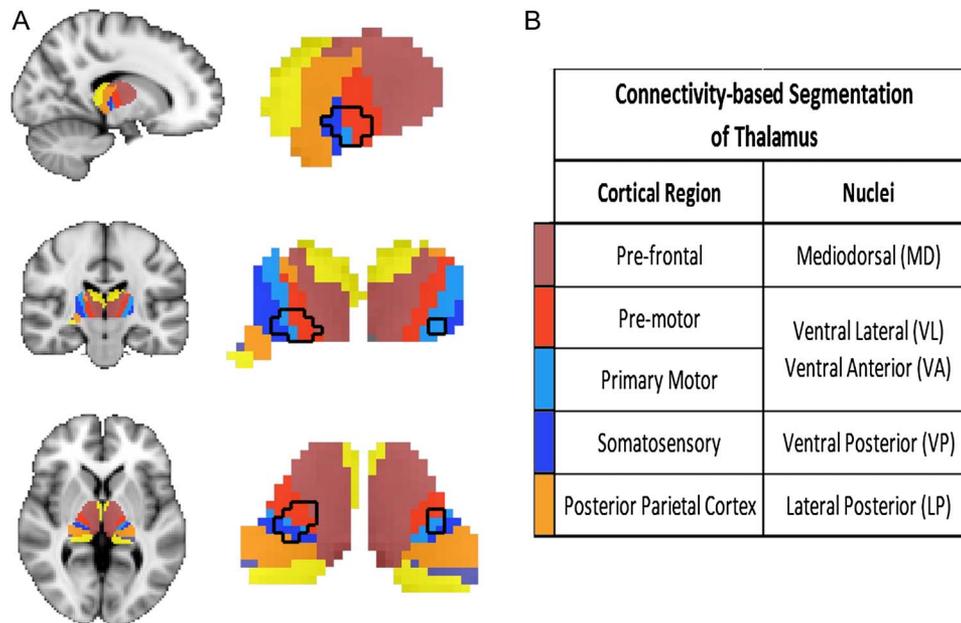
lowest cutoff thresholds we tested, only subcortical degree counts (encompassing all of the thalamus and basal ganglia) were related to the magnitude of chronic pain. Therefore, we can also make the opposite assertion, namely no cortical region degree count could be related to the magnitude of chronic pain, across OA and CBP. The observation is consistent with the notion of a lack of pain (or nociception)-specific tissue in the neocortex; a long-standing debate in the field and the one that remains to be resolved, see Ref. 4; and harking back to the position taken by Head and Holmes<sup>26</sup> over a 100 years ago, asserting that the thalamus and not the neocortex is the brain region specific for pain representation and for transmission (as shown here) to nonspecific cortical sites. Given the robust replication of our result in a large group of patients with OA and CBP, and as electrical stimulation of the lateral thalamus in patients with chronic pain replicates or exacerbates the subjects' own ongoing pain,<sup>27</sup> we expect that the specificity of degree count relationship with ongoing pain magnitude would generalize across chronic pain types.

We acknowledge that our assessment of cluster significance is prone to false positives,<sup>16</sup> which is of high profile concern within and outside the imaging community. Yet we believe that the internal replication of our results provides strong evidence that the peak degree count relationship with the magnitude of pain was localized to ventral lateral thalamus. This region corresponds to the most prominent terminations of the spinothalamic pathway within the primate thalamus.<sup>1,13,15</sup> It is reasonable then to conclude that the degree count within the thalamus in part depends on spinal cord activity, which would be in proportion to the extent of nociceptive information transmitted from the periphery. The present results together with our studies

identifying brain BOLD activity related to subjective fluctuations of chronic pain<sup>5,7,21,22,25,37</sup> suggest that nociceptive information transmitted from the lateral thalamus (although the current methodology cannot identify directionality of information flow) engages different cortical network circuits dependent on both time from pain inciting event, type of peripheral injury, and type of perception investigated, as the cortical network reorganizes anatomically and functionally with distinct types of chronic pain.<sup>17</sup>

