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CHRONIC PAIN (R STAUD, SECTION EDITOR)

Inflammation and the Central Nervous System in Inflammatory Rheumatic Disease

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Abstract

Purpose of Review To review how peripheral inflammation in rheumatic disease influences the central nervous system. We consider recent studies of rheumatic disease that employ functional and structural neuroimaging in the context of inflammation, as well as recent studies considering how immunosuppressive therapy is associated with changes in brain function and structure.
Recent Findings The most compelling evidence thus far comes from studies of rheumatoid arthritis and indicates that higher levels of inflammation are associated with changes in cognitive, affective, and pain-processing brain regions, some of which may be rectified by anti-inflammatory treatment. Comorbid symptoms such as widespread pain and fatigue may also be associated with these changes. Inflammation may be associated with compensatory activation of brain regions to offset structural changes.
Summary This emerging line of evidence suggests that communication between the brain and immune system are an important and underappreciated aspect of inflammatory rheumatic disease.

Keywords Inflammation · Arthritis · Rheumatoid · Central nervous system sensitization · Magnetic resonance imaging

Introduction

Many rheumatic diseases are characterized by altered or increased inflammatory activity. This activity is understood to play a significant if not essential role in the primary pathology of each condition [1–3]. Rheumatology routinely focuses on immunomodulation as a means of disease modification; if successful, there are clear indications that disease activity has been slowed or even arrested.

However, the inflammatory molecules that contribute to indices of the primary disease lead a parallel life in communication with the central nervous system (CNS) [4]. One reason that immune and CNS activity are often viewed independently is that the brain is an "immunologically privileged" organ. This view, while certainly correct, may lead to the misapprehension that the brain and immune system are not involved in coordinated activity, when, in fact, they engage in constant bidirectional communication [4]. One product of this communication is a set of conserved behavioral changes, mediated by the CNS that occur when an individual experiences serious injury or infection—social withdrawal, reduced activity, loss of appetite, hyperalgesia, and changes in affective and cognitive processes. These "sickness behaviors" are meant to prioritize the intense demands of a robust immune response at the cost of severely disrupting normal activity in the short term [4]. This relationship between acute inflammatory insults and behavioral changes is well described in the animal literature and reproducible in human study participants receiving experimental immunogenic insults such as lipopolysaccharide or vaccination [5, 6]. However, the effect of chronic or repeated inflammatory insults on symptoms and behaviors is more mysterious, particularly in the context of complex rheumatic disease. It is well established that some multisystem autoimmune illness can result in severe neuronal injury accompanied by gross neurological deficits and clear evidence of damage to white and gray matter, but this occurs in a very small subset of patients [7]. An emerging literature suggests that subtle inflammatory insults to the CNS might contribute to

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burdensome co-occurring symptoms that are prevalent across the spectrum of inflammatory rheumatic diseases.

The battery of symptoms recognized as "sickness behaviors" bear striking similarity to the complex comorbid symptoms observed in rheumatic diseases. In rheumatoid arthritis (RA), a third or more of patients show the complex battery of hyperalgesia, fatigue, and cognitive dysfunction that indicate co-occuring fibromyalgia (FM) [8], and even when biologic therapy is deemed successful in RA by disease activity metrics (e.g., no swollen joints, normal erythrocyte sedimentation rate [ESR]), a large number of patients continue to report significant pain and fatigue [9, 10]. In systemic lupus erythematosus (SLE), up to 90% of patients have some co-occurring neuropsychiatric symptoms, while cognitive dysfunction specifically affects 30–50% of those with SLE [11]. Within a given patient, symptoms tend to fluctuate considerably even in relatively short time frames, as seen in a study of 106 rheumatic disease patients monitored for 28 days where within-subject variance accounted for 34% of the total variance in pain and 41% of the total variance in fatigue [12]. In ankylosing spondylitis (AS), approximately half of patients have fatigue as a major symptom [13]. These behaviors in turn contribute greatly to deleterious quality of life and work disability [14]. Identifying risk factors, such as systemic inflammation, that modify the symptom presentation in rheumatic disease could have a large and positive impact on treatment.

