

# Can you feel the burn? Using neuroimaging to illuminate the mechanisms of mindfulness interventions for pain.

## A commentary on Wielgosz et al

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Chronic pain is one of the leading causes of disability and morbidity world-wide (1) and there is a real clinical need for non-opioid based treatment options. As such, there is a growing body of research investigating mindfulness interventions for pain. There have been two recent meta-analyses of RCTs in pain, both with modest positive conclusions, though both also commented on the heterogeneity and low quality of many of the trials included. One meta-analysis in patients with chronic pain (2) – focused on mindfulness-based stress reduction (MBSR) interventions – found evidence for a small effect size, and one in acute pain (3) concluded there is weak-moderate evidence for mindfulness improving pain tolerance or threshold, but no good quality evidence for reducing pain severity or pain-related distress.

Measuring pain, and the components of pain targeted by an intervention, is a challenging task. Pain research typically distinguishes between the sensory component of pain i.e. the intensity of pain, and the more affective component of pain i.e. the unpleasantness of pain. Neatly differentiating these components is not always easy (4), especially as we might expect a complex and dynamic relationship between these features of pain, but it is clear that there are numerous emotional, motivational and cognitive processes involved in the experience of pain beyond the sensory assessment of intensity, including anticipation, anxiety and catastrophising (5). Neither of the above meta-analyses provide direct evidence regarding which aspects of pain might be targeted by mindfulness interventions, but the latter (3) suggests that mindfulness appears to have more of an effect on cognitive appraisal and behavioural responses to pain.

As of yet, there have been limited studies investigating the neural effects of mindfulness on pain to provide insight into this question. Recent studies suggest that early reports of mindfulness changing brain structure are unlikely to be true (6), but there remains some indication, from the fMRI evidence available, that mindfulness may help people uncouple the sensory experience of pain from their emotional response to pain (7).

The study by Wielgosz et al in this issue provides valuable insight by using a novel neuroimaging approach - machine-learning derived signatures of pain - to unpick which aspects of pain may be targeted by mindfulness interventions. The authors looked at two pain signatures - the Neural Pain Signature (NPS) and the Stimulus Intensity Independent Pain Signature-1 (SIIPS-1). For both, a single numerical value is calculated by looking at activation and deactivation in voxels across the brain, and weighting activity at each individual voxel by how it matches the pattern of the neural signature. NPS is described as capturing “stimulus-dependent” aspects of pain i.e. intensity of pain, while SIIPS-1 is described as a complementary signature, trained specifically on “stimulus-independent” aspects of pain that aren’t captured by NPS, including psychological components such as sense of control or expectation. Both incorporate neural activity across the brain; specific details can be found in the paper’s Supplementary Materials.

Participants naive to mindfulness underwent fMRI during a thermal pain test, before and after a mindfulness intervention, and per-participant neural responses were computed for both signatures. The mindfulness-based stress reduction (MBSR) intervention was a standard, validated course, aligning with the most commonly studied mindfulness interventions in RCTs. It was compared to an active control group - a health enhancement program (HEP) - specifically designed to match the length, structure and content of MBSR, with the inclusion of group support and exercise and other non-specific therapeutic effects, but without the mindfulness component. For example, the “purpose of walking in MBSR is to cultivate awareness in movement, whereas the purpose of walking in HEP is the cardiovascular benefits of the physical activity for cardiovascular training” (8). This active control group is a strength of the study, ensuring conclusions can be drawn about the specific benefit of MBSR.

Comparison of both groups, and a waitlist group, found that both intervention groups reported significantly reduced subjective reports of pain unpleasantness post-intervention, and both intervention groups had marginal reductions in SIIPS-1 compared to waitlist (where SIIPS-1 non-significantly increased), but only the mindfulness intervention significantly reduced the NPS (with a reasonable effect size,  $>0.4$ ), compared to HEP and waitlist.

Wielgosz et al also did a cross-sectional comparison of all mindfulness-naive participants to long term meditators, who had at least 3 years of formal meditation experience, including multiple intensive retreats, and had an ongoing daily practice. This cross-sectional analysis found that, while long term meditators reported lower subjective reports of both pain intensity and unpleasantness compared to mindfulness-naive participants, there were no differences in either neural signature. They also found that, among long term meditators, SIIPS1 response and pain intensity and unpleasantness ratings were lower for those with greater retreat hours.

While Wielgosz et al argue that their findings are in line with their predictions, as a focus on physical sensation is common in early stages of mindfulness, it is perhaps surprising that the most compelling (and the only statistically significant,  $p < 0.5$ ) finding for change after mindfulness intervention was in the neural signature related to pain intensity rather than cognitive/affective aspects. This appears at odds with the indications from both the acute pain meta-analysis (3), and the review of initial neuroimaging studies (7), both of which suggested that mindfulness targets cognitive/affective appraisals. It is also interesting that this neural change occurred alongside the self-report measures indicating a reduction in unpleasantness but not intensity. When this trial was [registered](#), BOLD was the primary outcome but no specific directional hypotheses were given, so clear confirmatory analyses in follow-up studies would provide greater confidence in a definitive conclusion.

