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EDITORIAL

Functional Connectivity: Dissecting the Relationship Between the Brain and "Pain Centralization" in Rheumatoid Arthritis

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Pain is a frequent and disabling symptom experienced by individuals with inflammatory arthritis. More than 50% of patients with inflammatory arthritis report visual analog scale (VAS) pain scores ≥30/100 mm despite treatment with disease-modifying antirheumatic drugs (DMARDs) (1). Patients often equate pain with peripheral inflammation, as evidenced by studies demonstrating that pain is the primary factor influencing patient global assessment of disease activity (2). However, recent clinical studies suggest that rheumatoid arthritis (RA) patients may exhibit signs of central sensitization, which may be why treating peripheral inflammation does not always translate into effective pain relief (3). However, the only study to directly examine the predictive effect of temporal summation, a measure of central sensitization, did not reveal a significant association between temporal summation and DMARD response (4). Thus, the extent to which RA patients demonstrate neural mechanisms consistent with central sensitization is still unclear.

Advances in neuroimaging have enabled the assessment of functional connectivity between brain regions, allowing researchers to better understand the neural mechanisms underlying spontaneous clinical pain states. Functional brain connectivity assesses synchronization in activity displayed by two or more brain regions when they are "communicating" (e.g., when one region is exchanging information with the other). The connectivity between the insular cortex and a network of brain regions collectively known as the default mode network (DMN) (a group of interconnected brain regions including the medial prefrontal cortex, posterior cingulate cortex, precuneus, inferior parietal lobule, hippocampal formation, and lateral temporal cortex [5]) has attracted particular attention in recent years. In healthy subjects, anterior and middle insula activity typically shows no correlation (or, sometimes, weak negative correlation) with DMN regions. However, in patients with chronic pain disorders, insula subregions can become functionally connected with the DMN.

Following the original observation by our group in fibromyalgia (FM) patients (6), an elevation of connectivity between the insula and the DMN (or to a specific core DMN region, such as the medial prefrontal cortex) has been documented in several pain conditions, including noninflammatory and inflammatory chronic low back pain (7–9), osteoarthritis (8), and migraine (10). Intriguingly, the strength of DMN–insula connectivity was positively correlated with clinical pain severity in many studies (6–8), although investigators in at least one study reported negative correlations in the context of an acute migraine attack (10). In addition, DMN–insula connectivity was found to be reduced after successful pharmacologic (11) and nonpharmacologic (12) treatment, therefore raising the possibility that this feature may one day be considered an imaging biomarker of pain perception.

The study reported by Basu et al in this issue of *Arthritis & Rheumatology* tested the hypothesis that RA patients demonstrate neuronal hallmarks of pain centralization similar to those observed in FM (13). To this end, they enrolled 54 RA patients who met the 2010 American College of Rheumatology (ACR)/European

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League Against Rheumatism classification criteria (14) and who had experienced clinically significant fatigue during the past 3 months. The subjects underwent functional magnetic resonance imaging (fMRI), and an independent component analysis assessed functional connectivity between 4 networks of interest, including the DMN, and the rest of the brain. Subjects also completed the 2011 ACR FM survey, a measure of "fibromyalgianess" (FMness), which is thought to represent the clinical manifestations of pain centralization (15). In the study by Basu et al, the average score on the 2011 ACR FM survey was 13.2 (the cutoff for the ACR modified preliminary criteria for FM diagnosis is 13), which is compatible with previous studies suggesting that a significant number of RA patients demonstrate comorbid FM. Of note, the ACR FM survey score was significantly positively associated with DMN–insula functional connectivity.

With these results in a population of RA patients, Basu et al reinforce the generalizability of DMN–insula connectivity as a potential marker across etiologically heterogeneous pain conditions. However, the distinction between this study and studies of other conditions is that there was no correlation between DMN–insula connectivity and spontaneous clinical pain severity, assessed at the time of the scan. By showing that DMN–insula connectivity was more associated with FMness than with current pain severity, this study suggests another interpretation about the potential functional significance of this marker—that it is not a marker of "pain intensity" per se, but rather a marker of "pain centralization." It may be that previous studies demonstrated an association with clinical pain severity because pain intensity is more closely associated with measures of pain centralization (e.g., FMness) in functional pain disorders than in RA, which is known to have a significant peripheral component (e.g., peripheral joint inflammation). Of note, however, an fMRI study of patients with ankylosing spondylitis, a systemic rheumatic disease characterized by inflammatory back pain, did show associations between back pain severity and DMN connectivity with the salience network (of which the insula is a prominent component) (9). Thus, future studies are needed to better understand the relationship between DMN–insula activity and pain severity in systemic inflammatory conditions. In particular, we recommend that studies include different measures of pain (e.g., pain severity, FMness, pain interference, pain catastrophizing, etc.) to better define the nature of observed associations.

Strengths of the study by Basu et al include the assessment of multiple relevant clinical characteristics, including age, sex, amitriptyline use, inflammatory disease activity measures (e.g., C-reactive protein [CRP] level and the Disease Activity Score in 28 joints [16]), and levels of pain, fatigue, sleep disturbance, and depression. By including age, sex, CRP level, and amitriptyline use in the linear regression models, Basu et al were able to take into account the roles of these variables as possible confounders of the association between network–whole brain connectivity and FMness. Ultimately, adjusting for these variables did not change the magnitude of the association, which reassures that the observed associations are not an artifact of confounding due to relationships between the covariates, network–whole brain connectivity, and FMness. The assessment of pain, fatigue, sleep disturbance, and depression also enabled analyses examining correlations between these variables and DMN–insula connectivity. These analyses were post hoc and should therefore be considered exploratory. Nevertheless, these results provide clues to the underlying cause of the association between DMN–insula connectivity and FMness, suggesting that this association may reflect a distinct phenotype associated with pain centralization.

