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Altered network architecture of functional brain communities in chronic nociplastic pain

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ABSTRACT

Neuroimaging has enhanced our understanding of the neural correlates of pain. Yet, how neural circuits interact and contribute to persistent pain remain largely unknown. Here, we investigate the mesoscale organization of the brain through intrinsic functional communities generated from resting state functional MRI data from two independent datasets, a discovery cohort of 43 Fibromyalgia (FM) patients and 20 healthy controls (HC) as well as a replication sample of 34 FM patients and 21 HC. Using normalized mutual information, we found that the global network architecture in chronic pain patients is less stable (more variable). Subsequent analyses of node community assignment revealed the composition of the communities differed between FM and HC. Furthermore, differences in network organization were associated with the changes in the composition of communities between patients with varying levels of clinical pain. Together, this work demonstrates that intrinsic network communities differ substantially between patients with FM and controls. These differences may represent a novel aspect of the pathophysiology of chronic nociplastic pain.

1. Introduction

An elusive goal of pain research is the identification of an objective marker for the chronic pain state. Ideally this marker would be more salient among chronic pain patients and would quantitatively track with the severity of clinical pain sensation (Tracey et al., 2019). In nociplastic pain conditions, such as fibromyalgia (FM), altered central nervous system function contributes to the perception of pain in the absence of peripheral tissue damage or inflammation (Harte et al., 2018; Sluka and Clauw, 2016; Woolf, 2011). Resting state fMRI can be used to understand the intrinsic dynamics of the brain through measuring functional connectivity. Previous studies have identified disrupted intrinsic functional connectivity in patients with chronic pain (Baliki et al., 2008, 2014; Basu et al., 2018; Hemington et al., 2018; Ichesco et al., 2014; Kutch et al., 2017; Loggia et al., 2013; Napadow et al., 2012, 2010). Yet, these analyses examine functional connections between isolated brain regions or resting state networks (RSNs) based on *a priori* hypotheses (e.g., seed connectivity or Independent Component Analysis) (Chavez et al., 2010). The brain can also be studied as a *network* of nodes (i.e. brain regions) and edges (i.e. connections between each node) to measure the contribution of *all* functional connections present in the brain (Rubinov and Sporns, 2010; Telesford et al., 2011). Adopting a network-based approach provides insight to the global and local topology of large-scale functional networks.

Within most networks, a collection of nodes can be organized into interconnected groups known as communities. The nodes within these communities are intrinsically more connected to each other relative to nodes in other communities within the network. This relationship is quantified through a measure known as modularity, where networks that are modular, segregated, in structure have higher modularity (Girvan and Newman, 2002; Newman, 2006b; Rubinov and Sporns, 2011). The composition of community structure between two networks can be quantified using normalized mutual information (NMI) (Achard et al., 2012; Alexander-Bloch et al., 2012; Vinh et al., 2010). Specifically, NMI is a global measure that quantifies similarity of community structure between two networks based on the assignment of nodes within each community. Local measures, such as phi, node allegiance or flexibility, explore node community assignment across networks and how they may differ (Bassett et al., 2011; Lerman-Sinkoff and Barch, 2016). Yet, it remains unknown how the functional brain intrinsically organizes into modules or communities in FM.

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We hypothesized that the organization of functional communities within the brain provides a brain-based marker of FM. We also hypothesized that altered community assignment of specific nodes, or brain regions, contributes to differences in network structure in FM and is associated with the level of pain self-report.

2. Methods

2.1. Participants

The novel analysis for this study included female fibromyalgia (FM) patients and healthy controls (HC) included in studies previously published that investigated univariate resting state functional connectivity and hub structure in chronic pain. Participants were divided into distinct discovery (Cummiford et al., 2016; Harris et al., 2013; Ichesco et al., 2016; Kaplan et al., 2019) and replication (Harper et al., 2018; Ichesco et al., 2014; Schmidt-Wilcke et al., 2014) datasets of nonoverlapping FM patients and HC. Moreover, participants in both FM and HC groups were age matched within 2 years across discovery and replication datasets. The discovery dataset consisted of 43 female FM patients and 20 (HC). 8 participants (5 FM and 3 HC) were removed from the analysis due to excessive motion or artifacts in fMRI data, resulting in a total of 38 FM patients and 17 HC in the discovery dataset. A separate cohort of 34 female FM patients and 21 HCs were combined to create our replication dataset. 3 participants (2 FM and 1 HC) were removed from the analysis due to excessive motion, resulting in a total of 32 FM patients and 20 HC in the replication dataset (Supplementary Table 1). 1 FM patient was not included in the analysis among low, medium and high pain due to missing clinical variables.

The Institutional Review Board at the University of Michigan approved the studies and written consent was obtained from all participants in accordance with the Declaration of Helsinki. Inclusion and exclusion criteria varied across studies and were previously outlined in Kaplan et al. (2019). General inclusion criteria for FM patients in the discovery dataset were: meeting the American College of Rheumatology (ACR) 1990 criteria for FM (Wolfe et al., 1990) and at least 6 months of self-reported chronic widespread pain, a score of $\geq$ 40 mm on a 100 mm pain Visual Analog Scale (VAS) at the time of consenting. All participants were between 18 and 75 years of age, female, right-handed, and capable of giving written informed consent. HCs were excluded if they met the ACR criteria for FM. Additional exclusion for all participants were: contraindications of fMRI, positive urine drug screen or history of drug or alcohol abuse within the past two years, pregnant or nursing mothers, body mass index greater than 36, sever psychiatric illness, concurrent autoimmune or inflammatory disease that causes pain or systemic malignancy or infection such as HIV or hepatitis. In the replication dataset, inclusion criteria comprised: meeting the 1990 ACR FM criteria with at least one year of disease duration, self-reported persistent pain for more than 50% of each day, willingness to forgo new treatments and medication use for FM during the study, between 18 and 75 years of age, right-handed and capable of giving written informed consent. Participants were excluded based on current or past opioid or narcotic analgesics, history of substance abuse or severe psychiatric illness, concurrent autoimmune or inflammatory disease that may contribute to pain, or concurrent participation in other therapeutic trials

2.2. Clinical assessment of pain, depression and anxiety

Clinical pain, depression and anxiety ratings for each participant were acquired prior to the scan session (Supplemental Table 1). Clinical pain was assessed on a visual analog scale (0–100), with 0 being "no pain" and 100 being "worst pain imaginable" prior to the scan. In our discovery data, Hospital Anxiety and Depression Scale (HADS) were used to assess anxiety and depression (Zigmond and Snaith, 1983). A subset of patients in the replication dataset completed the Center for Epidemiologic Studies Depression Scale (CES-D) to assess depression and State-Trait Anxiety Inventory (STAI) to assess anxiety (Bieling et al., 1998; Radloff, 1977). In order to compare clinical variables across all subjects, cutoff values for depression and anxiety were used to split patients into two groups: possibly depressed or anxious, or not (Aparicio et al., 2013; Julian, 2011; Smarr and Keefer, 2011). Cut off values were as follow: HADS – Depression: greater than or equal to 8; HADS – Anxiety: greater than or equal to 9; STAI: greater than 40; CESD: greater than or equal to 18.

2.3. fMRI methods

2.3.1. fMRI data acquisition and preprocessing

Imaging data were acquired on a 3T GE Signa 9.0, VH3 scanner (Milwaukee, WI) using an 8-channel head coil. Six minutes of resting state fMRI data were acquired using a T2* weighted spiral-in sequence (TR/TE:2000/30 ms) with 180 vol., as previously described (Kaplan et al., 2019) (Supplemental Table 2). A T1-weighted high-resolution anatomical scan was also acquired. During the resting state scan subjects were instructed to stay awake with their eyes open on a fixation cross. Since cardiac and respiratory fluctuations are known to influence brain connectivity within several networks, physiological data were collected simultaneously using a chest plethysmograph and infrared pulse oximeter (Birn et al., 2006; Chang and Glover, 2009). fMRI data were preprocessed and analyzed using Statistical Parametric Mapping (SPM) software package version 12 (https://www.fil.ion.ucl.ac.uk/spm), and the Conn functional connectivity toolbox (Cognitive and affective neuroscience laboratory, MIT, Cambridge, USA) both running on MATLAB 2014a. Upon collection of fMRI data, physiological artifacts are first removed using RETROICOR algorithm in MATLAB and slice time corrected using FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl) software. Preprocessing steps include motion correction, realignment, co-registration to anatomical image, normalization to standard MNI template, and smoothing (FWHM Gaussian kernel of 8 mm). Preprocessed fMRI data were entered into the Conn Toolbox in which CompCor including six subject-specific motion parameters, fMRI signal from white matter and CSF, and their first order derivatives as confounds (Behzadi et al., 2007). A temporal filter of 0.01 – 0.1 Hz was applied to focus on low frequency fluctuations in the fMRI data.

2.3.2. Motion

Subjects were excluded at multiple steps in the preprocessing pipeline due to excess motion, consistent with previous methods from our group (Kaplan et al., 2019). Motion parameters were calculated from the six head realignment parameters (x, y, z, pitch, yaw, roll) during the resting state scan for each participant (Supplemental Fig. 1). First, participants were removed from the analyses if framewise displacement exceed $\pm$ 2 mm translation or $\pm$ 1° rotation in any directions during the scan session. The mean and standard deviation for each of the six motion parameters were also calculated for each subject to determine group differences in motion parameters for each dataset. The six motion parameters were combined into a scalar quantity, instantaneous framewise displacement (Power et al., 2012). Mean and maximum framewise displacement (meanFD and maxFD) were calculated as the average and maximum instantaneous framewise displacement across the entire fMRI scan session for each participant. Lastly, outliers were identified as participants that had meanFD more than three standard deviations (i.e. z-score > 3) above the mean and were also excluded from analyses. To confirm motion does not contribute to group differences in NMI or phi, meanFD and maxFD were included in the final model to test for group difference NMI (FM-FM vs. HC-HC) as nuisance covariates. Additionally, we assessed the correlation between both meanFD and maxFD with within group NMI (Supplemental Fig. 3).