There is also the null finding of no differences in neural signature in long term meditators compared to mindfulness-naive participants. Again, Wielgosz et al provide a potential explanation, positing that the lack of differences in neural signatures may be because of different baseline characteristics in those who seek out meditation practices, that then became normalised by meditation. Prior use of psychiatric medication was an exclusion, as was a psychiatric diagnosis in the past year, but this leaves significant scope for variability in undiagnosed mental health difficulties (current and historic) as well as psychiatric diagnoses older than a year. Nonetheless, confirmatory follow-up is important to justify this explanation for the lack of group difference.

There is significant interest in identifying neural biomarkers for pain, in part to address the limitations of self-report measures (9). In research, self-report measures may not sensitively discriminate the different components of pain, and are particularly susceptible to placebo

effects. In clinical settings, while self-report measures remain an essential part of patient assessment, there is a push for biomarkers to assist with pain detection in non-verbal patients or patients with barriers to communication such as babies or those with dementia. A 2020 Consensus Statement from a presidential task force of the International Association for the Study of Pain (10) highlights the potential benefits of biomarkers for understanding the mechanisms underlying pain and identifying targets for pain interventions, as in Wielgosz et al. The statement also raises concerns about the misuse of neural biomarkers for pain in legal settings (e.g. for assessing validity of insurance claims or eligibility for disability benefits), the importance of testing neural biomarkers in diverse populations, and the wider societal and ethical implications; these are concerns researchers involved in biomarker development should be conscious of and consider when publicising their work.

One of the key strengths of Wielgosz et al is the novel use of independently-derived machine learning neural signatures, made [available](#) for other researchers to use. These signatures have been shown to be robust against placebo i.e. participants who self-report reductions in pain after placebo treatment do not show reductions in their neural signatures for pain (11); this is particularly beneficial for trials of psychological interventions which cannot be fully blinded, though this study also has a robust active control group. Neural signatures such as these provide benefits for study design and analysis, reducing the likelihood of false positives and the need for substantial multiple-comparison adjustment, by focusing on comparison between one or two single computed values rather than individual voxels across the brain. More broadly, these neural signatures enable greater opportunities for precise reproduction and replication of findings, as well as more direct comparison between populations and interventions.

Comparison between different neural signatures is particularly helpful for teasing apart the target of mindfulness interventions, with the NPS being established as consistently reflecting the magnitude of pain experience and differentiating somatic pain from non-painful warmth (9). As neural responses to pain involve activity across numerous regions of the brain, including those involved in fear and cognitive appraisals, it is difficult to be certain that machine learning algorithms don't identify correlated features of pain or non-pain-specific features of the experience, especially as validation efforts still frequently rely on drawing a relationship between the outcomes of machine learning algorithms and self-report measures. However, established neural signatures that can be applied consistently and readily studied independently goes some way towards helping address that challenge and can increase our confidence in interpretation. In future studies, it may be interesting to look at other neural signatures of pain e.g. the Pain-Analgesic Network (12) which was specifically designed to capture analgesic effects in clinical trials; this could be used to compare mindfulness interventions to pharmacological interventions.

Using these neural signatures to explore other interventions for pain, beyond mindfulness, could also provide an insight into the parallels (or lack of) in the targets for these interventions. For example, deep brain stimulation has been used for decades to treat chronic pain, with recent targeting of the anterior cingulate cortex providing more promising outcomes; reports from patients indicate that this is due to a change in their emotional attachment to the pain (13) and it would be interesting to see if this is reflected in the same neural signatures investigated in Wielgosz et al.

Experimental medicine models in healthy populations are important, to explore the mechanisms of an intervention without the confound of symptom change and without the heterogeneity introduced by complex medical histories. However, ultimately findings need to be translated to clinical populations, to establish their impact and benefit in patients. As Wielgosz et al note, there are no neural signatures developed and validated for chronic pain specifically – a key priority for future research – and so it is unclear how their work using

acute methods of inducing pain would translate to chronic pain. Acute and ongoing pain are vastly different, with reports of significant distinctions in structural and functional magnetic resonance, as well as metabolite and neurotransmitter function (14), and differences in how this pain is experienced and reported; clinical experiences of pain are typically associated with reports of lower pain intensity and greater pain unpleasantness, with the reverse true in acute pain induction in experimental settings. This latter difference in experience of pain could provide an alternative explanation for why Wielgosz et al found the most robust differences in neural signatures associated with pain intensity; in chronic pain, there is significant distress associated with the medical concern, the unknown cause, and the uncertain trajectory of pain, whereas in a controlled, experimental setting these elements are less pertinent. This may mean acutely-induced pain provides less scope for improvement in cognitive/emotional responses. Chronic pain is also frequently associated with psychiatric comorbidity, such as depression - which is characterised by substantive differences in emotional cognition - so it would be interesting to translate these findings into a sample with well-characterised psychiatric symptoms.

Looking further afield, there are also indications that developing similar neural signatures in other research areas could benefit our understanding of psychiatric interventions for different conditions. A recent meta-analysis (15) concluded that antidepressants and psychotherapy appear to evoke neural changes in different regions of the brain, with antidepressants primarily targeting limbic regions such as the amygdala and psychotherapy primarily targeting regions involved regions such as the medial prefrontal cortex. If this clear distinction were borne out in future research, and/or refined further to specify relationships between features of interventions and neural pathways, perhaps neural signatures could be similarly developed to help evaluate and compare novel across and within-class treatments for depression.

### **Acknowledgements**

CJH is supported by the Oxford Health NIHR Biomedical Research Centre.

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