Another strength of the study is the large sample size. With a study sample of 54 RA patients, this is the largest fMRI study to assess functional connectivity in individuals with RA. A sufficient sample size is required for stable and reproducible results and to enable correction for multiple testing, which is inherent in neuroimaging studies. Each fMRI image volume can comprise hundreds of thousands of voxels, or volume elements, each of which is used for separate statistical testing (17). Fortunately, neuroimagers take advantage of the fact that "genuine brain activity" tends to cluster in regions usually spanning many adjacent voxels (as opposed to random noise, which can lead to spurious small clusters in a "salt and pepper" pattern) (18). In the study by Basu et al, per commonly adopted procedure, the statistical significance of each cluster was determined based on the size of the cluster and a family-wise error cluster corrected P value of less than 0.05, thereby accounting for multiple comparisons.

Despite these strengths, the study had some limitations. Perhaps the most important was the absence of a control group, which limits whether we can truly conclude that DMN–insula connectivity is significantly altered in RA patients. Another potential limitation is that the data used to perform functional connectivity analyses were collected while the participants were engaged in a cognitive task (the Paced Auditory Serial Addition Test) rather than at rest. While computing connectivity metrics during a task is not uncommon (19), this

feature may limit our ability to directly compare the results from Basu et al's study with those from previous studies evaluating the role of the DMN in chronic pain, as in most or all of those studies connectivity analyses were performed using unconstrained resting-state data.

As the authors note, another primary limitation is generalizability. Inclusion criteria required that participants have a score of >3 on the Chalder Fatigue Binary Scale (20), restricting the study sample to individuals with clinically meaningful levels of fatigue. Few studies have used the Chalder Fatigue Scale to assess fatigue in RA, and even fewer have reported on the binary scoring system (21). Thus, it is difficult to ascertain what a score of >3 means in the context of RA patients, and it would be informative to know the proportion of interested participants who were screened out because of this criterion. Future studies are needed to determine if the relationship between DMN–insula connectivity and FMness holds among individuals with lower levels of fatigue.

Finally, as with all fMRI studies, this study is limited in that it cannot provide direct information on the neurophysiologic processes underlying the observed neuroimaging signals. The investigators utilized a standard fMRI technique using an endogenous contrast mechanism called blood oxygen level–dependent (BOLD) imaging. BOLD fMRI takes advantage of neurovascular coupling in response to brain activity and serves as a proxy for neural activity. However, within each neuroimaging voxel, hundreds of thousands to millions of neurons exist, and the dynamic interrelationships between these neurons are complex. Thus, basing the interpretation of fMRI signal on neural activity, or "connectivity" as was used by Basu et al, requires several assumptions, the validity of which may differ from study to study (22).

Despite these limitations, fMRI can provide novel insights into the central nervous system (CNS) pathways involved in the expression of difficult-to-quantify symptoms, such as pain and fatigue, in RA. This study extends findings demonstrated in many previous studies of noninflammatory pain conditions to RA, a systemic inflammatory condition. Specifically, the study provides evidence highlighting DMN–insula connectivity as one of the most reliable imaging markers of chronic pain reported in the literature thus far.

For rheumatologists, the implications of this observation are broad. First, by identifying associations between aberrant brain functional connectivity and phenotypic characteristics (primarily FMness and secondarily fatigue and sleep disturbance), this study underscores the importance of considering CNS factors, in addition to peripheral joint inflammation, when evaluating symptoms experienced by our RA patients. Second, by showing that despite associations between DMN–insula connectivity and FMness, DMN–insula connectivity was not associated with pain severity, this study highlights the importance of carefully considering the types of pain measures included in studies. FMness includes assessments of widespread pain (e.g., pain distribution) and somatic symptoms, while the pain VAS only assesses pain intensity. Although they are related, these concepts are inherently different. Third, by providing evidence of a neurobiologic underpinning for FMness in RA, this study points toward the potential role of treatment strategies previously shown to modulate DMN–insula connectivity (e.g., acupuncture, γ-aminobutyric acid analogs) in individuals with RA and high levels of FM symptoms (23).

In summary, the study by Basu et al is an important step toward understanding the role of the brain in modulating pain in patients with systemic inflammatory conditions. Future investigations of these findings are needed to examine their generalizability (e.g., in studies including RA patients with lower levels of fatigue, studies of newly diagnosed and hence drug-naive RA patients, etc.) and reproducibility (e.g., in observational longitudinal studies), as well as the responsiveness of these neuroimaging markers to interventions (e.g., in clinical trials of DMARDs and/or analgesic medications). As more neuroimaging studies are performed and reported, rheumatologists should become familiar with the strengths and limitations of these types of studies. Characterizing the complex interrelationships between the brain, peripheral nervous system, and immune pathways (both peripheral and central) holds promise for the development of safe and effective pain management strategies, which are sorely needed to improve quality of life for our patients with systemic inflammatory conditions.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published.

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