Mechanistic investigation of these symptoms in human patients is limited by the difficulty in accessing the brain. The application of non-invasive surrogate assays of neurobiology—particularly innovative neuroimaging techniques—has provided helpful insights. Moreover, employing neuroimaging in the context of interventional longitudinal studies will be valuable if we are to better infer causality of inflammatory pathways.

In this brief critical review, we consider recently published literature on the role of inflammation in altering brain activity and structure in inflammatory rheumatic disease. We emphasize publications in approximately the last 5 years, particularly those that have considered inflammation in the context of functional neuroimaging and the effect of immunomodulation on neuroimaging measures.

How Does the Immune System Change the Brain?

Imagine an RA patient with elevated ESR or C-reactive protein (CRP). These two indices of inflammatory activity are closely associated with levels of IL-6, IL-1β, and TNF-α in circulating blood. Beyond the affected joints, what effects might these cytokines be having? Dantzer (2008) identifies several routes by which inflammatory actors can induce changes in the CNS: peripheral cytokine production can activate afferent nerves, such as the vagus, or perivascular immune cells in brain venules, that result in the production of new inflammatory mediators in the brain. It is also possible for macrophage-like cells in brain structures outside the blood brain barrier (BBB, e.g., circumventricular organs) to spur cytokine production that enters the brain through volume diffusion, and cytokines can cross the BBB through a saturable transport system [4]. Each of these routes provide a plausible pathway for inflammatory influences on the CNS in rheumatic diseases. It is again worth noting that these pathways need not result in severe neuronal injury and consequent gross anatomical changes to the CNS as is sometimes seen in conditions such as SLE. Instead, they may subtly influence the pattern of connections between different neural networks or result in more granular structural changes that require advanced neuroimaging techniques to detect.

Inflammation and Effects on the CNS in Rheumatic Disease—Functional and Structural Neuroimaging Findings

One method of assessing CNS plasticity related to peripheral inflammation is to measure the functional interactions between brain regions with MRI and their association with inflammatory measures. This methodology can only provide indirect evidence of neuroinflammatory processes, as in vivo measures of neuroinflammation, such as the PET ligand [^{11}C]PBR28, are still maturing and have not yet been used in inflammatory rheumatic disease.

Functional connectivity is defined as the temporal correlation of neural activity between brain regions (for a review on functional connectivity methods and interpretations, see Van den Heuvel and Pol [15]). The brain is organized into large-scale networks, wherein the neural activities of the component brain regions are highly correlated over time and spontaneously active even during the resting state. The most commonly reported networks include dorsal attention network (DAN), default mode network (DMN), fronto-parietal network (FPN), salience network (SLN), sensorimotor network (SMN), and the visual network.

Only a handful of studies have addressed the link between inflammation and functional connectivity of the brain in rheumatic conditions. Hou et al. [16] measured cerebral activation during a cognitive function task and resting state functional connectivity in SLE patients. Relative to healthy controls, the SLE patients had increased activation in the inferior/superior parietal lobule and inferior frontal gyrus during task execution. Additionally, these regions were more strongly connected to each other at rest in the SLE patients and the strength of this connectivity positively correlated with the SLE disease activity index. The authors interpreted these results as evidence of disease-related CNS plasticity. Since there was no difference in task performance between SLE patients and

controls, the increased brain activation may be compensatory in nature.

In another study of AS patients, Li and colleagues compared resting state functional connectivity between patients and controls and examined associations between connectivity and measures of disease activity and inflammation [17]. They found that functional connectivity between the left mid temporal gyrus and left precuneus was negatively correlated with the Bath AS disease activity index (BASDAI) score, CRP, and ESR.