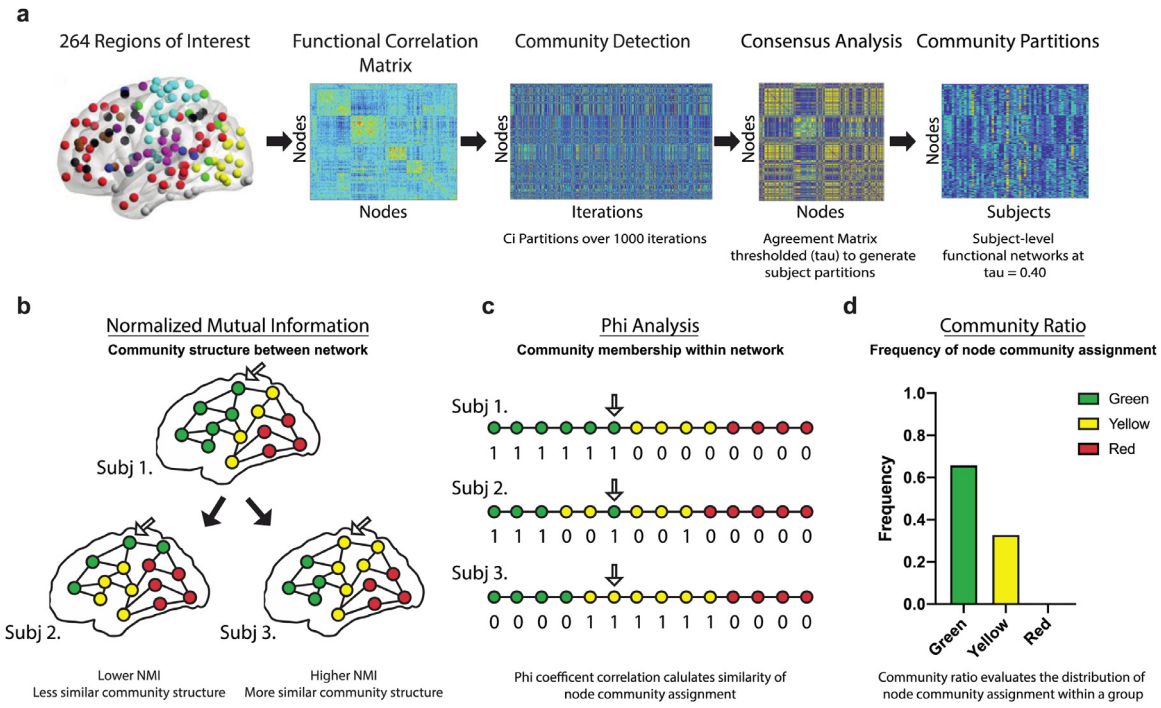

Fig. 1. Functional brain networks were constructed from resting state fMRI data. (a) Individual brain networks were generated from functional correlation matrices using community detection. (b) Normalized mutual information (NMI), a measure of global network similarity was used to determine whether network organization was conserved between two networks. Higher NMI values indicate greater similarity in community structure between two networks. (c) Nodal measures such as Pearson's phi coefficient (phi) quantifies the similarity of node community assignments between two networks. (d) The community ratio quantifies how nodes may differ in their community assignment based on the frequency distribution of node community assignment within a group. (Community were labeled in representative networks – Green, Yellow, Red. White arrow identifies node used to determine frequency distribution.)

2.4. Graph theoretical analyses

The steps for the creation of individual subject graphs are outlined in Fig. 1. Preprocessed fMRI data were entered into the Conn toolbox to create functional correlation matrices from regions of interest were based on the 264 brain regions previously shown to produce functional network topologies at rest and during task (Power et al., 2011; Whitfield-Gabrieli and Nieto-Castanon, 2012). Using the Brain Connectivity Toolbox and custom MATLAB codes, functional networks were generated for individual subjects using community detection methods that maximize modularity and consider the fully connected and weighted correlation matrix with 1000 repetitions (Blondel et al., 2008; Newman, 2004; Rubinov and Sporns, 2010, 2011). Consensus analyses were used to generate each subject-specific network. Specifically, agreement matrices were generated which calculate the number of times two nodes are in the same community. A threshold, tau, was applied to each matrix from 0.1 to 0.9 at an interval of 0.1 to create subject-level partitions (Betzel et al., 2014; Lancichinetti and Fortunato, 2012).

2.4.1. Modularity

A partition of networks into non-overlapping communities or modules can be achieved using modularity maximization (Blondel et al., 2008; Newman, 2006a). Measures of modularity quantify the goodness of modular partitions such that networks with stronger connections within a module, or community, compared to between modules have higher values. Modularity values were calculated based on the fully weighted matrix from the consensus generated subject level partition (Blondel et al., 2008; Rubinov and Sporns, 2011).

2.4.2. Normalized mutual information

To quantify group differences in global networks among participants, we used normalized mutual information (NMI). NMI measures pairwise similarity between two network partitions, across all participants (Alexander-Bloch et al., 2012; Vinh et al., 2010) (Fig. 1b). Stemming from information theory, mutual information (MI) quantifies the degree to which two clusters share similar solutions. MI is 0 when two networks are completely random and 1 when networks are identical. Normalization of mutual information (NMI) improves the sensitivity of network comparison of two networks with varying number of communities. Networks that have similar community structure have higher NMI values, as lower NMI suggests that networks are different in their organization. Details of the use of NMI measures on brain networks have been described previously (Achard et al., 2012; Alexander-Bloch et al., 2012; Chavez et al., 2010). For each subject, within-group NMI values were calculated from the mean NMI between all subjects within the same group (within: FM-FM, or HC-HC). We also calculated between-group NMI (FM-HC) as the mean pairwise NMI between all subjects in a different group. Higher NMI values suggest greater similarity in community structure between two networks.

2.4.3. Group consensus functional networks

Group consensus networks were constructed as previously described (Alexander-Bloch et al., 2012). Subject network partitions at threshold, tau = 0.40, were used to generate an agreement matrix for the FM and HC group independently. In this framework, the agreement matrix measures how consistent two nodes appear within the same community across subjects within the FM and HC group separately. Group consensus partition or networks were based on tau thresholds between 0.1 and 0.9, at intervals of 0.1. We found that the number of communities increase with tau thresholds. We report the group consensus networks generated at tau thresholds of 0.50 (50% agreement within the group) across each agreement matrix because the number of communities were consistent between FM patients and HC at this threshold (Supplemental Fig. 2).

2.4.4. Phi analysis

A node's community assignment is a local measure that identifies its contribution to the organization of a network. We identified which nodes may contribute to the group differences in NMI using a Phi test to quantify pairwise similarity of node community assignments (Fig. 1c) (Alexander-Bloch et al., 2012; Lerman-Sinkoff and Barch, 2016). For each subject, a binary matrix was generated based on whether a given node was in the same community as all other nodes (1) or in a different community (0). The binary matrices were then used to generate a node similarity measure (phi) using Pearson's phi coefficient. The within-group mean phi was calculated for all subject-by-subject node pairs. Higher phi values suggest the node is frequently a member of the same community across participants (i.e. strong allegiance). Low phi indicates that the node community assignment is variable and frequently shifts allegiance between different communities across participant networks.

2.4.5. Community ratio

To assess how a node differs in its community membership, we examined the variation of community assignment for each node within each group of low and high pain participants (See examples in Fig. 7). Among both groups, we discovered that nodes were either assigned to one community or split between two or more communities in our dataset. We grouped these nodes based on their patterns: Pattern A, Pattern B, Pattern C, and Pattern D. Nodes that follow Pattern A were split between communities 1 and 3. Pattern B consisted of nodes that are predominately in community 2. The nodes grouped in Pattern C and D are primarily in community 3 and community 1, respectively.

The community ratio examines the variation in node community assignment further through quantifying the distribution of node community assignment differs between low and high pain FM networks. The Alpha ratio quantifies the average frequency nodes were assigned to community 1 and 3 relative to community 2. A lower Alpha ratio suggests that a node may often be assigned in community 2. The Beta ratio examines whether nodes are assigned to community 1 or 3, by calculating the frequency nodes were assigned to community 1 relative to community 3. A lower Beta ratio suggests a node is primarily in community 3 among a group of networks. An alternative interpretation of the community ratio is that the Alpha ratio determines the scale in which a node exhibits Pattern A relative to Pattern B within a group. The Beta ratio explains the proportion in which a node exhibits Pattern D relative to Pattern C.

2.5. ROC analyses

Discrimination indices were determined based on receiver operator curve analyses in R statistical software. At each threshold, within-group NMI values were used to determine whether network topology accurately identified FM or HC group membership. Threshold values were determined based on the value that maximizes the distance to the identity line (Youden, 1950). Sensitivity, specificity, and accuracy values were also calculated from this threshold value.

2.6. Whole brain regression analyses

To explore the relationship between traditional intrinsic resting state networks (RSN) and our network measures, we conducted whole brain regression analyses correlating NMI with changes in functional connectivity of resting state networks shown to be altered in FM patients. RSN seeds were generated from independent component analysis using the GIFT toolbar (Calhoun et al., 2004). From the estimated components, salience (SLN) and default mode network (DMN) were identified by spatial correlation with RSN templates (Beckmann et al., 2005). Binary masks were generated for each RSN and used for seed-to-whole brain functional connectivity analyses in the Conn toolbox. To determine changes in RSN connectivity that were associated with NMI in FM, individual beta-maps were entered into a second-level whole brain regression analysis with NMI (within-group NMI:FM-FM) in SPM12. Age and motion (e.g. meanFD and maxFD) were included as nuisance regressors.

