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Mindfulness meditation–based pain relief: a mechanistic account

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Abstract

Pain is a multidimensional experience that involves sensory, cognitive, and affective factors. The constellation of interactions between these factors renders the treatment of chronic pain challenging and financially burdensome. Further, the widespread use of opioids to treat chronic pain has led to an opioid epidemic characterized by exponential growth in opioid misuse and addiction. The staggering statistics related to opioid use highlight the importance of developing, testing, and validating fast-acting nonpharmacological approaches to treat pain. Mindfulness meditation is a technique that has been found to significantly reduce pain in experimental and clinical settings. The present review delineates findings from recent studies demonstrating that mindfulness meditation significantly attenuates pain through multiple, unique mechanisms—an important consideration for the millions of chronic pain patients seeking narcotic-free, self-facilitated pain therapy.

Introduction

The construction and modulation of pain is mediated by sensory, cognitive, and affective factors, rendering the treatment of chronic pain difficult and often a financial burden. Chronic pain affects over 100 million Americans and 1.5 billion people worldwide and costs the United States approximately $635 billion per year in medical expenses and lost work productivity.[1] Furthermore, the pervasiveness and burden of chronic pain has dramatically increased Medicare expenditures for steroid injections (over 629%) and opioid treatments (over 423%).[2] The widespread use of opioids to alleviate chronic pain has led to an opioid epidemic[3] characterized by an exponential rise in opioid misuse and addiction.[4, 5] The importance of addressing concerns related to these staggering statistics are reflected in new

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far-reaching policy changes, such as the recommendations from the Centers for Disease Control and Prevention (CDC) to develop and employ fast-acting nonpharmacological approaches to treat chronic pain.[6–8] We postulate that mindfulness meditation could be such a suitable narcotic-free pain therapy for a number of reasons: firstly, mindfulness-based meditation has repeatedly been found to significantly reduce chronic pain symptomologies;[9–14] second, mindfulness meditation attenuates pain through multiple unique psychological and neural processes;[15–22] and further, it has recently been demonstrated that mindfulness meditation is more effective in reducing pain than placebo[23] and does not engage endogenously driven opioidergic systems to reduce pain.[20] However, lack of mechanistic classification and reproducibility has reduced the clinical acceptance of meditation to treat pain. While there are a wide variety of meditation traditions and techniques, the present review article will focus on delineating the analgesic mechanisms supporting mindfulness meditation in particular and take into consideration varying levels of meditative expertise and the utility of employing robust control/comparison conditions to better disentangle the specific mechanisms underlying mindfulness meditation.

What is mindfulness meditation?

Mindfulness meditation is a fairly loose term that applies to many meditation practices, which have been found to improve a wide spectrum of clinically relevant cognitive and health outcomes.[24–27] In patients, training in mindfulness improves self-reports of anxiety,[28–31] depression,[10, 32–36] stress,[37–39] and cognition.[40–46] Mindfulness-related health benefits are associated with enhancements in mechanisms supporting cognitive control, emotion regulation, positive mood, and acceptance.[47]

Mindfulness has been described as a "non-elaborative, non-judgmental awareness" of the present-moment experience.[9, 41] However, one does not need to be practicing, or even be trained in, meditation to be mindful. Varying degrees of trait mindfulness exist in the general population, outside of any formal training.[48–50] Mindfulness can also be developed with mental training routines, such as meditation, and there are a variety of different practices that are subsumed under the general rubric of mindfulness meditation. Thus, it is critical that the specifics of the practice being taught or employed be recognized. Here, we will focus on two rather coarse categories of mindfulness practice, namely, focused attention (samatha in the *Pali* language) and open monitoring (*Pali:* vipassana),[51] both of which are centered on developing a number of distinct cognitive skills.

During focused attention, or *samatha,*[52] the practitioner is taught to develop cognitive control and attentional stability by training the practitioner to sustain focus on the moment-to-moment quality and characteristics of sensory, emotional, and cognitive events. In brief, samatha involves directing one's attention to the dynamic nature of the chosen object of meditation, most often the sensations of breath or body. When attention drifts from the object of focus, for example, to a distracting sensory event, the practitioner is taught to acknowledge the event and disengage by returning their attention back to the meditative object (e.g., the breath). Often, samatha is taught as a series of distinct practices increasing in complexity (e.g., mindfulness of breath, emotions, and thoughts). While samatha practices aim primarily at gaining mental control and stabilization of attention, they naturally lead, in

a somewhat ambiguous way, to the traits associated with open-monitoring meditation. As a developmental derivative of focused-attention practice, the mindfulness practitioner almost naturally transitions into an open-monitoring mental stance, also known as vipassana. It is believed that extensive training in samatha is required before the open-monitoring aligned cognitive stance develops naturally. Whereas samatha often entails focus on a single, dynamic, meditative object, open-monitoring practices are more inclusive of perceived thoughts and emotions. When applied to the full extent, these practices are associated with a non-directed acknowledgement of any sensory, emotional, or cognitive event that arises in the mind. While practicing open monitoring, the practitioner is said to experience the current event without evaluation. To this extent, mindfulness meditation has been described as a state of non-appraisal and/or a non-elaborative mental stance.[51]