More recently, researchers have examined the whole brain network using graph theoretical techniques. Graph theory is a set of mathematical tools to examine the structure and function of networks. A network is simply a collection of nodes (i.e., brain regions) and edges (i.e., structural or functional connections between nodes). Network organization is important because it determines the efficiency and content of information transfer [18–20]. The brain network shares an optimal pattern of organization with many other physical and biological systems (e.g., the Internet or social networks). One such feature is the presence of highly connected and functionally central brain regions called hubs. Hub brain regions, just like hub airports, facilitate communication and information integration across distinct modules (i.e., functional systems) of the brain.

We examined the central response to inflammation in 54 patients with RA [21]. Employing a multi-modal approach, we correlated task-based functional connectivity and gray matter volume with peripheral inflammation (measured by ESR). We assessed both seed network-to-whole brain connectivity and every pairwise connection in the brain network using graph theoretical techniques. Finally, we determined the hub status of brain regions to assess if inflammation was related to network organization.

We found that two brain regions, the left inferior parietal lobule (IPL) and medial prefrontal cortex (mPFC), were consistently and significantly related to inflammation. First, we found that connectivity between several resting state networks (DMN, DAN, SLN, and medial visual networks) and the left IPL and mPFC were positively associated with ESR. Additionally, we found that the gray matter volume of the left IPL was negatively correlated with ESR. Using a more detailed approach to examine the whole brain network (all pairwise connections between 264 nodes), we found a significant configuration that was associated with inflammation. This configuration included multiple nodes in the left IPL and mPFC that overlapped with the clusters mentioned above. In individuals with high levels of peripheral inflammation, the nodes in this configuration are more hub-like, meaning that they are more connected and functionally important to communication within the brain network. Many of these results were replicated in the same individuals 6 months later.

We recently expanded this effort by examining the interaction between inflammation and comorbid symptoms of FM in the same RA patient group. We hypothesized that RA patients with comorbid symptoms of FM might show a different or more pronounced CNS response to inflammatory activity. We therefore analyzed the association between inflammation and functional connectivity in RA patients with and without comorbid FM. In RA patients with comorbid FM, there was a significant positive association between inflammation and functional connectivity between the posterior insula and the left IPL, and between the left IPL and the dorsal anterior cingulate cortex (ACC) [22]. The posterior insula and dorsal ACC are classic pro-nociceptive brain regions [23–25], and alterations in the structure, function, and neurochemistry of these regions have been frequently reported in FM [26–29]. These results indicate that in some RA patients, there is an interaction, and perhaps integration, of inflammation-linked brain connectivity and classic pro-nociceptive circuitry leading to sensitization of the CNS.

Another approach to examine CNS plasticity in response to inflammation is to measure brain structure, such as the concentration of gray matter volume (GMV) using voxel-based morphometry [30]. Reductions in GMV in disease states are generally interpreted as cortical atrophy. Mak and colleagues [31] found reduced GMV in SLE patients without overt neuropsychiatric symptoms in multiple cortical regions, including the orbital frontal cortex, left IPL, insula, and left primary somatosensory cortex (S1) compared to healthy controls. A second MRI scan was completed in patients after treatment which revealed increases in GMV that correlated with the reduction in systemic disease activity.

Effects of Immunosuppressive Therapy on the CNS in Inflammatory Rheumatic Disease

A second emerging line of evidence examining inflammation in rheumatic disease examines how inflammation-suppressing therapies could alter CNS activity. As noted above, these studies provide indirect evidence of the relationship between the CNS and inflammatory activity. Hess et al. were the first group we are aware of to demonstrate changes in brain function secondary to anti-inflammatory treatment [32]. Specifically, they monitored fMRI activity before and after TNF-alpha inhibition (TNFi; infliximab) in RA ($n = 5$) during an evoked pain task. The paradigm used compression of the most affected hand to induce BOLD activation. As expected, this task produced activation in the contralateral hemisphere of the brain in many pain-processing regions, and this activity was reduced post-treatment in the thalamus, secondary somatosensory, insular, and cingulate cortices.