2.7. Statistical analysis

Independent t-tests were used to test group differences in motion, clinical variables and modularity values between groups in R statistical software. We tested for group differences in within-group NMI values using permutation tests with age and motion (e.g. meanFD and maxFD) as regressors of no interests. Permutation test significance was determined by the number of occurrences the 10,000 random permuted group differences in NMI were more extreme than the observed difference. Permutated p-values were corrected for multiple comparisons across thresholds, based on false discovery rate (FDR) corrected p-value <0.05. Between-group NMI values were calculated based on the mean of the NMI values associated with the comparison of each FM patient to each HC. Paired-t-tests were conducted to determine whether the within-group NMI were significantly different from the between group NMI. Results were deemed significant at $p < 0.05$. For the phi analyses, we ran permutation tests to determine whether the observed within-group differences were different from 10,000 random permutations. Age and motion were included as regressors of no interest. Permutation test significance were determined by the number of times the observed group difference was more extreme than the permutated difference. To correct for multiple comparisons, across 264 nodes in the phi analysis, results were deemed significant at a false discovery rate corrected p-value < 0.05. Results of whole brain regression analyses were deemed significant based on a FDR cluster level corrected p-value < 0.05, derived from a voxel-wise uncorrected p-value < 0.001. Post-hoc correlations were performed between functional connectivity values and NMI (within: FM-FM) using R statistical software ($p < 0.05$).

3. Results

3.1. Intrinsic network architecture is altered in chronic pain patients

We first determined whether there were differences in network architecture between FM patients and HC. We compared the organization of brain networks both within group (FM to FM and HC to HC) and between groups (FM to HC). We found that within the FM group, the mean NMI between each pair of FM patients was lower than between pairs of HCs, suggesting that the organization of functional networks is more variable in FM. HCs, on the other hand, had relatively stable network configurations (high pairwise NMI). The within group NMI was significantly different between FM and HCs and this remained true across thresholds (for tau = 0.4, permutation test P value < 0.0001; Fig. 2a, Supplemental Fig. 2). Next, we compared network similarity across groups. We found that FM patients have significantly lower between-group NMI relative to the within-group FM NMI measure (*paired t-test,* $t(37)=19.916$, $p < 2.2 \times 10^{-16}$), suggesting that FM network organization is even less similar to HC. There were no differences in the average number of communities and modularity between FM and HC (Fig. 2b and c). Motion was assessed through mean framewise displacement for the entire length of the scan for each subject. While meanFD was significantly different between FM and HC, there were no significant correlations between NMI and motion suggesting that motion does not contribute to the variability of subject networks (NMI). Further, group differences in NMI remained when meanFD and maxFD were included as nuisance covariates (Supplemental Fig. 2).

Next, we tested if these results replicated in a separate population of FM patients and HCs. In our replication cohort, we again found that FM patients had lower within- and between-group NMI compared to HCs (within-group NMI - permutation test P value < 0.0001; between group

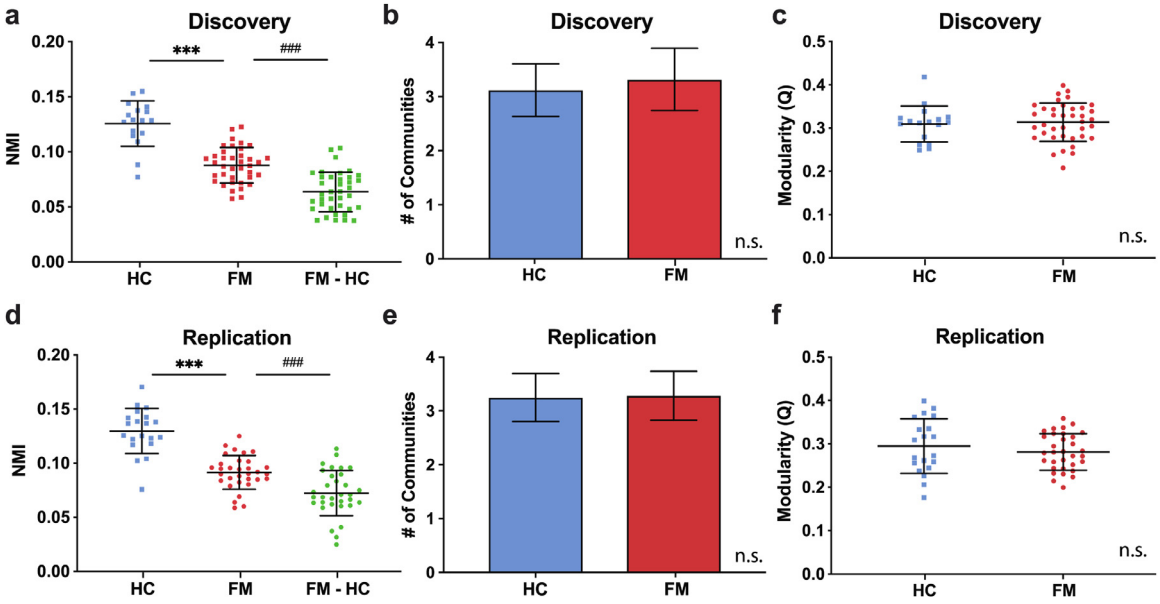

Fig. 2. Comparison of functional networks between FM and HC. Lower normalized mutual information (NMI) indicated that network organization was more variable among FM patients (red) relative to within HCs (blue) Further, FM and HC networks were even less similar to each other (green) (a). There were no differences in the number of communities (b) or modularity (c). These results were consistent in the replication group (d-f). (*** designates significance based on permutation test – $p < 0.001$; ### designates significance based on paired *t*-test - $p < 0.001$; n.s. not significant).

NMI - paired *t*-test t(31)=12.796, $p < 6.567 \times 10^{-14}$; (Fig. 2c–e, Supplemental Fig. 2). In short, chronic pain patients have lower within- and between-group NMI compared to HCs, suggesting that their network architecture is more variable and different. The lack of group difference in both modularity and number of communities further implies that while the strength of connections within relative to between communities are similar, the nodes that make up the communities differ between groups.

3.2. Sensitivity and specificity of NMI identifies FM networks

To investigate whether global network structure can be used to identify FM networks, we measured whether NMI can accurately discriminate networks of FM patients and HCs. Receiver operating curve (ROC) analyses showed that within-group NMI successfully identified patients and controls across multiple thresholds, with an average (±SD) accuracy of 85 ± 13.9 and 86 ± 10, and area under the curve (AUC) of 87 ± 10.8 and 86 ± 12.8, for the discovery and replication datasets, respectively (Fig. 3a). Across thresholds up to 70% agreement (tau = 0.70), within-group NMI accurately identified FM patients from controls with an average 88% sensitivity and 94% specificity in the discovery dataset, and average 79% sensitivity and 91% specificity in the replication dataset (Fig. 3b). In both datasets the accuracy, sensitivity, specificity and AUC decreased as tau increased over 0.7.

3.3. Changes in resting state network connectivity are associated with normalized mutual information

To explore the relationship between intrinsic network connectivity and NMI in FM, we conducted whole brain regression analyses correlating resting state network connectivity with NMI. Functional connectivity between the salience (SLN) and default mode (DMN) networks were associated with within group NMI (FM-FM). Specifically, we found salience connectivity between the posterior and anterior cingulate/subcallosal gyrus, cuneus, middle temporal gyrus and angular gyrus were negatively associated with NMI (Fig. 4a). Functional connectivity between the salience network and the anterior cingulate cortex (ACC) suggests stronger within salience network connectivity is as-

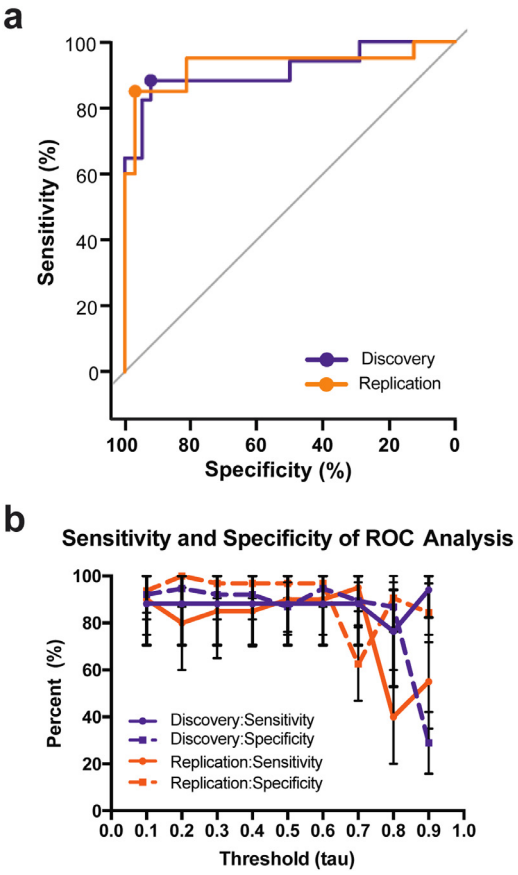

Fig. 3. Within-group NMI reliably discriminates FM patients from HC. (a) ROC curves for within group NMI at tau = 0.40 for the discovery (AUC = 91%) and replication, (AUC = 93%) datasets. (b) NMI could discriminate networks FM patients from HC between tau thresholds of 0.1 and 0.7. (purple - discovery; orange - replication; solid line - sensitivity; dashed line - specificity).

