Professor Peter C. Taylor, PhD

Pain in the joints and beyond; the challenge of rheumatoid arthritis.

Corresponding author

Peter C. Taylor MA, PhD, FRCP, FRCPE
Norman Collisson Professor of Musculoskeletal Sciences
Botnar Research Centre
Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences
University of Oxford
Windmill Road
Headington
Oxford
OX3 7LD.

Email: peter.taylor@kennedy.ox.ac.uk

ORCID: 0000-0001-7766-6167

Summary

Pain is a common and often debilitating symptom for people living with rheumatoid arthritis (RA). Although pain is a generic feature of inflammation, and often improves with successful treatment that targets inflammatory pathways, pain experience may persist. Emerging data suggest that the magnitude of pain relief may vary according to the therapeutic target of pharmacologic intervention within the inflammatory cascade. Both inflammatory and non-inflammatory causes contribute to the pain experience which depends upon tissue origin, peripheral sensory mechanisms and their transmission, integration, and interpretation within the nervous system. Contemporary neuroimaging is transforming our understanding of these mechanisms and the role of sensory, emotional, and cognitive contributions to the experience of pain. This understanding paves the way for therapeutic approaches that recognise the existence of multiple, cognitively driven, supraspinal mechanisms for pain modulation and may complement pharmacologic inflammation suppression. Such approaches include neuropsychological interventions with the potential to modify human brain cortical structure and reduce suffering that may be associated with pain experience.

Introduction

Pain is one of the most common symptoms in patients with rheumatoid arthritis (RA) and often the primary complaint.[1] When people living with RA are asked about symptoms that matter most to them, pain is generally considered to be the highest priority domain,[2-4] up to 70% ranking pain improvement as their first concern relative to other symptoms.[5] Pain has a major impact on health-related quality of life, as illustrated by findings of a multinational survey that being pain-free was one of the main indicators of patients with RA having a "good day".[6] Furthermore, health-related quality of life is commonly impacted by pain, poor sleep, depression, and anxiety[7] with interdependent causality.[8]

One of the early theories to explain pain was devised by Rene Descartes in 1644. He proposed that pain intensity is directly related to the amount of associated tissue injury. In contrast, the contemporary view is that pain is a complex set of neural, humoral and emotional events. It includes release of noxious mediators, inflammation, peripheral and central sensitization, and remodelling of synaptic contacts.[9] The gate control theory of pain, proposed by Melzack and Wall in 1965[10], highlighted the role of spinal and brain mechanisms in pain experience. The sensory transmission mechanisms underpinning acute pain experience evoked by brief noxious inputs are generally well understood. In contrast, chronic pain syndromes, in which severe pain experience may be associated with little or no discernible tissue injury or pathology, remain more enigmatic. Moreover, in the context of RA, chronic pain is often associated with psychological issues although the relationship is poorly understood. The neuromatrix theory of pain was proposed by Melzack as a conceptual framework to examine these problems.[11] In this theoretical model, the central nervous system (CNS), comprising the brain and spinal cord, is where pain is produced, multiple parts of the brain and spinal cord working together as a neuromatrix in response to stimuli from the body and/or the environment to create the experience of pain. With respect to RA, while such "neurosignature" patterns may be triggered by sensory inputs, as might occur in association with inflamed or damaged joints, they may also be generated independently of them.

Pain has long been known to be a generic feature of inflammation and it has largely been this insight, and the continuing influence of the Cartesian view of pain, that has guided the contemporary approach to management of pain in RA. In this approach, great emphasis is given to a "treat-to-target" strategy which aims to regularly adjust and escalate treatment according to response with a view to abrogating inflammation as far as safely and feasibly possible with the primary aim of preserving function and optimising a range of long-term outcomes.[12]

However, we must ask ourselves whether we can manage pain solely by focusing on treatment of the inflammatory burden of arthritis? The neuromatrix theory of pain would suggest otherwise. Furthermore, as the range of targeted therapies approved for RA treatment has expanded, we should consider whether pharmacological approaches targeting different elements of the inflammatory cascade have a similar outcome with respect to pain relief. In this viewpoint article, we will explore these issues as well as the experiential consequences of living with pain in RA, and how advances in understanding of the neurobiological correlates of

these experiences might open the doors to the introduction of neuropsychological interventions as adjunctive management approaches beyond pharmacological suppression of inflammation.

Do all targeted therapies provide similar relief of pain?

Despite distinct mechanisms of action, all targeted therapies have demonstrated similar efficacy for improvement in composite scores of disease activity. But do all treatments give rise to similar responses in terms of the subjective features of RA, such as pain?

Before we further explore this question, let us first consider how pain experience is measured in clinical trials and practice. It is most commonly by means of a 100mm visual analogue scale (or numerical rating scale version) representing a continuum between "no pain" and "worst imaginable pain." The subject is asked to indicate a score on this scale in response to a question such as "how much pain did you have in the last seven days". Although well validated and sensitive to change, such a measure (based on this commonly formulated lead question) does not even tell us where in the body the pain is being experienced, let alone take into account the many potential anatomical sources of a nociceptive signal around the joint! Furthermore, if we consider the rich vocabulary used by patients to articulate the nature of experienced pain; i.e. stabbing, burning, pinching, dull, sharp, pounding, stinging, to name but a few expressions, can the simplicity of the 100mm visual analogue scale capture this complexity? Bodily pain, measured on a categorical rating scale, is also one of the variables of the 36-Item Short Form Health Survey (SF-36), a validated measure of health-related quality of life often employed in clinical trials of RA.[13,14] It is assessed in two questions, "how much bodily pain have you had during the past week" and "how much did pain interfere with your normal work (including both work outside the home and housework)". Single-item tools such as the pain visual analogue scale have a value for measurement of overall pain in routine clinical practice. However, the crude nature of these measurement tools widely employed in RA clinical trials is such that there are many challenging issues around reporting and interpreting pain outcomes.[1517] More sophisticated tools are available. For example, the McGill Pain questionnaire is a multi-dimensional, self-reporting measure of pain, validated for use in a variety of disease settings, that assesses both the quality and intensity of experienced pain.[18] Although contemporary clinical trials in RA capture data for multiple outcomes, pain is only one of several core measures assessed and the McGill Pain questionnaire is not used routinely because of the length of time required for the patient to correctly complete it.