Rech et al. [33] followed these analyses in a slightly larger sample ($n = 10$), again exploring the effects of short (i.e., 3 days) and medium term (28 days) effects of TNFi

(subcutaneous certolizumab pegol) on fMRI measures in RA patients. Similar to the preceding analyses, compression of the most affected hand resulted in increased BOLD activity in regions associated with pain processing including S1, the insula, and dorsolateral prefrontal cortex. After 3 days of TNFi, there were substantial decreases in BOLD activity in these regions, decreases that were largely maintained after seven and 28 days as well. Furthermore, those patients who showed a robust clinical response to TNFi (n = 5) showed greater baseline BOLD activation in response to the compression paradigm, suggesting that neural signatures may be useful in distinguishing patients most likely to benefit from anti-inflamamtory treatment.

Mak et al. [34] examined brain activation during a neuropsychological test (the Wisconsin card sorting test) in 14 SLE patients without overt neuropsychiatric symptoms. Treatment consisted of prednisolone for all patients with most receiving additional immunosuppressive therapies such as hydroxychloroquine and/or azathioprine. Following treatment, SLE patients showed increased activation of the anterior cingulate cortex, but decreased activation of the frontal gyri and IPL in addition to several other regions.

Wu et al. [35] examined the impact of TNFi on cortical thickness in 14 AS patients. The included patients had clinically significant levels of fatigue and back pain (at least 3 on a 0–10 scale) and were not using biologic therapy at the time of the first scan prior to the intiation of a minimum of 10 weeks of TNFi treatment. TNFi treatment produced a substantial decrease in back pain but not fatigue scores. The analysis of cortical thickness focused on those regions where cortical thickness was associated with back pain prior to treatment. Post-treatment, three a priori areas of interest showed cortical thinning—the left primary motor area/supplementary motor area, left inferior parietal sulcus, and the right premotor area. The thinning of the right premotor area was furthermore associated with the magnitude of pain relief experienced following treatment. Because cortical thinning was associated with the severity of back pain prior to treatment the discovery of further thinning during a period of pain relief was viewed as counter-intuitive by the authors.

Other Rheumatic Disease

Rheumatic conditions that are not viewed as primarily inflammatory or autoimmune, such as FM and ostearthritis, may still involve inflammatory communication to the CNS in a subset of patients. A recent study used the ligand [^{11}C]PBR28, a putative marker of glial activation in the CNS [36], in FM. Eleven FM patients were compared to the same number healthy controls on the degree of [^{11}C]PBR28 binding. FM patients showed widespread increases in binding across the cerebral cortex with particularly pronounced elevations in the frontal and parietal lobes compared to healthy controls, suggestive of neuroinflammatory processes. The elevations in binding in the midcinguate cortex were furthermore associated with current levels of patient reported fatigue [37]. FM provides an interesting context for neuroinflammatory processes, as attempts to define FM using peripheral markers of inflammation have been quite mixed [38]. Nonetheless, FM does appear to feature altered inflammatory activity in cerebrospinal fluid [39]. Osteoarthritis, which is not considered an autoimmune condition, nonetheless features a substantial proportion of patients with elevated levels of circulating inflammatory markers and increased inflammation from circulating immune cells [40, 41]. Interestingly, following treatment with Naproxen, osteoarthritis patients showed substantial reductions in brain activity in the bilateral somatosensory cortices, as well as the thalamus and amygdala [42], though similar effects have been observed in a study using paracetamol, so these changes may be due to generic COX inhibition [43].

Discussion

Peripheral inflammation influences the CNS in many patients with rheumatic diseases, likely in ways that are subtle and do not result in obvious neurologic deficits. The best evidence for this phenomenon thus far is concentrated in RA. Furthermore, anti-inflammatory treatments may well alter brain function and even structure in many RA patients. These conclusions may sound provocative on the surface given the tendency to compartmentalize immune and CNS activity, but they are supported by a large and consistent body of pre-clinical research [44, 45]. At the same time, research into the interaction of inflammation and the CNS in human rheumatic disease patients is a new outgrowth that will certainly branch in many directions as the complexities of each disease and the great variability in symptoms is further explored. The methodological variability in the fields of neuroimaging and psychoneuroimmunology will also present a challenge to synthesizing the results of these studies.