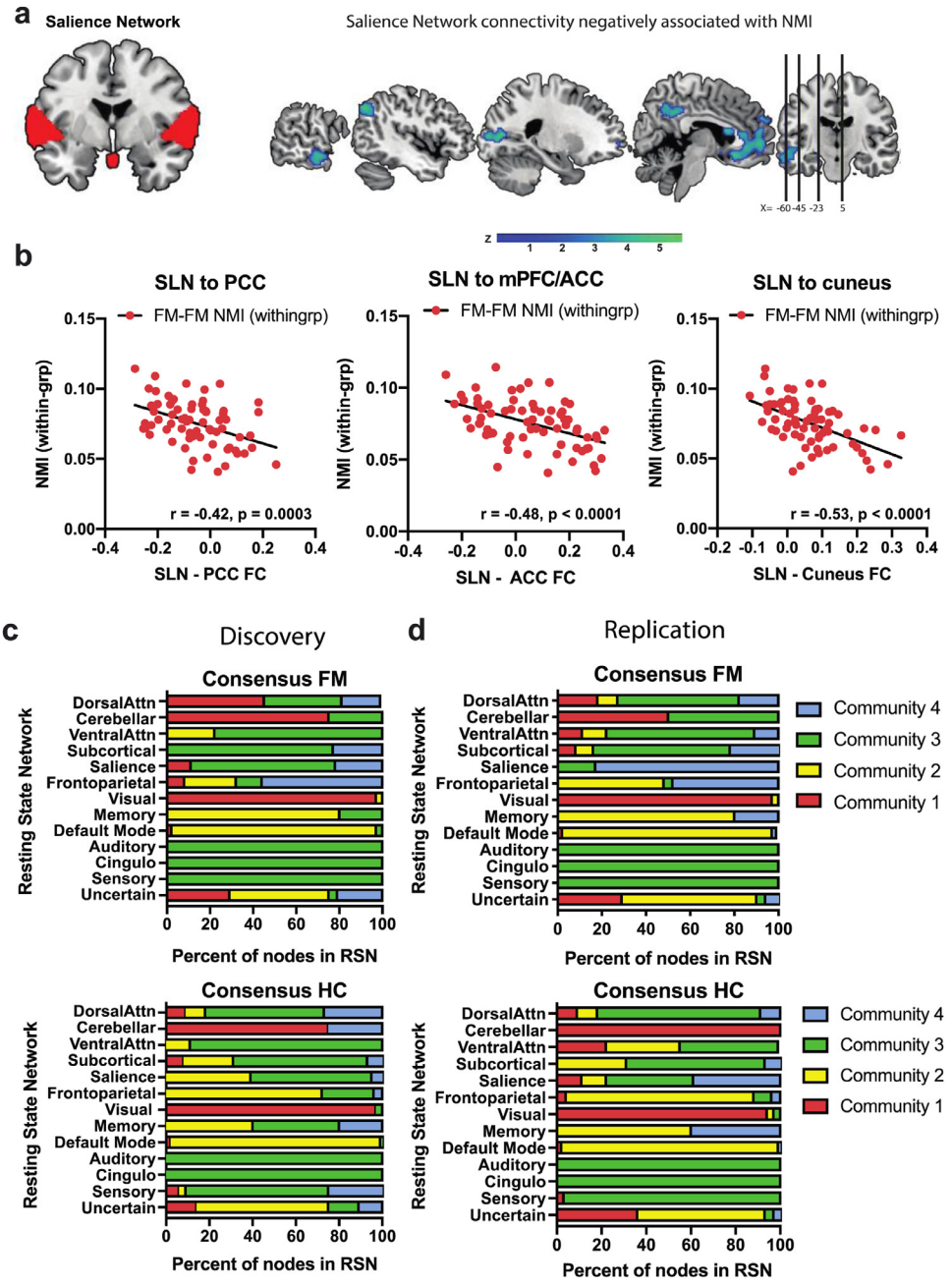

Fig. 4. Intrinsic resting state network functional connectivity is associated with NMI. (a) Salience network (SLN) connectivity between the posterior cingulate cortex (PCC), mPFC/ACC, cuneus, middle temporal gyrus and angular gyrus were negatively associated with NMI. (b)Within the FM group, FM networks that were less similar have stronger functional connectivity. (c and d) Group consensus networks were constructed from subject networks generated at tau of 0.40 in the discovery and replication dataset. Resting state networks spanned multiple communities. Moreover, the community assignment of nodes within a RSN was different across FM and HC groups. The composition of communities 1 (visual), 2 (default mode and frontoparietal), and 3 (sensorimotor and attention) were consistent among FM and HC networks across both datasets. Community 4 was the smallest community with respect to the number of nodes and included nodes from different RSN between datasets and groups suggesting community organization may be different in FM. (Community 1 – red; Community 2 – yellow; Community 3 – green; Community 4 – blue).

sociated with lower NMI. As the posterior cingulate cortex (PCC) and angular gyrus are part of the default mode network, these results suggest that functional connectivity between the salience network and default mode network is also associated with FM networks that were less similar among the group. Of note, we also found that DMN functional connectivity between the insula cortex, lingual, inferior frontal, supramarginal, and precentral gyri is negatively associated with NMI in FM (Supplemental Fig. 4).

3.4. Group consensus analyses reveals community structure

To visualize the community structure of FM patients and HC we generated consensus networks based on 50% agreement (tau=0.50) within each group separately. We chose 50% as the agreement threshold because the number of communities between patient and control consensus networks was consistent (Supplemental Fig. 5). To examine how nodes within resting state networks (RSNs) spread across communities, we quantified the percent of nodes in each community for each resting state network (Fig. 4c and d). Nodes in the visual network (VIS) and default mode network (DMN) were found predominately (i.e. at least 90% of the nodes) in one community for both FM and HC networks respectively. In contrast, sensorimotor (SMN) nodes were split between communities 3 (66%) and 4 (26%) in the consensus HC network, yet only in community 3 in the FM network from the discovery dataset. Frontoparietal, salience and subcortical nodes also differed in how they were distributed across multiple communities between FM and HC.

To determine the composition of each community, we quantified the percent of nodes in each resting state network, within each community (Supplemental Fig. 5). The composition of communities 1, 2, and 3 were consistent among patients and controls across both datasets. Community 1 consisted of nodes from the visual and cerebellar networks, community 2 consisted of nodes from the DMN, and community 3 comprised of

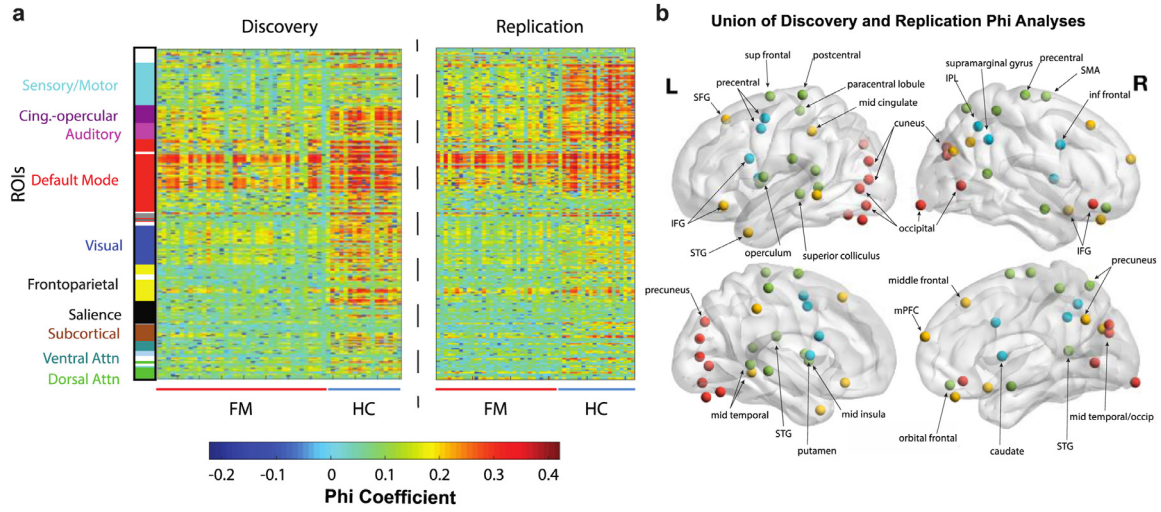

Fig. 5. Phi analysis identifies variable nodes in brain networks of FM patients. (a) Lower Phi values were observed for nodes across functional networks in FM patients compared to HC. 118 (44.7%) and 121 (45.8%) out of 264 nodes had significantly lower phi value among FM patients in the discovery and replication dataset, respectively. (b) Together, 47 (17.8%) nodes have significantly lower phi values in chronic pain patients across both datasets. Node color based on community assignment from consensus network of FM patients. (Community 1 - red; Community 2 - yellow; Community 3 - green; Community 4 – blue).

sensorimotor, cingulo-opercular, subcortical, dorsal and ventral attention network nodes in FM and HC in both datasets. Community 4, the smallest community, differed with respect to the number and composition of nodes which varied between datasets and groups. In the discovery dataset, 48% of the nodes in community 4 were affiliated with the frontoparietal network in the FM consensus network, whereas 45% of the nodes in community 4 of the HC network corresponded with the sensorimotor network. In the replication dataset, 32% of the nodes in community 4 in the FM consensus network consisted of frontoparietal network nodes, consistent with the discovery dataset. However, salience network nodes in both FM and HC consensus networks made up 41% and 50% of the nodes in community 4, respectively. Overall, these data support the notion that nodes within each resting state network differ in community assignment across FM and HC groups.

3.5. Chronic pain patients have nodes that are more variable in their community assignment

Differences in consensus networks suggest that communities consist of nodes from multiple resting state networks which may reveal differences in intrinsic resting state network connectivity. Moreover, the organization of nodes into different communities within the networks of FM patients compared to HCs may reflect differences in network architecture in chronic pain and be associated with patients' clinical pain intensity. We examined which nodes are associated with differences in the composition of communities between FM and HC. Pearson's phi coefficient (phi), quantifies the pairwise similarity of node community assignments between two networks from a binary vector that defines whether two nodes are within the same community (1) or not (0) (Alexander-Bloch et al., 2012; Lerman-Sinkoff and Barch, 2016) (Fig. 1c). Higher phi values indicate a node is consistently a member of the same community across individuals within the FM or HC group. We found that many brain regions significantly differed in their community assignment between groups, having lower Phi values among FM patients compared to HC. Specifically, 118 (44.7%) and 121 (45.8%) nodes had a significantly lower phi value among FM patients in the discovery and replication dataset respectively (permutation test; FDR-corrected $p < 0.05$), (Fig. 5a). The remaining nodes were not statistically different in their phi values between FM patients and HCs. Together, 47 (17.8%) of the 264 nodes had consistently lower phi in FM individuals across the both discovery and replication datasets, suggesting that they were significantly more variable among FM patients (Fig. 5b).

3.6. Intrinsic functional network structure differs between patients with varying degrees of clinical pain

While nodes appear more variable among FM networks, we were particularly interested in identifying whether the variability of community structure in FM is associated with clinical pain. To examine this possibility, FM networks from both datasets were combined and then split into tertiles ($n = 23$ per group) based on clinical pain ratings (Visual analog scale from 0 = "no pain" to 100 = " worst pain imaginable"), creating a low (31.04 ± 12.92), medium (58.48 ± 5.99) and high pain (76.87 ± 7.32) group. High pain patients had significantly lower within-group NMI compared to low pain patients (tau = 0.40, permutation test, $p = 0.0142$), suggesting differences in community structure between patients with low and high pain (Fig. 6a). There were no differences in within-group NMI between low and medium pain, or medium and high pain patients (low versus medium: permutation test P value = 0.3765; medium versus high: permutation test P value = 0.0977). While examining the medium pain group could help in identifying network signatures, here our subsequent analyses focused on the extreme cases of clinical pain intensity, among FM patients with low and high pain.