The only "small molecule", targeted therapies in clinical use at present are inhibitors of Janus kinase (JAK) enzymes. Four JAK inhibitors (tofacitinib, baricitinib, upadacitinib and filgotinib) are currently approved in Europe for the treatment of RA. In clinical trials, JAK inhibitors in combination with methotrexate demonstrated rapid and robust efficacy outcomes that are at least comparable to biologic anti-TNF in combination with methotrexate.[19-22] In the case of some endpoints, comparisons have demonstrated multiplicity-controlled statistical superiority although the clinical relevance of the relatively small magnitude differences in these endpoints has been questioned. However, all approved JAK inhibitors offer rapid and significant improvements in patient reported outcomes, with particularly striking improvements in pain.[23-27] In the case of tofactinib, a relatively selective JAK1,3 inhibitor, when used as a monotherapy in patients with an inadequate response to conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs), differentiation from baseline was seen as early as 3 days after treatment initiation for interactive voice response system reported pain.[28] In the first study powered to provide direct comparison of patient-reported outcomes such as pain following treatment with tofacitinib monotherapy (5mg bd) versus tofacitinib (5mg bd) or adalimumab in combination with methotrexate in patients with RA and an inadequate response to methotrexate, both combination treatments conferred statistically significant and comparable improvements in pain versus tofacitinib monotherapy.[29] Tofacitinib and adalimumab were also compared in combination with concomitant methotrexate therapy in the ORAL Standard phase III trial although this was not powered for comparisons. However, both the currently approved tofacitinib 5mg bd and higher, but no longer approved, 10mg bd doses were tested with the finding that the higher tofacitinib dose give rise to numerically larger improvements in pain measures than observed with adalimumab.[30]

In the case of baricitinib, a JAK1,2 selective inhibitor, and upadacitinib, a JAK1 selective inhibitor, pain amelioration differentiated from anti-TNF after only 2 or 4 weeks respectively and remained significantly greater throughout 52 weeks of treatment. [19,20] These head-to-head data generated two different hypotheses.

First, that multi-cytokine inhibition with a JAK inhibitor might account for a greater improvement in inflammation than anti-TNF, and therefore a correspondingly larger magnitude of improvement in pain as a generic feature of inflammation. Or second, that JAK inhibition may have a direct effect on the experience of pain that is *in addition to that* mediated by suppression of inflammation. The second of these hypotheses was investigated in a post hoc, multiple mediation analysis of data derived from the RA BEAM study[19] in which the indirect effect of treatment on pain, attributable to inflammation change, was calculated using CRP, ESR and the swollen joint count as objective markers that represent surrogates for inflammation. The findings were compared with the direct effect of treatment on pain, which was independent of change in CRP, ESR and swollen joint count.[31] The results were a surprise! They suggested that the indirect effect of treatment on pain, via modulation of these inflammation surrogates, was remarkably similar between the JAK inhibitor and anti-TNF. But the direct effect with JAK1,2 inhibition was almost double that of anti-TNF, raising the possibility that JAK signaling may be involved in the pathobiology of non-inflammatory pain. In another exploratory analysis of this data set, for patients achieving remission or low disease activity, improvements in mean pain scores at week 24 were significantly greater with baricitinib than with adalimumab.[32] In contrast, in a post hoc analysis assessing the effect of tofacitinib or adalimumab on residual pain in subjects with RA and psoriatic arthritis who achieved zero swollen joints and normalised CRP after three months of treatment, no differences in the magnitude of residual pain reduction were observed between the two therapies.[33] These observations are consistent with the understanding that many cytokines involved in the pathogenesis of RA signal through the JAK/STAT pathway, some of which are also be involved in pain signaling and central sensitization, where they can mitigate pain, such as IL-4 and IL-10, or enhance pain sensitivity, such as IL-6 and GM-CSF.[34] However, it remains unclear whether JAK inhibition in general, or selective JAK inhibition in particular, has an effect on non-inflammatory pain.

Upadacitinib 15mg od has also been compared with the biologic co-stimulation inhibitor abatacept in patients with RA with inadequate response or intolerance to biologic disease-modifying antirheumatic drugs in the SELECT-CHOICE phase III trial.[35] All subjects received background csDMARDs. Primary efficacy data demonstrated that upadacitinib was superior to abatacept in the change from baseline in DAS28-CRP components and achievement of remission after 12 weeks of treatment. At week 12, upadacitinib treated patients had significantly greater absolute improvements in pain than those receiving abatacept and significant differences persisted at week 24 for SF-36 physical component scale and bodily pain domain.[36] However, the median time to pain response was not significantly different for the two treatment interventions and there was no statistically significant difference in the proportion of patients achieving minimal clinically important differences in pain VAS at weeks 12 and 24. The patients enrolled to SELECT-CHOICE represent a population that may be more difficult to treat. The differential improvements in pain outcomes between JAK inhibition and active comparator seem less marked in this population than those reported in patients with an inadequate response to methotrexate. It might be speculated that the proportional contribution of non-inflammatory mechanisms to the reported pain endpoints may have been greater in this population than was the case in trials recruiting subjects with an inadequate response to methotrexate. Further research will be required to investigate the mechanisms accounting for pain amelioration and the relevance of JAK/STAT signaling in these populations.

Interestingly, in clinical trials in people with active psoriatic arthritis and ankylosing spondylitis, upadacitinib 15 mg once daily consistently demonstrated rapid, clinically meaningful and sustained benefits on various pain end points, including global pain, peripheral/entheseal pain, back pain and nocturnal back pain.[37] Furthermore, where an anti-TNF was employed in a comparator arm, higher proportions of patients with psoriatic arthritis receiving upadacitinib 15 mg once daily versus adalimumab 40 mg every other week achieved improvements in several pain assessments from week 20 onward, following comparable outcomes at earlier timepoints.

Do we treat disease activity or treat the person who has the disease?

As a result of a burgeoning array of efficacious targeted therapies, the outlook for people presenting with RA is better than ever before in terms of inhibition of structural damage, preservation of functional status, and even mortality. For many patients with access to these therapeutics, remission or low disease activity are achievable goals with a corresponding reduction in disease progression and disability over time.[38] Furthermore, the

benefit:risk for targeted therapies is firmly established with the advantage of long-term efficacy and safety data for the differing drug classes.[38] However, despite this expanded therapeutic armamentarium and a target driven approach to treatment in which *the disease* can be so successfully treated as assessed by the target metrics, it can be notoriously difficult to address the subjective symptoms of the *person who has the disease* and, in particular, the experience of pain.