One of our working hypotheses is that in some patients, chronic inflammation produces neuroinflammatory stress in the CNS forces additional cortical resources to be employed in the completion of "everyday" activities. It bears repeating that the ability to work and socialize is heavily dependent on cognitive function and energy—two symptom domains that are greatly impaired in many rheumatic disease patients. In multiple sclerosis, the literature suggests that most patients are able to perform isolated cognitive tasks on par with healthy individuals, but require participation of more cerebral cortex to do so [46]. In healthy individuals, greatly increasing the complexity of cognitive tasks results in activation of brain regions normally associated with the DMN, a brain network that is thought to be quiescent during the performance of tasks

[47]. We found that DMN regions become more connected areas involved in cognitive processing as inflammation increased across the RA patient sample [21]. One interpretation of these findings is that the brain requires "reserve" resources to perform cognitive tasks under the duress of inflammatory signaling, similar to what is observed in multiple sclerosis and what may occur in healthy people engaging in highly complicated tasks. This compensatory activity provides welcome resources, but may actually conceal the degree of strain that inflammatory activity places on the CNS. These changes in brain function may be secondary to changes in brain structure—we found an area of reduced gray matter associated with higher inflammation in the left IPL, which appears to play a critical role in the functional changes associated with inflammation [21].

Future Directions

Functional neuroimaging has revealed much about the complexity of the CNS in rheumatic diseases, but understanding the role inflammation plays in this complexity will require several new lines of inquiry. Studies are needed that explore brain structure and function in the context of inflammation for several common rheumatic conditions including SLE, AS, psoriatic arthritis, and osteoarthritis, while results in RA need to be replicated in a new sample. Though we know that symptoms resembling classic "sickness behaviors" are ubiquitous in inflammatory rheumatic diseases, we do not yet know if a generic mechanism is involved (e.g., the central IL-1β pathway) or if the biologic drivers are disease-specific. Studies are needed that are designed a priori to address the role of inflammation in symptom heterogeneity. Our work in RA suggests that there may be important differences in the way inflammation acts on the CNS when patients display co-occurring fatigue, widespread pain, and cognitive dysfunction. If it is true that some individuals are more vulnerable to the central impact of inflammation, then we need to understand what contributes to this vulnerability. A promising lead comes from research on how the BBB can be more or less permissive in allowing immune communication with the CNS, a topic covered comprehensively in a recent review [48]. Finally, it is possible and even likely that the inflammatory mediators used to monitor disease activity may not provide the clearest indication of inflammatory signaling to the CNS. As we and other groups explore biomarkers that better reflect inflammatory sensitization of the CNS, it may be possible to monitor different aspects of the inflammatory response in rheumatic disease simultaneously.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Wells G, et al. Validation of the 28-joint Disease Activity Score (DAS28) and European League Against Rheumatism response criteria based on C-reactive protein against disease progression in patients with rheumatoid arthritis, and comparison with the DAS28 based on erythrocyte sedimentation rate. Ann Rheum Dis. 2009;68(6):954–60.
2. Carli L, et al. Leukopenia, lymphopenia, and neutropenia in systemic lupus erythematosus: Prevalence and clinical impact–A systematic literature review. Semin Arthritis Rheum. 2015;45(2):190–4.
3. Gratacos J, et al. Serum cytokines (IL-6, TNF-alpha, IL-1 beta and IFN-gamma) in ankylosing spondylitis: a close correlation between serum IL-6 and disease activity and severity. Br J Rheumatol. 1994;33(10):927–31.
4. Dantzer R, et al. From inflammation to sickness and depression: when the immune system subjugates the brain. Nat Rev Neurosci. 2008;9:46–56.
5. Lekander M, et al. Intrinsic functional connectivity of insular cortex and symptoms of sickness during acute experimental inflammation. Brain Behav Immun. 2016;56:34–41.
6. Harrison NA, et al. Inflammation causes mood changes through alterations in subgenual cingulate activity and mesolimbic connectivity. Biol Psychiatry. 2009;66(5):407–14.
7. Luyendijk J, et al. Neuropsychiatric systemic lupus erythematosus: lessons learned from magnetic resonance imaging. Arthritis Rheum. 2011;63(3):722–32.
8. Gist AC, et al. Fibromyalgia remains a significant burden in rheumatoid arthritis patients in Australia. Int J Rheum Dis. 2018;21(3):639–46.
9. McWilliams DF, et al. Discordant inflammation and pain in early and established rheumatoid arthritis: latent class analysis of early rheumatoid arthritis network and British Society for Rheumatology Biologics Register data. Arthritis Res Ther. 2016;18(1):295.
10. Druce KL, et al. Most patients who reach disease remission following anti-TNF therapy continue to report fatigue: results from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis. Rheumatology (Oxford). 2016;55(10):1786–90.
11. Gulinello M, Wen J, Putterman C. Neuropsychiatric symptoms in lupus. Psychiatr Ann. 2012;42(9):322–8.
12. Schneider S, et al. Individual differences in the day-to-day variability of pain, fatigue, and well-being in patients with rheumatic disease: associations with psychological variables. Pain. 2012;153(4):813–22.