Contrasting whole-brain functional connectivity between healthy subjects and patients with chronic pain, we observe in the patients, multiple cortical regions with decreased functional connectivity with the peak thalamic nodes related to magnitude of chronic pain. Together, the cortical regions identified closely correspond to multiple portions of the DMN and DAN, and some of the words best associated with these circuits are as follows: beliefs, recall, episodic memory, and calculation. In healthy subjects, the correlation between thalamic nodes and these cortical circuits are not different from zero. In contrast, in chronic pain, thalamic nodes are negatively correlated with these components of the DMN and DAN, suggesting that the nociceptive thalamus is now competing and thus probably interfering with these cortical networks, which are important for evaluating internal states, processing memories, and performing cognitive tasks.

The PAG was the other brain region that showed distinct connectivity with the thalamic nodes related to chronic pain magnitude. If we consider that PAG activity, at least in part, reflects descending nociception modulating activity (as demonstrated both in human brain imaging studies<sup>12,42,46,53,55</sup> and extensive animal model research<sup>19,36,45</sup>), then the thalamic-PAG connectivity changes can be conceptualized from the viewpoint



**Figure 4.** Thalamic regions with strongest relationship between pain intensity and functional connectivity (degree) exhibit structural connections to somatosensory, premotor, and primary motor cortical regions. (A) Segmentation (colored regions) of the thalamus is based on probabilistic diffusion tensor imaging (DTI) tractography, available as FSL's thalamic connectivity atlas. The black outlines indicate the thalamic regions with the highest relationship between degree and pain intensity (same as shown in A). (B) The table shows the correspondence of thalamic clusters to histologically defined locations of major nuclei and their probabilistic DTI connectivity to respective cortical regions. The 2 clusters outlined by the black line in A, are thought to include VL, VA, and VP nuclei and project mainly to somatosensory, primary motor, and premotor cortical regions. FSL, FMRIB's Software Library.

of the relationship between nociception and descending modulation. We observe that in healthy subjects this relationship is negatively correlated with each other, consistent with the idea that in healthy subjects descending modulation is antinociceptive. In contrast, in patients with chronic pain, the relationship is reversed, and now the 2 systems are positively correlated, suggesting that descending modulation has reverted to a pronociceptive state. The change in modulatory effects of PAG between healthy subjects and chronic pain is consistent and complimentary to results observed in animal models of neuropathic pain,<sup>20,23,33,39,51</sup> and yet, to our knowledge, this study is the first demonstration of this switch with chronic pain.

Overall, although we were unable to identify a replicable brain circuit for depression in chronic pain, we demonstrate that magnitude of chronic pain, independently from depression, is reflected in the brain functional connectivity, identifying the lateral thalamus transmitting or sharing pain magnitude with the rest of the brain. We suspect that the low levels of depression seen in our patients with OA and CBP are a reflection of our recruitment strategy; participants were primarily from the Chicago city region population at large. Therefore, future efforts to specifically identify depression-related brain functional networks in chronic pain would require recruiting patients from tertiary clinics where comorbidity of chronic pain and depression is more prevalent.<sup>10,47</sup> On anatomical grounds, we argue that the nodes best related to chronic pain magnitude underlie spinothalamic activity, and thus, we conclude that the observed degree counts should be considered related to nociceptive signaling. The dissociation of these thalamic nodes from the DMN and DAN networks and their shift from a negative to a positive association with PAG suggest that nociceptive information in chronic pain distorts cognitive processing and positively engages descending modulatory pathways. Therefore, we conclude that by studying network functional

connectivity degree count we have uncovered circuitry underlying nociceptive information transmission to the cortex. The present results are also complimentary to recent evidence<sup>28,31,32</sup> doubting the existence of nociceptive-specific cortical regions in healthy subjects.

### Appendix A. Supplemental Digital Content

Supplemental Digital Content associated with this article can be found online at <http://links.lww.com/PR9/A2>.

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