Traditionally, symptomatic pain in RA is ascribed largely to peripheral joint inflammation. However, patients may continue to report pain even when inflammatory indices have normalised.[3943] Although this is often attributed to subclinical inflammation, in keeping with the neuromatrix model, residual pain may also be linked to non-inflammatory mechanisms, and contributions from peripheral and central sensitization.[4446] There are many examples of pain which are not readily reversible and considered to be due to non-inflammatory causes. These include bone and cartilage destruction, with or without secondary osteoarthritis, that may cause mechanical pain despite disease remission. Better understanding of these mechanisms may assist clinicians make treatment decisions that optimize both inflammation control and pain relief.

Where do the triggers of RA pain experience originate?

The anatomical origin of peripheral arthritis pain is complex. Joints are richly innervated by sensory and sympathetic nerves. Sensory nerves detect and transmit mechanical information from the joint to the CNS. Postganglionic sympathetic fibres terminate near articular blood vessels where they regulate vascular tone and blood flow.[47] Nociceptors are located throughout the joint so that pain may be triggered by numerous structures including synovium, joint capsule, ligaments, enthesis, subchondral bone, periosteum, bursae, muscle, or others.[48] But it does not arise from cartilage which is aneural. Diarthroidal joints are enveloped by a fibrous capsule that contains synovial fluid. During inflammation, synovial blood vessels become increasingly permeable to plasma proteins, which can leak out of the vasculature and accumulate in the intra-articular space, raising intra-articular pressure which may be experienced as pain.[49] Rupture or damage to articular ligaments may lead to joint instability and associated pain although the mechanisms whereby altered joint biomechanics heighten mechanosensitivity remain unclear. Conversely, mechanical stress is now emerging as a potential trigger for RA[50] and tenosynovitis is predictive for development of RA.[51]

Intra-articular structures are mostly innervated by C-sensory and sympathetic fibres and Aδ fibres innervate ligaments (Figure 1). Interestingly, where there is intense local inflammation in synovial joints of established RA, sensory and sympathetic nerve fibres are absent from the superficial synovium while the deeper synovium retains its innervation. This may reflect inflammatory damage to the peripheral terminals of nerve fibres or it is possible that the proliferating synovium outstrips the capability of the nerve supply to innervate it.[52] Central terminals of nociceptive C fibres would normally input into laminae I and II of the dorsal horn of the spinal cord. However, if peripheral terminals of nociceptive fibres become damaged with evolving persistence of joint inflammation in early RA, this may lead to withdrawal of central terminals of nociceptive fibres. Subsequently, laminae I and II become occupied by Aβ nerve fibres, responsible for proprioception in the joint, which sprout in from the adjacent laminae III and IV. If proprioceptive nerve fibres input into a nociceptive area of the spinal cord, the patient might report the experience of pain on normal range of movement.

In *acute* pain of early RA, patients generally report that pain is experienced as localised to an inflamed area, suggesting rapid afferent transmission via the neospinothalamic tract which has few synapses and constitutes the classical lateral spinothalamic tract. In more established RA, patients often report diffuse, poorly localised *chronic* pain suggesting transmission via the phylogenetically older paleospinothalamic tract (Figure 2). Most of the first-order nociceptive neurons make synaptic connections in lamina II (substantia gelatinosa) of the dorsal horn and the second-order neurons make synaptic connections in laminae IV-VIII. Second-order neurons also receive input from mechanoreceptors and thermoreceptors so that nerve cells that furnish the paleospinothalamic tract are multi-receptive, or wide dynamic range, nociceptors. The paleospinothalamic pathway also activates brain stem nuclei which are the origin of a descending pain suppression pathway regulating noxious input at the spinal cord level. [53]

RA is associated with reduced intracranial volume in comparison to healthy control subjects.[54] However, cortical gray matter is not reduced and there is increased subcortical gray matter content in the basal ganglia. These

changes may be the result of altered motor control or prolonged pain processing and influence behaviour responses to adverse stimuli.[54] Functional magnetic resonance imaging (fMRI) has been employed to investigate brain activation in response to painful stimulation over a finger joint compared with a neutral area (thumbnail) in patients suffering from RA compared to healthy controls. Subjects with RA exhibited significantly less activation in brain regions related to pain and somatosensory processing during painful joint stimulation, as compared to healthy control subjects. However, no group difference in cerebral pain processing was found for the non-affected thumbnail. Within subjects with RA, significantly less brain activation was found in response to painful stimulation over disease-affected joints compared to non-affected thumbnails in bilateral primary and secondary somatosensory cortex, and anterior insula. The findings indicate normal pain sensitivity and cerebral pain processing in RA for non-affected sites, while the increased sensitivity at inflamed joints suggest peripheral/spinal sensitization. Of note, brain imaging data suggest that there is aberrant disease-relevant pain processing in RA and failure to initiate top-down regulation from the cortical regions.[55] In fact, contemporary neuroimaging data derived from structural and functional MRI are transforming the understanding of brain pain processing in RA and suggest that symptoms may be related to aberrant brain functional connectivity rather than classic inflammatory mechanisms.[56] There is increased connectivity in people with RA between frontal midline brain regions that are implicated in affective pain processing and bilateral sensorimotor regions. These same individuals with RA also show increased sensitivity to supra-threshold pressure pain in affected joints and report a higher global pain intensity.[57] Interestingly, resting-state functional connectivity between the left anterior long insular gyrus (a subdivision of the insular cortex) and the anterior cingulate cortex is significantly associated with improvement in global assessment of disease (which is highly influenced by pain experience) on therapeutic response to biologic treatment.[58]

Pain is the greatest predictor for failure to achieve a patient global assessment (PGA) ≤1 and therefore not achieving Boolean remission.[59,60] The presence of neuropathic pain may be a particular barrier to achieving "deep remission" in RA: 13% of a cohort of 115 people with early RA treated with csDMARDs and bDMARDs and assessed at 6 months were classified as having neuropathic pain according to the painDETECT Questionnaire.[61] Central sensitization refers to a situation in which there is increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input. As a consequence, non-painful peripheral stimuli become interpreted as painful (allodynia) and painful peripheral stimuli, for example, pinprick, are interpreted as overly painful (hyperalgesia). Inflammatory conditions such as arthritis share many of the features that are observed following peripheral nerve damage. A fundamental difference between tissue hypersensitivity in association with inflammation and neuropathic pain is that in the former the pain is relieved when inflammation has resolved but in the latter, it may persist after healing of the primary event.[62]