13. van Tubergen A, et al. Assessment of fatigue in patients with ankylosing spondylitis: a psychometric analysis. Arthritis Rheum. 2002;47(1):8–16.
14. Stebbings S, Treharne GJ. Fatigue in rheumatic disease: an overview. Int J Clin Rheumatol. 2010;5:487.
15. van den Heuvel MP, Pol HEH. Exploring the brain network: a review on resting-state fMRI functional connectivity. Eur Neuropsychopharmacol. 2010;20(8):519–34.
16. Hou J, et al. Abnormalities of frontal-parietal resting-state functional connectivity are related to disease activity in patients with systemic lupus erythematosus. PLoS One. 2013;8(9):e74530.
17. Li C, et al. Cerebral functional deficits in patients with ankylosing spondylitis- an fMRI study. Brain Imaging Behav. 2017;11(4):936–42.
18. Bullmore E, Sporns O. The economy of brain network organization. Nat Rev Neurosci. 2012:1–14.
19. Moon J-Y, et al. Structure shapes dynamics and directionality in diverse brain networks: mathematical principles and empirical confirmation in three species. Sci Rep. 2017;7:46606.
20. Moon J-Y, et al. General relationship of global topology, local dynamics, and directionality in large-scale brain networks. PLoS Comput Biol. 2015;11(4):e1004225.
21.•• Schrepf A, et al. A multi-modal MRI study of the central response to inflammation in rheumatoid arthritis. Nat Commun. 2018;9(1):2243. **The first study to show altered brain network activity associated with inflammation in rheumatoid arthritis.**
22.• Kaplan CM, et al. Inflammation is associated with pro-nociceptive brain connections in rheumatoid arthritis patients with concomitant fibromyalgia. Arthritis Rheumatol. 0(ja) **The first study to show that inflammation-linked brain connectivity is associated with comorbid symptoms in rheumatoid arthritis.**
23. Segerdahl AR, et al. The dorsal posterior insula subserves a fundamental role in human pain. Nat Neurosci. 2015;18(4):499–500.
24. Lieberman MD, Eisenberger NI. The dorsal anterior cingulate cortex is selective for pain: results from large-scale reverse inference. Proc Natl Acad Sci U S A. 2015;112(49):15250–5.
25. Mouraux A, Iannetti GD. The search for pain biomarkers in the human brain. Brain. 2018;141(12):3290–307.
26. Harris RE, et al. Elevated insular glutamate in fibromyalgia is associated with experimental pain. Arthritis &amp. Rheumatism. 2009;60(10):3146–52.
27. Ichesco E, et al. Altered resting state connectivity of the insular cortex in individuals with fibromyalgia. J Pain. 2014;15(8):815–826.e1.
28. Kuchinad A, et al. Accelerated brain gray matter loss in fibromyalgia patients: premature aging of the brain? J Neurosci. 2007;27(15):4004–7.
29. Gracely RH, et al. Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia. Arthritis &amp. Rheumatism. 2002;46(5):1333–43.
30. Ashburner J, Friston KJ. Voxel-based morphometry–the methods. Neuroimage. 2000;11(6 Pt 1):805–21.