To explore the relationship between clinical pain and the variability of community structure in FM, we identified which nodes may be contributing to the differences in network structure between low and high pain patients (Fig. 6b). Phi test revealed forty-three nodes that were significantly different in their community assignments between low and high pain patients (permutation test; FDR-corrected $p < 0.05$; Fig. 6b). Cluster analysis showed that these nodes form a two-cluster solution that differ between low and high pain cohorts further suggesting the variability of nodal community assignment is associated with pain intensity among FM patients. (Supplemental Fig. 6). Twelve of the forty-three nodes were stable in their community assignment among high pain patients (i.e. higher within-group phi values among high pain patients). These nodes were associated with the default mode, frontoparietal and salience networks (Fig. 6c). The remaining thirty-one nodes were stable in their community assignment among low pain patients and associated with the sensorimotor, cingulo-opercular, visual, attention, frontoparietal and salience resting state networks (Fig. 6d).

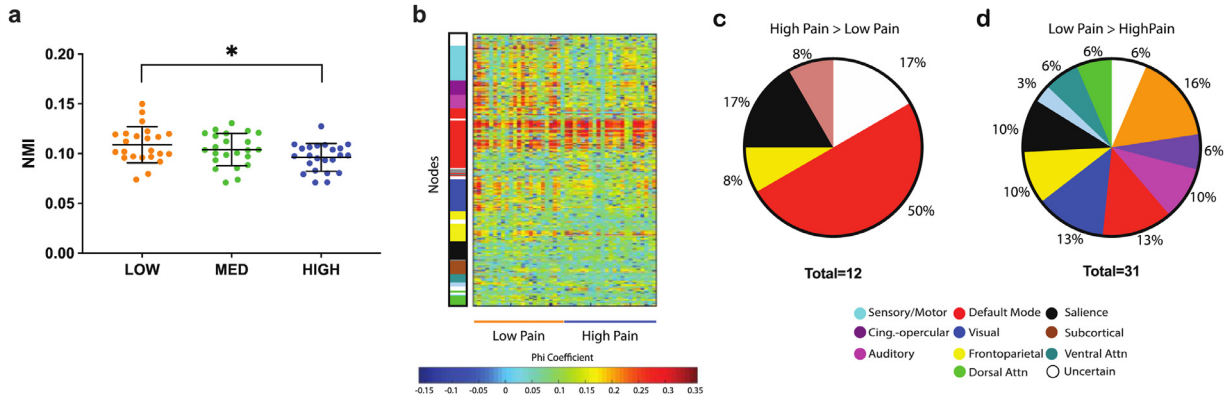

Fig. 6. Network structure tracks with level of clinical pain. FM patients from both the discovery and replication dataset were combined and then split into tertiles based on the degree of spontaneous pain: low pain (31.04 ± 12.92), medium pain (58.48 ± 5.99) and high pain (76.87 ± 7.32). (a) Differences in network structure were observed between patients, such that high pain patients had lower within-group NMI compared to patients with low clinical pain. (b) Forty-three nodes significantly differed in their community assignment between patients with low and high pain. (c) Twelve out of forty-three nodes were more stable among patients with high pain compared to low. These nodes consisted of primarily DMN (red), SLN (black), FPN (yellow) and Uncertain (white) nodes. (d) Thirty-one of the forty-three nodes were more stable among low pain patients and consisted of nodes across all RSNs. (* designates significance based on permutation test – $p < 0.05$; DMN-default mode network; SLN-salience network; FPN-frontoparietal network).

3.7. Community ratio reveals differences of node community assignment across chronic pain intensity

To examine how a node may differ in community membership between the two groups, we used the community ratio to quantify node community assignment between low and high pain networks. For the nodes that significantly differed in their community assignment between low and high pain networks, we quantified how the variation in community assignment differed between low and high pain networks by calculating the frequency distribution of node community assignment for each group.

We measured the alpha ratio for nodes with greater phi in high pain networks. These nodes were differentially assigned to community 1 and 3 (Pattern A) versus community 2 (Pattern B). For example, the right angular gyrus was commonly found between communities 1 and 3 (as opposed to community 2) and had a higher Alpha ratio among high pain networks relative to low pain networks. The right anterior insula, in contrast, was primarily found in community 2 in networks of high pain patients and had a lower Alpha ratio (Fig. 7a and c). We also calculated the Beta ratio which assessed how nodes stable in low pain differed in community assignment between community 3 (Pattern C) or community 1 (Pattern D). The left postcentral gyrus was assigned to community 3 across low pain networks. As a result, the Beta ratio is lower in low pain compared to the high pain group. The right medial orbital frontal gyrus is found in community 1 among low pain networks compared to high pain networks where they are found more commonly in community 3. As a result, the Beta ratio for this node is lower in the high pain group compared to the low pain group (Fig. 7b and d).

Lastly, we investigated the community ratio among nodes using the community labels based on the group consensus analysis and how they differ between low and high pain networks. Differences in the Alpha ratio revealed that nodes in the middle temporal gyrus, superior frontal gyrus, mid frontal gyrus, and angular gyrus, affiliated with the default mode network, are stable in high pain and are found in communities associated with visual and sensorimotor resting state networks. The two nodes affiliated with the salience network (i.e. the anterior insula and frontal precentral) were found in the default mode network communities among high pain patients (Fig. 8a and c). Of note, the medial thalamus differences between low and high pain networks reflect nodes assigned to community 2 or 3 between low and high pain networks.

The Beta ratio highlights differences in visual and sensorimotor network community assignment associated with varying pain intensity (Fig. 8b and d). Among high pain networks, the medial orbital frontal gyrus, superior temporal gyrus, supplemental motor area/paracentral lobule, dorsal anterior cingulate nodes have a lower Beta ratio indicating these nodes were assigned to the sensorimotor network in high pain. In low pain networks, these nodes varied between visual and sensorimotor communities and as a result the beta ratio was closer to 1. Interestingly, a third group of nodes that include the precentral gyrus, middle insula, superior temporal gyrus frontal middle orbital gyrus and visual regions: lingual, inferior temporal and inferior occipital gyrus, also have a higher Beta ratio in high pain compared to low pain. These nodes appeared to be in the visual community in high pain networks compared to low pain networks. Together these results demonstrate that the community ratio quantifies nodal differences in community composition associated with clinical pain intensity in FM.

4. Discussion

The main finding of this investigation was that NMI, a measure of pairwise similarity based on community membership, is different between chronic pain patients compared to HC. FM patients had significantly lower within- and between-group NMI, suggesting that the composition of communities is more variable amongst FM patients and significantly different from HCs. Furthermore, NMI accurately predicted whether a network came from an FM patient or HC with 85% accuracy. We found that the differences in community structure were attributed to changes in node allegiance across networks in chronic pain patients. In short, certain brain regions were more variable or less predictable in their community assignment among chronic pain patients. Next, we determined if these changes in community structure were related to clinical pain levels. Patients with high clinical pain had lower NMI compared to low pain chronic pain patients. These differences in network topology were attributed to intrinsic composition of functional communities across networks and associated with varying levels of clinical pain (Fig. 8). A significant strength of this study is that we replicated the differences in community structure in a novel cohort of FM and HC participants.

Through expanding the scope of functional connectivity analyses to whole brain networks, this work makes three crucial contributions to the field of pain and neuroimaging: First, connectome-based measures of the brain may improve diagnosis of conditions with underlying brain pathology or prediction of subgroups or states within a clinical population (Tracey et al., 2019). We show that NMI reliably identified net-