Nociplastic pain is the semantic term suggested by pain researchers to describe a third category of pain that is mechanistically distinct from nociceptive pain, which is caused by ongoing inflammation and damage of tissues, and neuropathic pain, which is caused by nerve damage. The mechanisms that underlie this type of pain are not entirely understood, but it is thought that augmented CNS pain and sensory processing and altered pain modulation play prominent roles.[63] Although the proposed definition identifies nociplastic pain as a unique category devoid of actual or threatened tissue or somatosensory damage, there is evidence for the overlap of nociceptive, neuropathic, and nociplastic pain, indicating that nociplastic pain is not a distinct entity, but part of a chronic pain continuum that characterises patients with fibromyalgic features which may also co-exist in people with RA.

Many factors contribute to the experience of pain for people with RA

When we consider the reported pain experience by an individual with a diagnosis of RA, it is important to remember that many factors unique to that person may impact their perception of pain.[64] For example, in individuals with RA, sleep disturbance is reported to affect between 38-86% and may contribute to enhanced pain sensitivity;[65] anxiety may affect 23-46% and is associated with higher pain scores;[66] similarly, depression may affect 5-41% and pain scores may be correspondingly elevated.[66] There is a reciprocal relationship between pain experience, emotional health, psychosocial function and cognition in RA. [67] For example, the magnitude of functional impairment due to RA-related pain is positively correlated with measures of depression and anxiety[68,69] and anxiety and depression are predictive of increased pain intensity[70] and decreased physical

function.[71] Conversely, the introduction of positive emotions may ameliorate this relationship between pain and negative affect,[72] and reduce pain intensity over time.[73] Pain catastrophizing, characterised by feelings of helplessness, ruminative thoughts, and the tendency to magnify negative consequences of pain, is predictive of poor physical and psychological outcomes in RA.[67]

In every day clinical practice, rheumatologists commonly observe that sensory (pain, stiffness), emotional (stress, depression, anxiety) and cognitive (catastrophizing) domains negatively impact our patients with RA. Contemporary advances in neurobiological understanding shed light on this overlap between people who may present either to psychiatry or rheumatology clinics.[74] Brain regions that are commonly implicated in affective and cognitive disorders including the prefrontal cortex, anterior cingulate cortex, amygdala, insula and nucleus accumbens are also involved in negative affectivity that may accompany persistent pain. The pain experience for an individual with RA will depend on cerebral processing involving sensory, associative and limbic neocortical structures that play a critical role in shaping the perceived unpleasantness of the incoming noxious signals.[75] The anterior cingulate cortex is strongly implicated in contributing to the various negative experiences in the context of chronic pain, including that of unpleasantness.[76] The perceived unpleasantness of chronic pain may be encoded by postsynaptic long-term potentiation and involve alterations in AMPA-receptor function. In contrast, anxiety associated with chronic pain may be encoded by presynaptic long-term potentiation, involving an increase chance of transmitter release. As the signal (unpleasantness) and salience (how prominent or emotionally striking it is) are encoded by entirely independent mechanisms, they may even be additive.[76,77]

As pain is a highly subjective experience that is difficult to assess objectively, much of the literature purporting to be about "pain" is actually to do with "suffering". Suffering, according to Cassell's seminal conceptualisation,[78] is a state of severe distress associated with events that threaten the intactness of the person. A definition of pain has recently been revised by a task force for the International Association for the Study of Pain (IASP) following two years of deliberation and published in 2020. The revised IASP definition of pain is now "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage".[79] Pain is more likely to give rise to suffering when it is difficult to control, if its effects are intrusive in everyday life, or if no resolution can be envisaged. Unlike pain, suffering is not a phenomenon that can be reduced beyond the whole person. This is acknowledged in everyday language; for example, a knee or a wrist may hurt, but only "I" suffer. Suffering is thus a property of personhood, a psychological state which is not itself embodied. Suffering may *appear* to be embodied when it is due to pain. It occurs when an impending destruction of the person is perceived and continues until the threat of disintegration has passed or until the integrity of the person can be restored in some other manner. Rheumatologists will recognise that some patients may experience pain and not perceive it as suffering while conversely, for others an apparently mild pain may be perceived as causing significant suffering. But what relevance do these observations have for the care of our patients living with RA? I suggest that the relevance is that if we only partially address the needs of our people living with RA and pain by focusing on inflammation suppression alone, we can expect suboptimum outcomes for many. By adopting a "mind-body" framework in thinking about chronic pain in the context of RA, more therapeutic doors open up, including non-pharmacological and pharmacological interventions for each of the sensory, emotional and cognitive contributions to experienced pain.[7]

Do neuropsychological interventions have a role in pain management in RA?

Many non-pharmacologic interventions are known to have benefits for the sense of well-being and pain relief in a holistic approach to RA management.[80,81] However, for the purposes of this viewpoint article with a focus on the mind-body framework in the context of the neurobiology underpinning the experience of pain and associated suffering for people living with RA, we will finish by asking whether neuropsychological interventions can positively impact the brain, and subjective experience, of a person with chronic pain? Emerging evidence suggests that the answer is "yes"![82] Remarkably, in a comparison of 13 healthy control participants with 13 patients with mixed chronic pain types before and after an 11-week cognitive behavioural therapy (CBT) treatment, MRI imaging confirmed that the pain group had increased cerebral gray matter volume in prefrontal and somatosensory brain regions, as well as increased dorsolateral prefrontal volume associated with reduced pain catastrophizing. Patients pre-CBT and controls had no significant differences in gray matter. However, after CBT the gray matter in most of the brain regions increased beyond the gray matter level of controls. These findings point to the potential for plasticity of the human cortex in response to neuropsychological interventions.

A recent systematic review and meta-analysis of the effects of CBT for patients with RA identified 6 randomized controlled trials in which CBT was compared with usual treatment or placebo.[83] CBT was found to have positive impacts on relieving anxiety, depression, and fatigue. Although one study reported that CBT was an effective method for pain management in people with RA,[84] the overall effect size in meta-analysis was small, both at postintervention and at follow-up.