31. Mak A, et al. Early cerebral volume reductions and their associations with reduced lupus disease activity in patients with newly-diagnosed systemic lupus erythematosus. Sci Rep. 2016;6:22231.
32. Hess A, et al. Blockade of TNF-alpha rapidly inhibits pain responses in the central nervous system. Proc Natl Acad Sci U S A. 2011;108(9):3731–6.
33. Rech J, et al. Association of brain functional magnetic resonance activity with response to tumor necrosis factor inhibition in rheumatoid arthritis. Arthritis Rheum. 2013;65(2):325–33.
34. Mak A, et al. A prospective functional MRI study for executive function in patients with systemic lupus erythematosus without neuropsychiatric symptoms. Semin Arthritis Rheum. 2012;41(6):849–58.
35. Wu Q, Inman RD, Davis KD. Tumor necrosis factor inhibitor therapy in ankylosing spondylitis: differential effects on pain and fatigue and brain correlates. Pain. 2015;156(2):297–304.
36. Loggia ML, et al. Evidence for brain glial activation in chronic pain patients. Brain. 2015;138(Pt 3):604–15.
37. Albrecht DS, et al. Brain glial activation in fibromyalgia – a multisite positron emission tomography investigation. Brain Behav Immun. 2019;75:72–83.
38. Uçeyler N, Häuser W, Sommer C. Systematic review with meta-analysis: cytokines in fibromyalgia syndrome. BMC Musculoskelet Disord. 2011;12:245.
39. Kosek E, et al. Evidence of different mediators of central inflammation in dysfunctional and inflammatory pain–interleukin-8 in fibromyalgia and interleukin-1 beta in rheumatoid arthritis. J Neuroimmunol. 2015;280:49–55.
40. Attur M, et al. Low-grade inflammation in symptomatic knee osteoarthritis: prognostic value of inflammatory plasma lipids and peripheral blood leukocyte biomarkers. Arthritis Rheum. 2015;67(11):2905–15.
41. Attur M, et al. Increased interleukin-1beta gene expression in peripheral blood leukocytes is associated with increased pain and predicts risk for progression of symptomatic knee osteoarthritis. Arthritis Rheum. 2011;63(7):1908–17.
42. Sanders D, et al. Pharmacologic modulation of hand pain in osteoarthritis: a double-blind placebo-controlled functional magnetic resonance imaging study using naproxen. Arthritis Rheum. 2015;67(3):741–51.
43. Yue Y, Collaku A. Correlation of pain reduction with fMRI BOLD response in osteoarthritis patients treated with paracetamol: randomized, double-blind, crossover clinical efficacy study. Pain Med. 2018;19(2):355–67.
44. Grace PM, et al. Pathological pain and the neuroimmune interface. Nat Rev Immunol. 2014;14:217–31.
45. Harrington ME. Neurobiological studies of fatigue. Prog Neurobiol. 2012;99(2):93–105.
46. Rocca MA, et al. Clinical and imaging assessment of cognitive dysfunction in multiple sclerosis. Lancet Neurol. 2015;14(3):302–17.
47. Vatansever D, et al. Default mode network connectivity during task execution. Neuroimage. 2015;122:96–104.
48. Varatharaj A, Galea I. The blood-brain barrier in systemic inflammation. Brain Behav Immun. 2017;60:1–12.