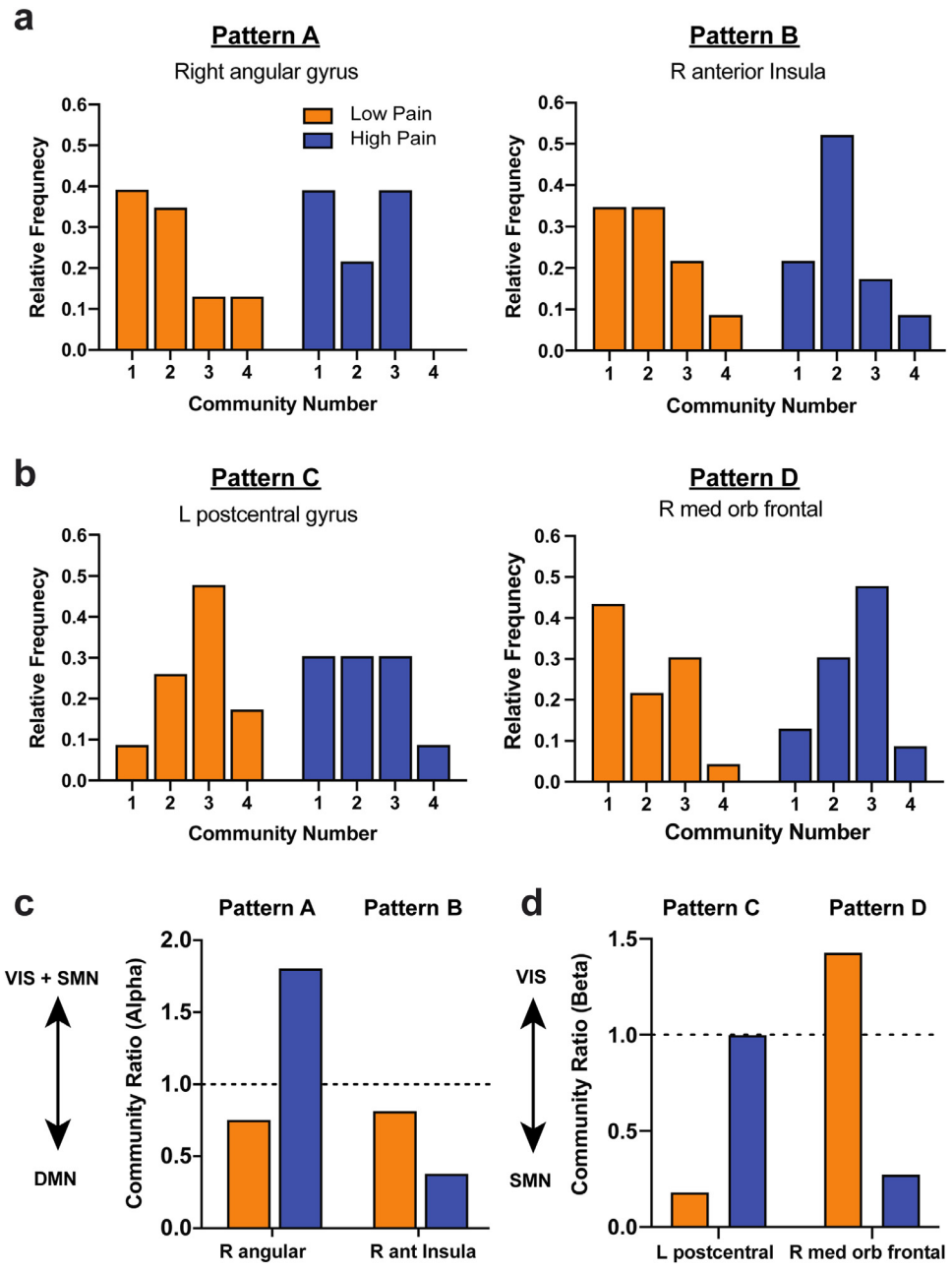

Fig. 7. Community Ratio reveals the distribution of node community assignments across low and high pain. The relative frequency in which nodes were assigned to different communities displayed distinct patterns of community distribution across FM networks of low and high pain patients. (a) Among high pain networks, Pattern A consisted of nodes typically assigned to communities 1 or 3. Pattern B among high pain patients were nodes found in community 2. (b) Among low pain networks, Pattern C consisted of nodes assigned to community 3 and Pattern D consisted of nodes assigned to community 1. The community ratio of these nodes quantifies the distribution of nodes across communities within a network. (c) In Pattern A nodes have a higher Alpha ratio, where Pattern B nodes have a lower alpha ratio. (d) The Beta ratio was lower for Pattern C nodes and higher for Pattern D nodes among low pain patients. (orange – low pain patients; blue – high pain patients. DMN-default mode network; VIS-Visual network; SMN-sensorimotor network.)

works within FM patients from healthy controls in both our discovery and replication datasets. Differences in community structure using NMI have been previously reported in neurologic (e.g. epilepsy), psychiatric (e.g. schizophrenia, major depression disorder), and chronic pain (e.g. chronic low back pain) suggesting that NMI may be a neural marker of underlying brain pathology. (Alexander-Bloch et al., 2012; Chavez et al., 2010; He et al., 2018; Mansour et al., 2016). Measures of global network structure, like NMI, may be useful in clinical settings to identify different subgroups of chronic pain conditions (i.e. neuropathic vs. nociplastic).

It is important to note that prior to application of network measures in a clinical setting, we understand how these measures relate to the underlying pathophysiology of these conditions, independently. In FM, salience nodes more stable in their community assignment in high pain networks had a lower alpha ratio, indicating these nodes are commonly found in community 2 with other DMN nodes. Moreover, these nodes overlap with changes in DMN connectivity negatively associated with NMI, linking the relationship between differences in functional connectivity and network structure to clinical pain intensity in FM (Supplemental Fig. 4) (Baliki et al., 2008, 2014; Napadow et al., 2012, 2010). The community ratio also revealed that DMN nodes stable in high pain have a higher alpha ratio and are found in community 1 and 3. These regions may have increased connectivity to sensory or attention communities and decreased connectivity to the DMN in networks of high pain FM patients (Mansour et al., 2016).

Interestingly, the nodes with higher phi values in low pain differ largely between sensory communities (e.g. visual and sensorimotor) when comparing networks of low and high pain. The insula, superior temporal gyrus and occipital brain regions, have a higher beta ratio in high pain compared to low pain, suggesting these nodes were typically found in community 1 and may be more connected to visual regions in high pain networks. The beta ratio for the precentral and postcentral nodes was also higher in high pain compared to low pain, but largely reflects the increase variability in community assignment among high pain networks. The dorsal ACC, medial orbitofrontal cortex, superior

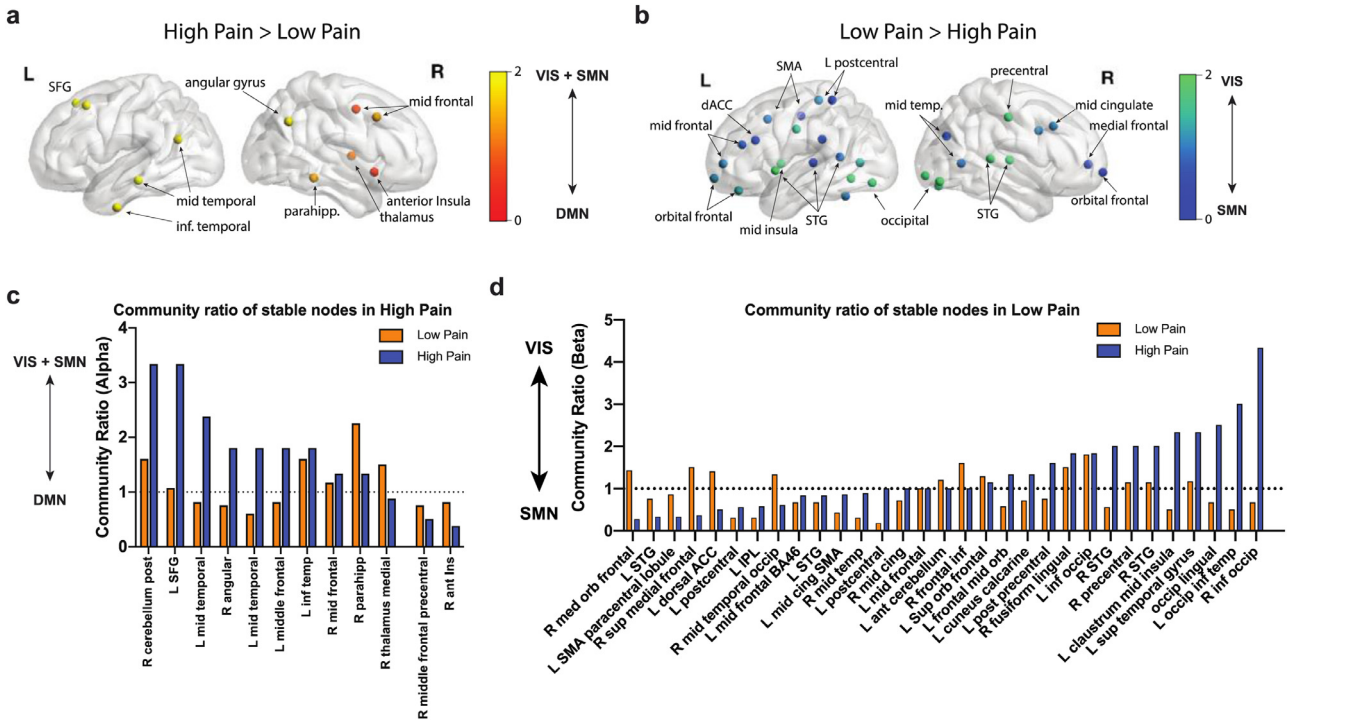

Fig. 8. Network reorganization among FM. FM patients have variable community structure compared to HC. This variability in network structure is attributed to differences in node community assignment across FM networks with varying degrees of clinical pain, as changes in the composition of communities are associated with clinical pain. The community ratio reveals how nodes are assigned to different communities between low pain and high pain groups for the nodes stable across (a and c) high pain networks and (b and d) low pain networks. (a) The alpha ratio measures whether nodes are assigned to the DMN (i.e. lower alpha ratio) or sensory communities (i.e. higher alpha ratio) for nodes stable among high pain networks. (b) The beta ratio measures whether nodes are assigned to visual (i.e. higher beta ratio) or sensorimotor (i.e. lower beta ratio) for nodes stable across low pain networks. (c) Differences in the alpha ratio show that DMN nodes are found in visual and sensorimotor communities while SLN nodes were found in the DMN communities among high pain networks. (d) SMN nodes have a higher beta ratio in high pain relative to low pain indicating they are assigned to the visual community more in high pain networks relative to low pain networks. (Orange-yellow color bar for nodes stable among high pain networks is based on alpha ratio within the group. Blue-green color bar for nodes stable among low pain networks is based on beta ratio within the group. DMN-default mode network; VIS-visual network; SLN-salience network; SMN-sensorimotor network.).

medial frontal gyrus and supplementary motor area had a lower beta ratio among high pain patients compared to low pain patients. Of note, these nodes were found in community 3 in high pain networks compared to being more variable or community 1 in low pain patients (Fig. 8). These brain regions are involved in modulation of pain via placebo analgesia and the descending inhibitory pathways. Clinical pain may arise from disrupted descending pain modulatory activity in chronic pain patients (Bingel et al., 2006; Bushnell et al., 2013; Jensen et al., 2012; Schrepf et al., 2016; Watson et al., 2009). Whether the differences in the assignment of these nodes into their respective communities reflect altered pro- or antinociceptive mechanisms among chronic pain conditions is a point worth exploration in future studies.

Second, analyses of the intrinsic mesoscale organization of the brain through communities explore changes in resting state network connectivity that are associated with clinical pain intensity. Functional connectivity between the salience and default mode network is negatively associated with NMI such that stronger connectivity was associated with networks that are more variable in network structure in FM. These findings were consistent whether we used the salience or default mode network as regions of interest indicating changes in the intrinsic resting state functional connectivity may contribute to global properties of the network via changes in the community composition within the network (Bertolero et al., 2015). In our analyses we show that communities may consist of nodes from one resting state network (e.g. community 1: visual) or multiple resting state networks (community 2 and 3). Observing the network organization of the brain within communities may reveal intrinsic functional connectivity between resting state networks. The present study shows that brain regions typically involved in pain processing are differentially assigned to communities between patients with varying levels of clinical pain.