Mindfulness is the awareness that emerges from paying attention to things as they are, on purpose, in the present moment and non-judgementally. Although mindfulness has its roots in Buddhist meditation, the secular practice of mindfulness has been brought to light in recent years, in part through the work of Jon Kabat-Zinn.[85] The effects of mindfulness-based stress reduction (MSBR) in RA has been investigated in a pilot study of subjects reporting depressive symptoms and/or high PGA despite controlled disease activity measures.[86] The intervention had a marked and enduring impact on depression, anxiety, sleep quality, emotion-oriented coping and a strong positive impact on function. However, these improvements translated into minor or no changes in other RA-related symptoms such as pain and PGA. The effects of MBSR on disease activity in people with RA has also been investigated in a randomised, controlled trial.[87] The mindfulness training involved cultivation of non-judgemental attention to unwanted thoughts, feelings and bodily experiences via meditation. In this 6-month study in patients with active disease at baseline, while mindfulness had no influence with respect to CRP level or swollen joint counts, there were improvements which differentiated from control subjects with respect to tender joint counts and PGA, suggesting that the neuropsychological intervention had altered the perceived unpleasantness of the condition or reduced associated suffering. In the context of randomised trials of pharmacological intervention, rheumatologists are very familiar with placebo responses, particularly with respect to more subjective outcome measures. This raises the question as to whether the observed benefits of MSBR in the randomised controlled study might be attributable to a placebo response and whether both might have a common neurophysiological basis? But once again, advances in contemporary neuroimaging point to the possibility of a more remarkable explanation.

To determine whether the neurobiology of analgesia associated with mindfulness meditation is different from placebo, Zeidan et al randomly assigned 75 healthy, human volunteers to four days of one of three neuropsychological interventions, namely mindfulness meditation, placebo conditioning, or sham mindfulness meditation, or to a book-listening control intervention .[88] In the placebo conditioning regimen, participants were told that they were participating in an “experimental trial of a new formulation of a topical, local anaesthetic being tested for its pain reducing effects over time.” The intervention efficacy was assessed using psychophysical evaluation of experimental pain and functional neuroimaging. All three neuropsychological manipulations were observed to significantly attenuate pain intensity and unpleasantness ratings when compared to rest and the control intervention. Mindfulness meditation reduced pain intensity and ratings for pain unpleasantness more than observed with placebo analgesia or sham mindfulness meditation. Amelioration of pain following mindfulness meditation was associated with greater activation in brain regions associated with the cognitive modulation of pain. In contrast, placebo analgesia was associated with activation of the dorsolateral prefrontal cortex and deactivation of sensory processing regions. Sham mindfulness meditation-induced analgesia was not correlated with significant neural activity. Not only do these findings emphasise the role of sensory, emotional, and cognitive contributions to experienced pain but they also suggest for the first time that the neurobiological mechanisms associated with an attenuated pain experience following mindfulness meditation may be distinct from any effects of the placebo response.

Conclusion

The considerations provided in this viewpoint article highlight the multifactorial nature of reported pain in RA and emphasise the importance of a holistic approach to pain management and that of any associated distress or suffering. Sensory (pain, stiffness), emotional (stress, depression, anxiety) and cognitive (catastrophizing) domains negatively impact patients’ lives and cannot be adequately managed solely by a treat-to-target approach aiming to attain composite scores of disease activity that are acceptable to the treating physician. Identifying the cause of pain, where feasible, and how it impacts the individual, will help inform the best management approaches beyond treatment of the inflammatory component of the disease, whether pharmacological, neuropsychological or other.

Figure Legends.

Figure 1.

Pain experienced as arising in the joint may originate from adjacent or peri-articular structures including bursae, ligaments and tendons. Intraarticular structures are mostly innervated by C-sensory and sympathetic fibres whereas cartilage is aneural. C fibres are smaller-diameter (1.0 μm) unmyelinated primary afferents. Aδ fibres are small diameter (1 to 6 μm), myelinated primary afferent fibres and innervate ligaments.

Figure 2.

The nociceptive message is transmitted from the periphery to the central nervous system by the axon of the primary afferent nociceptor. This neuron has its cell body in the dorsal root ganglion and a long process, the axon, that divides and sends one branch out to the periphery and one into the spinal cord. These fibres converge at the dorsal horn of the spinal cord and activate post-synaptic neurons that ascend to higher cortical centres via the spinothalamic tract. The neospinothalamic tract has few synapses allowing rapid afferent transmission. The phylogenetically older, paleospinothalamic tract transmits pain mainly from the peripheral slow-chronic type C pain fibres and terminates widely in the brain stem. It activates brain stem nuclei which are the origin of a descending pain suppression pathway regulating noxious input at the spinal cord level.

Disclosures:

Research grants from Galapagos.

Consultation fees from AbbVie, Biogen, Galapagos, Gilead, GlaxoSmithKline, Janssen, Lilly, Pfizer, BMS, Roche, Sanofi, Nordic Pharma, Fresenius and UCB

Search strategy and selection criteria

References for this Personal Viewpoint article were identified through searches of the authors' own files. Only papers published in English were reviewed. The final reference list was generated on the basis of originality and relevance to the broad scope of this manuscript.

References

1. Taylor P, Manger B, Alvaro-Gracia J, et al. Patient perceptions concerning pain management in the treatment of rheumatoid arthritis. *J Int Med Res* 2010; **38**: 1213-24.
2. American College of Rheumatology Pain Management Task F. Report of the American College of Rheumatology Pain Management Task Force. *Arthritis Care Res (Hoboken)* 2010; **62**: 590-9.
3. Gossec L, Dougados M, Rincheval N, et al. Elaboration of the preliminary Rheumatoid Arthritis Impact of Disease (RAID) score: a EULAR initiative. *Ann Rheum Dis* 2009; **68**: 1680-5.
4. Sanderson T, Morris M, Calnan M, Richards P, Hewlett S. Patient perspective of measuring treatment efficacy: the rheumatoid arthritis patient priorities for pharmacologic interventions outcomes. *Arthritis Care Res (Hoboken)* 2010; **62**: 647-56.
5. Heiberg T, Finset A, Uhlig T, Kvien TK. Seven year changes in health status and priorities for improvement of health in patients with rheumatoid arthritis. *Ann Rheum Dis* 2005; **64**: 191-5.
6. Strand V, Wright GC, Bergman MJ, Tambiah J, Taylor PC. Patient Expectations and Perceptions of Goal-setting Strategies for Disease Management in Rheumatoid Arthritis. *J Rheumatol* 2015; **42**: 2046-54.
7. Taylor PC, Jain R. The Odd Couple?-Hardly. *Rheumatology (Oxford)* 2018; **57**: 1313-5.
8. Wolfe F, Michaud K, Li T. Sleep disturbance in patients with rheumatoid arthritis: evaluation by medical outcomes study and visual analog sleep scales. *J Rheumatol* 2006; **33**: 1942-51.
9. Moayedi M, Davis KD. Theories of pain: from specificity to gate control. *J Neurophysiol* 2013; **109**: 5-12.
10. Melzack R, Wall PD. Pain mechanisms: a new theory. *Science* 1965;**150**: 971-9.
11. Melzack R. From the gate to the neuromatrix. *Pain,* 1999; **S6**; S121-S126.
12. Taylor PC, Pope J. Treating to target or treating the patient in rheumatoid arthritis? . *Lancet Rheumatol* 2019; **1**: E8-E10.
13. Brazier JE, Harper R, Jones NM, et al. Validating the SF-36 health survey questionnaire: new outcome measure for primary care. *BMJ* 1992; **305**(: 160-4.

14. Pollard L, Choy EH, Scott DL. The consequences of rheumatoid arthritis: quality of life measures in the individual patient. *Clin Exp Rheumatol* 2005; **23**: S43-52.
15. Dworkin RH, Turk DC, Wyrwich KW, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. *J Pain* 2008; **9**: 105-21.
16. Moore RA, Straube S, Aldington D. Pain measures and cut-offs - 'no worse than mild pain' as a simple, universal outcome. *Anaesthesia* 2013; **68** 400-12.
17. Turk DC, Dworkin RH, McDermott MP, et al. Analyzing multiple endpoints in clinical trials of pain treatments: IMMPACT recommendations. Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials. *Pain* 2008; **139**: 485-93.
18 Melzack R. The McGill Pain Questionnaire: major properties and scoring methods. *Pain* 1975: **1**: 277-299.
19. Taylor PC, Keystone EC, van der Heijde D, et al. Baricitinib versus Placebo or Adalimumab in Rheumatoid Arthritis. *N Engl J Med* 2017; **376**: 652-62.
20. Fleischmann R, Pangan AL, Song IH, et al. Upadacitinib versus placebo or adalimumab in patients with rheumatoid arthritis and an inadequate response to methotrexate: results of a phase III, double-blind, randomized controlled trial. *Arthritis Rheumatol* 2019; **71**, 1788–1800.
21 Combe B, Kivitz A, Tanaka Y, et al. Filgotinib versus placebo or adalimumab in patients with rheumatoid arthritis and inadequate response to methotrexate: a phase III randomised clinical trial. *Ann Rheum Dis* 2021; **80**: 848–58.
22. Fleischmann R, et al. Efficacy and safety of tofacitinib monotherapy, tofacitinib with methotrexate, and adalimumab with methotrexae in patients with rheumatoid arthritis (ORAL Strategy): a phase 3b/4, double-blind, head-to-head, randomised controlled trial. *Lancet* 2017; **390**: 457−68.
23. Fautrel B, Zhu B, Taylor PC, et al. Comparative effectiveness of improvement in pain and physical function for baricitinib versus adalimumab, tocilizumab and tofacitinib monotherapies in rheumatoid arthritis patients who are naïve to treatment with biologic or conventional synthetic disease-modifying antirheumatic drugs: a matching-adjusted indirect comparison. *RMD Open* 2020; **6**:e001131.doi:10.1136/rmdopen-2019-001131
24. Strand V, van Vollenhoven RF, Lee EB, et al. Tofacitinib or adalimumab versus placebo: patient-reported outcomes from a phase 3 study of active rheumatoid arthritis. *Rheumatology (Oxford).* 2016; **55**: 1031-41.
25. Smolen JS, Kremer JM, Gaich CL, et al. Patient-Reported outcomes from a randomised phase III study of baricitinib in patients with rheumatoid arthritis and an inadequate response to biological agents (RA-BEACON). *Ann Rheum Dis* 2017; **76**: 694–700
26 Strand V, Tundia N, Bergman M, Ostor A, et al. Upadacitinib improves patient-reported outcomes vs placebo or adalimumab in patients with rheumatoid arthritis: results from SELECT-COMPARE. *Rheumatology (Oxford)* 2021; **60**: 5583-94.
27. Taylor PC, Kavanaugh A, Nash P, Pope J, Bartok B, Hasegawa K, Rao S, Strengholt S, Westhovens R. Effect of Filgotinib on Pain in Patients with Rheumatoid Arthritis: Results from Phase 3 Clinical Trials [abstract]. *Arthritis Rheumatol.* 2020; 72 (suppl 10). https://acrabstracts.org/abstract/effect-of-filgotinib-on-pain-in-patients-with-rheumatoid-arthritis-results-from-phase-3-clinical-trials/.
28. Strand V, Kremer J, Wallenstein G, et al. Effects of tofacitinib monotherapy on patient-reported outcomes in a randomized phase 3 study of patients with active rheumatoid arthritis and inadequate responses to DMARDs. *Arthritis Res Ther.* 2015; **17**: 307. https://doi.org/10.1186/s13075-015-0825-9
29. Strand V, Mysler E, Moots RJ, et al. Patient-reported outcomes for tofacitinib with and without methotrexate, or adalimumab with methotrexate, in rheumatoid arthritis: a phase IIIB/IV trial. *RMD Open.* 2019; **5**: e001040
30. Strand V, van Vollenhoven RF, Lee EB, et al. Tofacitinib or adalimumab versus placebo: patient-reported outcomes from a phase 3 study of active rheumatoid arthritis. *Rheumatology (Oxford).* 2016; **55**: 1031-41
31. Taylor PC, Lee YC, Fleischmann R, et al. Achieving Pain Control in Rheumatoid Arthritis with Baricitinib or Adalimumab Plus Methotrexate: Results from the RA-BEAM Trial. *J Clin Med* 2019; **8**: 831. doi: 10.3390/jcm8060831
32. Fautrel B, Kirkham B, Pope JE, et al. Effect of Baricitinib and Adalimumab in Reducing Pain and Improving Function in Patients with Rheumatoid Arthritis in Low Disease Activity: Exploratory Analyses from RA-BEAM. *J Clin Med* 2019; **8**: pii: E1394. doi: 10.3390/jcm8091394
33. Dougados M, Taylor PC, Bingham III CO, et al. The effect of tofacitinib on residual pain in patients with rheumatoid arthritis and psoriatic arthritis. *RMD Open* 2022: **8** :e002478. doi:10.1136/rmdopen-2022-002478
34. Simon LS, Taylor PC, Choy EH, et al. The Jak/STAT pathway: A focus on pain in rheumatoid arthritis. *Semin Arthritis Rheum* 2021; **51**: 278-84.