Third, the current study shows that intrinsic functional brain networks are reorganized in FM. It is important to note that differences in the organization of networks are not completely random, but instead there are specific changes in connectivity or network organization, consistent with previous studies (Kaplan et al., 2019; Mansour et al., 2016). We show that the variations in community structure in FM is associated with clinical pain in FM. Higher clinical pain is associated with lower NMI in FM patients notably contributing to the within group FM having lower NMI. A second factor potentially contributing to lower NMI in FM patients may be that there are multiple ways of engendering pain in FM. Patients may have increased connectivity in pronociceptive regions, insufficient anti-nociceptive activity, or a combination of both (Ichesco et al., 2014; Jensen et al., 2009). Together these differences would increase variability in the FM group and lower within FM NMI outcomes. The lack of difference in modularity and number of communities suggest that the composition of communities contributes to the difference in network architecture.

Fibromyalgia may be an example of maladaptive reorganization of brain networks in which changes in the network composition are a result of, or response to, persistent pain among patients (Achard et al., 2012; Kuner and Flor, 2017). In both the discovery and replication dataset, our phi analyses revealed only nodes that were more variable in the community assignment in FM, relative HC. The nodes that are different in their community assignment across both datasets were brain regions affiliated with classic pain and sensory processing pathways. How and when these changes occur are still unknown and require both longitu-

dinal studies to understand the transition from acute to chronic pain, along with innovative network analyses to understand how networks change over time, or remain the same (Vachon-Presseau et al., 2018).

The current study has a number of limitations. The cross-sectional design limits our ability to directly test whether the reorganization of the subject networks causes pain or whether pain causes network reorganization. Longitudinal studies will provide the opportunity to determine whether intrinsic network organization contributes to state or trait measures of chronic nociplastic pain. Secondly, previous studies have shown that patients with Major Depression Disorder have altered intrinsic network architecture (He et al., 2018). Additionally, many patients with FM have multiple comorbid clinical diagnoses including anxiety and depression (Arnold et al., 2006; Hooten, 2016). While the differences in network architecture in the current study are not affected by comorbid depression and anxiety, these symptoms may contribute to the intrinsic reorganization of the brain and could be explored further in future studies.

5. Conclusion

Intrinsic functional brain networks are more variable among FM patients compared to HC. Furthermore, changes in community composition of intrinsic brain networks varies between patients with high and low levels of clinical pain. This work suggests that mesoscale community structure may be of use as a diagnostic tool for patients with FM.

Declaration of Competing Interest

D.J.C has received consultant fees, speaking fees, and/or honoraria from Aptinyx, Daiichi Sankyo, Intec Pharma, Eli Lilly, Pfizer, Nix Patterson LLP, Samumed, Theravance, Tonix, Williams, & Connolly LLP and Zynerba. D.J.C has also received research support from Aptinyx and Pfizer. S.E.H. has received Grants and personal fees from Pfizer, Aptinyx, Arbor Medical Innovations; grants from Cerephex, Lilly, and Forest. R.E.H has consulted for Pfizer, Aptinyx Inc. He has received grant funding from Pfizer, Aptinyx and Cerephex. T.E.L., C.M.K., A.S., E.I., I.M., S.E.H., G.A.M., D.J.C., and R.E.H., have all received funding from the National Institutes of Health. The remaining authors declare no competing interests.

Credit authorship contribution statement

Tony E. Larkin: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing - original draft, Writing - review & editing, Visualization, Funding acquisition. **Chelsea M. Kaplan:** Conceptualization, Methodology, Software, Resources, Data curation, Writing - review & editing. **Andrew Schrepf:** Methodology, Software, Validation, Investigation, Data curation, Writing - review & editing, Visualization. **Eric Ichesco:** Software, Resources, Data curation, Writing - review & editing. **Ishtiaq Mawla:** Software, Writing - review & editing, Visualization. **Steven E. Harte:** Resources, Data curation, Writing - review & editing, Funding acquisition. **George A. Mashour:** Conceptualization, Methodology, Writing - review & editing, Supervision. **Daniel J. Clauw:** Conceptualization, Resources, Writing - review & editing, Funding acquisition, Supervision. **Richard E. Harris:** Conceptualization, Methodology, Writing - review & editing, Funding acquisition, Supervision.

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Author contributions

Primary analyses were performed by T.E.L., C.M.K., A.S., and E.I, I.M., S.E.H, G.A.M, D.J.C., and R.E.H. assisted in interpretation of data and writing. T.E.L., C.M.K., A.S., G.A.M. and R.E.H. were responsible for primary planning and conduct of the experiments. All authors provided critical revision of the manuscript.

Data and code availability

The data and code supporting these analyzes will be made available following reasonable requests to the corresponding author.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2020.117504.

References

Achard, S., Delon-Martin, C., Vértes, P.E., Renard, F., Schenck, M., Schneider, F., Heinrich, C., Kremer, S., Bullmore, E.T., 2012. Hubs of brain functional networks are radically reorganized in comatose patients. Proc. Natl. Acad. Sci. U. S. A. 109, 20608–20613.

Alexander-Bloch, A., Lambiotte, R., Roberts, B., Giedd, J., Gogtay, N., Bullmore, E., 2012. The discovery of population differences in network community structure: new methods and applications to brain functional networks in schizophrenia. Neuroimage 59, 3889–3900.

Aparicio, V.A., Ortega, F.B., Carbonell-Baeza, A., Cuevas, A.M., Delgado-Fernandez, M., Ruiz, J., 2013. Anxiety, depression and fibromyalgia pain and severity. Behav. Psychol. Psicol. Cond. 21, 381–392.

Arnold, L.M., Hudson, J.I., Keck, P.E., Auchenbach, M.B., Javaras, K.N., Hess, E.V., 2006. Comorbidity of fibromyalgia and psychiatric disorders. J. Clin. Psychiatry 67, 1219–1225.

Baliki, M.N., Geha, P.Y., Apkarian, A.V., Chialvo, D.R., 2008. Beyond feeling: chronic pain hurts the brain, disrupting the default-mode network dynamics. J. Neurosci. 28, 1398–1403.

Baliki, M.N., Mansour, A.R., Baria, A.T., Apkarian, A.V., 2014. Functional reorganization of the default mode network across chronic pain conditions. PLoS ONE 9, e106133.

Bassett, D.S., Wymbs, N.F., Porter, M.A., Mucha, P.J., Carlson, J.M., Grafton, S.T., 2011. Dynamic reconfiguration of human brain networks during learning. Proc. Natl. Acad. Sci. U. S. A. 108, 7641–7646.

Basu, N., Kaplan, C.M., Ichesco, E., Larkin, T., Harris, R.E., Murray, A., Waiter, G., Clauw, D.J., 2018. Neurobiologic features of fibromyalgia are also present among rheumatoid arthritis patients. Arthritis Rheumatol. 70, 1000–1007.

Beckmann, C. F., DeLuca, M., Devlin, J. T., Smith, S. M., 2005. Investigations into resting-state connectivity using independent component analysis. Philos. Trans. R. Soc. B 360, 1001–1013.

Behzadi, Y., Restom, K., Liau, J., Liu, T.T., 2007. A component based noise correction method (CompCor) for BOLD and perfusion based fMRI. Neuroimage 37, 90–101.

Bertolero, M.A., Yeo, B.T., D'Esposito, M., 2015. The modular and integrative functional architecture of the human brain. Proc. Natl. Acad. Sci. U. S. A. 112, E6798–E6807.

Betzel, R.F., Griffa, A., Avena-Koenigsberger, A., GoÑI, J., Thiran, J.-P., Hagmann, P., Sporns, O., 2014. Multi-scale community organization of the human structural connectome and its relationship with resting-state functional connectivity. Netw. Sci. 1, 353–373.

Bieling, P.J., Antony, M.M., Swinson, R.P., 1998. The state-trait anxiety inventory, trait version: structure and content re-examined. Behav. Res. Ther. 36, 777–788.

Bingel, U., Lorenz, J., Schoell, E., Weiller, C., Buchel, C., 2006. Mechanisms of placebo analgesia: rACC recruitment of a subcortical antinociceptive network. Pain 120, 8–15.

Birn, R.M., Diamond, J.B., Smith, M.A., Bandettini, P.A., 2006. Separating respiratory-variation-related fluctuations from neuronal-activity-related fluctuations in fMRI. Neuroimage 31, 1536–1548.

Blondel, V.D., Guillaume, J.-.L., Lambiotte, R., Lefebvre, E., 2008. Fast unfolding of communities in large networks. J. Stat. Mech.: theory and experiment (10) P10008.

Bushnell, M.C., Čeko, M., Low, L.A., 2013. Cognitive and emotional control of pain and its disruption in chronic pain. Nat. Publ. Group 14, 502–511.

Calhoun, V.D., Adali, T., Pekar, J.J., 2004. A method for comparing group fMRI data using independent component analysis: application to visual, motor and visuomotor tasks. Magn. Reson. Imaging 22, 1181–1191.

Chang, C., Glover, G.H., 2009. Effects of model-based physiological noise correction on default mode network anti-correlations and correlations. Neuroimage 47, 1448–1459.

Chavez, M., Valencia, M., Navarro, V., Latora, V., Martinerie, J., 2010. Functional modularity of background activities in normal and epileptic brain networks. Phys. Rev. Lett. 104, 118701.

Cummiford, C.M., Nascimento, T.D., Foerster, B.R., Clauw, D.J., Zubieta, J.K., Harris, R.E., DaSilva, A.F., 2016. Changes in resting state functional connectivity after repetitive transcranial direct current stimulation applied to motor cortex in fibromyalgia patients. Arthritis Res. Ther. 18, 40.

Girvan, M., Newman, M.E., 2002. Community structure in social and biological networks. In: Proceedings of the national academy of sciences, 99(12). Chicago, pp. 7821–7826.

Harper, D.E., Ichesco, E., Schrepf, A., Hampson, J.P., Clauw, D.J., Schmidt-Wilcke, T., Harris, R.E., Harte, S.E., 2018. Resting functional connectivity of the periaqueductal gray is associated with normal inhibition and pathological facilitation in conditioned pain modulation. J. Pain 19, e631–e635 635e615.

Harris, R.E., Napadow, V., Huggins, J.P., Pauer, L., Kim, J., Hampson, J., Sundgren, P.C., Foerster, B., Petrou, M., Schmidt-Wilcke, T., Clauw, D.J., 2013. Pregabalin rectifies aberrant brain chemistry, connectivity, and functional response in chronic pain patients. Anesthesiology 119, 1453–1464.

Harte, S.E., Harris, R.E., Clauw, D.J., 2018. The neurobiology of central sensitization. J. Appl. Biobehav. Res. 23 (2), e12137.

He, Y., Lim, S., Fortunato, S., Sporns, O., Zhang, L., Qiu, J., Xie, P., Zuo, X.N., 2018. Reconfiguration of cortical networks in MDD uncovered by multiscale community detection with fMRI. Cereb. Cortex 28, 1383–1395.

Hemington, K.S., Rogachov, A., Cheng, J.C., Bosma, R.L., Kim, J.A., Osborne, N.R., Inman, R.D., Davis, K.D., 2018. Patients with chronic pain exhibit a complex relationship triad between pain, resilience, and within- and cross-network functional connectivity of the default mode network. Pain 159, 1621–1630.

Hooten, W.M., 2016. Chronic pain and mental health disorders: shared neural mechanisms, epidemiology, and treatment. Mayo Clin. Proc. 91, 955–970.

Ichesco, E., Puiu, T., Hampson, J.P., Kairys, A.E., Clauw, D.J., Harte, S.E., Peltier, S.J., Harris, R.E., Schmidt-Wilcke, T., 2016. Altered fMRI resting-state connectivity in individuals with fibromyalgia on acute pain stimulation. Eur. J. Pain 20, 1079–1089.

Ichesco, E., Schmidt-Wilcke, T., Bhavsar, R., Clauw, D.J., Peltier, S.J., Kim, J., Napadow, V., Hampson, J.P., Kairys, A.E., Williams, D.A., Harris, R.E., 2014. Altered resting state connectivity of the insular cortex in individuals with fibromyalgia. J. Pain 15, 815–826 e811.

Jensen, K.B., Kosek, E., Petzke, F., Carville, S., Fransson, P., Marcus, H., Williams, S.C.R., Choy, E., Giesecke, T., Mainguy, Y., Gracely, R., Ingvar, M., 2009. Evidence of dysfunctional pain inhibition in fibromyalgia reflected in rACC during provoked pain. Pain 144, 95–100.

Jensen, K.B., Loitoile, R., Kosek, E., Petzke, F., Carville, S., Fransson, P., Marcus, H., Williams, S.C., Choy, E., Mainguy, Y., Vitton, O., Gracely, R.H., Gollub, R., Ingvar, M., Kong, J., 2012. Patients with fibromyalgia display less functional connectivity in the brain's pain inhibitory network. Mol. Pain 8, 32.

Julian, L.J., 2011. Measures of anxiety: state-trait anxiety inventory (STAI), beck anxiety inventory (BAI), and hospital anxiety and depression scale-anxiety (HADS-A). Arthritis Care Res. Hoboken 63 (Suppl 11), S467–S472.

Kaplan, C.M., Schrepf, A., Vatansever, D., Larkin, T.E., Mawla, I., Ichesco, E., Kochlefl, L., Harte, S.E., Clauw, D.J., Mashour, G.A., Harris, R.E., 2019. Functional and neurochemical disruptions of brain hub topology in chronic pain. Pain 160, 973–983.

Kuner, R., Flor, H., 2017. Structural plasticity and reorganisation in chronic pain. Nat. Publ. Group 18, 20–30.

Kutch, J.J., Ichesco, E., Hampson, J.P., Labus, J.S., Farmer, M.A., Martucci, K.T., Ness, T.J., Deutsch, G., Apkarian, A.V., Mackey, S.C., Klumpp, D.J., Schaeffer, A.J., Rodriguez, L.V., Kreder, K.J., Buchwald, D., Andriole, G.L., Lai, H.H., Mullins, C., Kusek, J.W., Landis, J.R., Mayer, E.A., Clemens, J.Q., Clauw, D.J., Harris, R.E., Network, M.R., 2017. Brain signature and functional impact of centralized pain: a multidisciplinary approach to the study of chronic pelvic pain (MAPP) network study. Pain 158, 1979–1991.

Lancichinetti, A., Fortunato, S., 2012. Consensus clustering in complex networks. Sci. Rep. 2, 336.

Lerman-Sinkoff, D.B., Barch, D.M., 2016. Network community structure alterations in adult schizophrenia: identification and localization of alterations. NeuroImage Clin. 10, 96–106.

Loggia, M.L., Kim, J., Gollub, R.L., Vangel, M.G., Kirsch, I., Kong, J., Wasan, A.D., Napadow, V., 2013. Default mode network connectivity encodes clinical pain: an arterial spin labeling study. Pain 154, 24–33.

Mansour, A., Baria, A.T., Tétreault, P., Vachon-Presseau, E., Chang, P.-C., Huang, L., Apkarian, A.V., Baliki, M.N., 2016. Global disruption of degree rank order: a hallmark of chronic pain. Sci. Rep. 6, 1–17.

Napadow, V., Kim, J., Clauw, D.J., Harris, R.E., 2012. Decreased intrinsic brain connectivity is associated with reduced clinical pain in fibromyalgia. Arthritis Rheum. 64, 2398–2403.

Napadow, V., LaCount, L., Park, K., As-Sanie, S., Clauw, D.J., Harris, R.E., 2010. Intrinsic brain connectivity in fibromyalgia is associated with chronic pain intensity. Arthritis Rheum. 62, 2545–2555.

Newman, M.E., 2006a. Modularity and community structure in networks. Proc. Natl. Acad. Sci. U. S. A. 103, 8577–8582.

Newman, M.E.J., 2004. Detecting community structure in networks. Eur. Phys. J. B 38, 321–330.

Newman, M.E.J., 2006b. Modularity and community structure in networks. Proc. Natl. Acad. Sci. U. S. A. 103, 8577–8582.

Power, J.D., Barnes, K.A., Snyder, A.Z., Schlaggar, B.L., Petersen, S.E., 2012. Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. Neuroimage 59, 2142–2154.

Power, J.D., Cohen, A.L., Nelson, S.M., Wig, G.S., Barnes, K.A., Church, J.A., Vogel, A.C., Laumann, T.O., Miezin, F.M., Schlaggar, B.L., Petersen, S.E., 2011. Functional network organization of the human brain. Neuron 72, 665–678.

Radloff, L.S., 1977. The CES-D scale: A self-report depression scale for research in the general population. Appl Psychol Meas 1, 385–401.

Rubinov, M., Sporns, O., 2010. Complex network measures of brain connectivity: uses and interpretations. Neuroimage 52, 1059–1069.

Rubinov, M., Sporns, O., 2011. Weight-conserving characterization of complex functional brain networks. Neuroimage 56, 2068–2079.

Schmidt-Wilcke, T., Ichesco, E., Hampson, J.P., Kairys, A., Peltier, S., Harte, S., Clauw, D.J., Harris, R.E., 2014. Resting state connectivity correlates with drug and placebo response in fibromyalgia patients. Neuroimage Clin. 6, 252–261.

Schrepf, A., Harper, D.E., Harte, S.E., Wang, H., Ichesco, E., Hampson, J.P., Zubieta, J.-K., Clauw, D.J., Harris, R.E., 2016. Endogenous opioidergic dysregulation of pain in fibromyalgia. Pain 157, 2217–2225.

Sluka, K.A., Clauw, D.J., 2016. Neurobiology of fibromyalgia and chronic widespread pain. Neuroscience 338, 114–129.

Smarr, K.L., Keefer, A.L., 2011. Measures of depression and depressive symptoms: beck depression inventory-II (BDI-II), center for epidemiologic studies depression scale (CES-D), geriatric depression scale (GDS), hospital anxiety and depression scale (HADS), and patient health questionna. Arthritis Care Res. 63, S454–S466.

Telesford, Q.K., Simpson, S.L., Burdette, J.H., Hayasaka, S., Laurienti, P.J., 2011. The brain as a complex system: using network science as a tool for understanding the brain. Brain Connect. 1, 295–308.

Tracey, I., Woolf, C.J., Andrews, N.A., 2019. Composite pain biomarker signatures for objective assessment and effective treatment. Neuron 101, 783–800.

Vachon-Presseau, E., Berger, S.E., Abdullah, T.B., Huang, L., Cecchi, G.A., Griffith, J.W., Schnitzer, T.J., Apkarian, A.V., 2018. Brain and psychological determinants of placebo pill response in chronic pain patients. Nat. Commun. 9, 3397.

Vinh, N.X., Epps, J., Bailey, J., 2010. Information theoretic measures for clusterings comparison: variants, properties, normalization and correction for chance. J. Mach. Learn. Res. 11, 2837–2854.

Watson, A., El-Deredy, W., Iannetti, G.D., Lloyd, D., Tracey, I., Vogt, B.A., Nadeau, V., Jones, A.K.P., 2009. Placebo conditioning and placebo analgesia modulate a common brain network during pain anticipation and perception. Pain 145, 24–30.

Whitfield-Gabrieli, S., Nieto-Castanon, A., 2012. Conn: a functional connectivity toolbox for correlated and anticorrelated brain networks. Brain Connect. 2, 125–141.

Wolfe, F., Smythe, H.A., Yunus, M.B., Bennett, R.M., Bombardier, C., Goldenberg, D.L., Tugwell, P., Campbell, S.M., Abeles, M., Clark, P., et al., 1990. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia. Report of the multicenter criteria committee. Arthritis Rheum. 33, 160–172.

Woolf, C.J., 2011. Central sensitization: implications for the diagnosis and treatment of pain. Pain 152, S2–15.

Youden, W.J., 1950. Index for rating diagnostic tests. Cancer 3, 32–35.

Zigmond, A.S., Snaith, R.P., 1983. The hospital anxiety and depression scale. Acta Psychiatr. Scand. 67, 361–370.