35. Rubbert-Roth A, Enejosa J, Pangan AL, et al. Trial of Upadacitinib or Abatacept in Rheumatoid Arthritis. *N Engl J Med.* 2020; **383**: 1511-1521.
36. Bergman M, Tundia N, Martin N. et al. Patient-reported outcomes of upadacitinib versus abatacept in patients with rheumatoid arthritis and an inadequate response to biologic disease-modifying antirheumatic drugs: 12- and 24-week results of a phase 3 trial. *Arthritis Res Ther*. 2022; **24**: 155.
37. McInnes IB, Ostor AJK, Mease PJ, et al. Effect of upadacitinib on reducing pain in patients with active psoriatic arthritis or ankylosing spondylitis: post hoc analysis of three randomised clinical trials. *RMD Open*. 2022; **8**: e002049. doi: 10.1136/rmdopen-2021-002049.
38. Findeisen KE, Sewell J, Ostor AJK. Biological Therapies for Rheumatoid Arthritis: An Overview for the Clinician. *Biologics* 202;**15**:343-352.
39. Altawil R, Saevarsdottir S, Wedren S, Alfredsson L, Klareskog L, Lampa J. Remaining Pain in Early Rheumatoid Arthritis Patients Treated With Methotrexate. *Arthritis Care Res (Hoboken)* 2016; **68**: 1061-8.
40. Ishida M, Kuroiwa Y, Yoshida E, et al. Residual symptoms and disease burden among patients with rheumatoid arthritis in remission or low disease activity: a systematic literature review. *Mod Rheumatol* 2018; **28**: 789-99.
41. Lee YC, Cui J, Lu B, et al. Pain persists in DAS28 rheumatoid arthritis remission but not in ACR/EULAR remission: a longitudinal observational study. *Arthritis Res Ther* 2011; **13**: R83.
42. Olofsson T, Wallman JK, Joud A, et al. Pain Over Two Years After Start of Biologic Versus Conventional Combination Treatment in Early Rheumatoid Arthritis: Results From a Swedish Randomized Controlled Trial. *Arthritis Care Res (Hoboken)* 2021; **73**: 1312-21.
43. Rifbjerg-Madsen S, Christensen AW, Christensen R, et al. Pain and pain mechanisms in patients with inflammatory arthritis: A Danish nationwide cross-sectional DANBIO registry survey. *PLoS One* 2017; **12**: e0180014.
44 McWilliams DF, Walsh DA. Pain mechanisms in rheumatoid arthritis. *Clin Exp Rheumatol* 2017; **35 Suppl 107**: 94-101.
45. Walsh DA, McWilliams DF. Mechanisms, impact and management of pain in rheumatoid arthritis. *Nat Rev Rheumatol* 2014; **10**: 581-92.
46. Zhang A, Lee YC. Mechanisms for Joint Pain in Rheumatoid Arthritis (RA): from Cytokines to Central Sensitization. *Curr Osteoporos Rep* 2018; **16**: 603-10.
47. Samuel EP: The autonomic and somatic innervation of the articular capsule. *Anat Rec* 1952;**113**:53-70.
48. McDougall JJ. Arthritis and pain. Neurogenic origin of joint pain. *Arthritis Res Ther* 2006; **8**: 220.
49. Jayson MI, St Dixon AJ: Intra-articular pressure in rheumatoid arthritis of the knee. I. Pressure changes during passive joint distension. *Ann Rheum Dis* 1970; **29**: 261-65.
50 Gracey E, Burssens A, Cambré I, et al. Tendon and ligament mechanical loading in the pathogenesis of inflammatory arthritis. *Nat Rev Rheumatol* 2020; **16**: 193-207.
51. Mankia K, D'Agostino MA, Wakefield RJ, Nam JL, Mahmood W, Grainger AJ, Emery P. Identification of a distinct imaging phenotype may improve the management of palindromic rheumatism. *Ann Rheum Dis* 2019; **78**: 43-50.
52. Mapp PI. Innervation of the synovium. *Ann Rheum Dis* 1995; **54**: 398-403.
53. Dafny N. Chapter 7: Pain Tracts and Sources. Department of Neurobiology and Anatomy. . Neuroscience online: The UT Medical School at Houston 2020.
54. Wartolowska K, Hough MG, Jenkinson M, Andersson J, Wordsworth BP, Tracey I. Structural changes of the brain in rheumatoid arthritis. *Arthritis Rheum* 2012; **64**: 371-9.
55. Sandstrom A, Ellerbrock I, Jensen KB, et al. Altered cerebral pain processing of noxious stimuli from inflamed joints in rheumatoid arthritis: An event-related fMRI study. *Brain Behav Immun* 2019; **81**: 272-9.
56. Schrepf A, Kaplan CM, Ichesco E, et al. A multi-modal MRI study of the central response to inflammation in rheumatoid arthritis. *Nat Commun* 2018; **9**: 2243.
57. Flodin P, Martinsen S, Altawil R, et al. Intrinsic Brain Connectivity in Chronic Pain: A Resting-State fMRI Study in Patients with Rheumatoid Arthritis. *Front Hum Neurosci* 2016; **10**: 107.
58. Abe N, Fujieda Y, Tha KK, et al. Aberrant functional connectivity between anterior cingulate cortex and left insula in association with therapeutic response to biologics in inflammatory arthritis. 2022 Aug;55:151994. . *Semin Arthritis Rheum* 2022; **55**: 151994.
59. Studenic P, Radner H, Smolen JS, Aletaha D. Discrepancies between patients and physicians in their perceptions of rheumatoid arthritis disease activity. *Arthritis Rheum* 2012; **64**: 2814-23.
60. Studenic P, Smolen JS, Aletaha D. Near misses of ACR/EULAR criteria for remission: effects of patient global assessment in Boolean and index-based definitions. *Ann Rheum Dis* 2012; **71**: 1702-5.
61. Salaffi F, Di Carlo M, Carotti M, Sarzi-Puttini P. The Effect of Neuropathic Pain Symptoms on Remission in Patients with Early Rheumatoid Arthritis. *Curr Rheumatol Rev* 2019; **15**: 154-61.

62. Schwartzman RJ, Grothusen J, Kiefer TR, Rohr P. Neuropathic central pain: epidemiology, etiology, and treatment options. *Arch Neurol* 2001; **58**): 1547-50.
63. Fitzcharles MA, Cohen SP, Clauw DJ, Littlejohn G, Usui C, Hauser W. Nociplastic pain: towards an understanding of prevalent pain conditions. *Lancet* 2021; **397**: 2098-110.
64. Boyden SD, Hossain IN, Wohlfahrt A, Lee YC. Non-inflammatory Causes of Pain in Patients with Rheumatoid Arthritis. *Curr Rheumatol Rep* 2016; **18**: 30.
65. Irwin MR, Olmstead R, Carrillo C, et al. Sleep loss exacerbates fatigue, depression, and pain in rheumatoid arthritis. *Sleep* 2012; **35**: 537-43.
66 Michelsen B, Kristianslund EK, Sexton J, et al. Do depression and anxiety reduce the likelihood of remission in rheumatoid arthritis and psoriatic arthritis? Data from the prospective multicentre NOR-DMARD study. *Ann Rheum Dis* 2017; **76**: 1906-10.
67. Sturgeon JA, Finan PH, Zautra AJ. Affective disturbance in rheumatoid arthritis: psychological and disease-related pathways. *Nat Rev Rheumatol* 2016; **12**: 532-42.
68. Söderlin MK, Hakala M, Nieminen P. Anxiety and depression in a community-based rheumatoid arthritis population. *Scand J Rheumatol* 2000; **29**: 177–183.
69. Bazzichi L, Maser J, Piccinni A, et al. Quality of life in rheumatoid arthritis: impact of disability and lifetime depressive spectrum symptomatology. *Clin Exp Rheumatol* 2005; **23**: 783-88.
70. Smith BW, Zautra AJ. The effects of anxiety and depression on weekly pain in women with arthritis. *Pain* 2008; **138**: 354–61.
71. Morris A, Yelin EH, Panopalis P, Julian L, Katz PP. Long-term patterns of depression and associations with health and function in a panel study of rheumatoid arthritis. *J Health Psychol* 2011; **16**: 667–77.
72. Strand EB, Zautra AJ, Thoresen M, Ødegård S, Uhlig T, Finset A. Positive affect as a factor of resilience in the pain—negative affect relationship in patients with rheumatoid arthritis. *J Psychosom Res.* 2006; **60**: 477–484.
734. Zautra AJ, Johnson LM, Davis MC. Positive affect as a source of resilience for women in chronic pain. *J Consult Clin Psychol* 2005; **73**: 212–20.
74. Chaurasia N, Singh A, Singh IL, Singh T, Tiwari T. Cognitive dysfunction in patients of rheumatoid arthritis. *J Family Med Prim Care* 2020; **9**: 2219-25.
75 Tan LL, Kuner R. Neocortical circuits in pain and pain relief. *Nat Rev Neurosci* 2021; **22**: 458-71.
76. Bliss TV, Collingridge GL, Kaang BK, Zhuo M. Synaptic plasticity in the anterior cingulate cortex in acute and chronic pain. *Nat Rev Neurosci* 2016; **17**: 485-96.
77. Koga K, Descalzi G, Chen T, et al. Coexistence of Two Forms of LTP in ACC Provides a Synaptic Mechanism for the Interactions between Anxiety and Chronic Pain. *Neuron* 2015; **86**: 1109.
78. Cassel EJ. The nature of suffering and the goals of medicine. *N Engl J Med* 1982; **306**: 639-45.
79. Raja SN, Carr DB, Cohen M, et al. The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises. *Pain*. 2020; **161**: 1976-1982.
80. Taylor PC, Van de Laar M, Laster A, et al. Call for action: incorporating wellness practices into a holistic management plan for rheumatoid arthritis-going beyond treat to target. *RMD Open* 2021; **7**: e001959.
81. Nikiphorou E, Santos EJF, Marques A, et al. 2021 EULAR recommendations for the implementation of self-management strategies in patients with inflammatory arthritis. *Ann Rheum Dis* 2021; **80**: 1278-85.
82. Seminowicz DA, Shpaner M, Keaser ML, et al. Cognitive-behavioral therapy increases prefrontal cortex gray matter in patients with chronic pain. *J Pain* 2013; **14**: 1573-84.
83. Shen B, Li Y, Du X, Chen H, Xu Y, Li H, Xu GY. Effects of cognitive behavioral therapy for patients with rheumatoid arthritis: a systematic review and meta-analysis. *Psychol Health Med* 2020;**25**: 1179-91.
84. Sharpe L, Sensky T, Timberlake N, Ryan B, Brewin C, Allard S. A blind, randomized, controlled trial of cognitive-behavioural intervention for patients with recent onset rheumatoid arthritis: Preventing psychological and physical morbidity. *Pain* 2001; **89**: 275–83.
85 Kabat-Zinn J. *Full Catastrophe Living: Using the Wisdom of Your Body and Mind to Face Stress, Pain, and Illness*. 2013 New York: Bantam Dell. ISBN 978-0345539724
86. Gaboury I, Dobkin PL, Gendron F, et al. . *Rheumatol Adv Pract* 2022; **6**: rkac074. doi: 10.1093/rap/rkac074. eCollection 2022.
87. Fogarty FA, Booth RJ, Gamble GD, Dalbeth N, Consedine NS. The effect of mindfulness-based stress reduction on disease activity in people with rheumatoid arthritis: a randomised controlled trial. *Ann Rheum Dis* 2015; **74**: 472-4.
88. Zeidan F, Emerson NM, Farris SR, et al. Mindfulness Meditation-Based Pain Relief Employs Different Neural Mechanisms Than Placebo and Sham Mindfulness Meditation-Induced Analgesia. *J Neurosci* 2015; **35**: 15307-25.