Mindfulness and pain

For thousands of years, Buddhist monks have postulated that the practice of mindfulness meditation can significantly alter the subjective experience of pain. For instance, the ancient Buddhist text, the *Sullatta Sutta* (The Arrow), states that meditation practitioners have the unique ability to fully experience the sensory aspect of pain (first arrow) but to "let go" of the evaluation (second arrow) of pain. However, only recently have scientists examined the mechanisms underlying mindfulness meditation–induced pain relief and health improvements. In 1980, Nepalese "porters" were found to report significantly higher pain thresholds in response to pain-evoking electrical stimulation when compared to a well-matched control group.[53] While the authors attributed these effects to religious practices (presumably meditation), it was not clear, at the time, if meditation practice directly produced analgesia. We have recently witnessed a significant increase in studies demonstrating that mindfulness meditation reduces pain reports across a spectrum of chronic pain conditions.[54–66] Furthermore, the advent of neuroimaging methodologies has provided cognitive scientists the means to identify the specific neural mechanisms supporting mindfulness meditation–based analgesia.

Mindfulness meditation improves chronic pain symptomology

Mindfulness meditation–based interventions improve pain symptomology across a wide spectrum of pain-related disorders, including fibromyalgia,[14, 67] migraine,[68] chronic pelvic pain,[61] irritable bowel syndrome,[12, 13] and other conditions.[69] Given that chronic low back pain is the most common clinical pain condition[70] and the leading cause of disability in the United States, it is imperative to better determine if and how mindfulness meditation training affects chronic low back pain. The 8-week mindfulness-based stress reduction (MBSR) program[9] is one the most studied and validated approaches for the treatment of chronic low back pain. In a seminal study, Kabat-Zinn and colleagues revealed that chronic pain patients reported improvements in pain symptomology and quality of life after completing the MBSR program[9] and improvements were sustained after a 3-year follow-up.[10] The work by Kabat-Zinn spawned a burgeoning of research initiatives focusing on mindfulness meditation, including a number of more recent investigations that have employed robust, carefully controlled experimental designs to examine the effectiveness of mindfulness meditation interventions on chronic pain. In an elegant study, Cherkin and colleagues

compared the effects of 8 weeks of MBSR to an 8-week cognitive behavioral therapy (CBT) intervention and usual care across a number of chronic low back pain outcomes.[71] The MBSR and CBT programs were found to be significantly more effective at reducing pain intensity and reports of pain being bothersome when compared to usual care after 8, 26, and 52 weeks.[71] While there were no significant differences between the CBT and MBSR programs in pain-related outcomes, these findings demonstrate that mindfulness-based improvements in chronic pain could be enhanced across time. In another recent study, Morone and colleagues found that an 8-week MBSR program significantly improved numerical pain scale ratings and pain-symptom severity in older adults (i.e., older than 65 years of age) suffering from chronic low back pain when compared to a "very active" pain-related health education group.[55] Taken together, these findings demonstrate that relatively brief bouts of mindfulness meditation training can significantly attenuate chronic low back pain symptomology. However, the specific analgesic neural mechanisms demonstrating how mindfulness meditation interventions produce chronic pain have yet to determined, which is a critical step in fostering the clinical validity of this ancient technique.

The construction and modulation of pain: a brief neurophysiological synopsis

Pain is a complex and subjective conscious experience constructed and modulated by a constellation of sensory, cognitive, and affective factors, including mood, psychological disposition, meaning-related cognitions (e.g., suffering), learning, desires, and pre-pain cognitive states (e.g., expectations; anxiety) to provide a continually changing experience. Feedback connections between low-level afferent and higher-order neural processes foster the cultivation of a distributed, multidimensional network associated with the subjective experience of pain. Nociceptive sensory events are first registered by peripheral primary afferents (first pain, A-delta fibers; second pain, C fibers) at the site of injury/tissue damage, which then relay this nociceptive information to the dorsal horn of the spinal cord. From the spinal cord, nociceptive information ascends contralateral to the site of pain to the brain, largely through the spinothalamic pathway. Nociceptive input is subsequently processed through feedback connections between lower-level sensory regions, including the parabrachial nucleus, periaqueductal gray matter (PAG), thalamus, and primary somatosensory (SI) and secondary somatosensory (SII) cortices.[72–78] Ascending nociceptive information is then transmitted to the posterior and anterior insular cortices where it is fine-tuned to foster the subsequent evaluation of pain.[79, 80] The contextual meaning of pain is then facilitated through activation of higher-order brain regions, including the anterior cingulate cortex (ACC), dorsal ACC (dACC), and prefrontal cortex (PFC).[80–82] Yet, the subjective experience of pain remains to be highly influenced by the context in which it occurs. That is, previous experiences, expectations, mood, conditioning, desires, sensitization/habituation, and other cognitive factors can dramatically amplify and/or attenuate pain.[78, 83–87]

Nonpharmacological-based pain manipulations attenuate the subjective experience of pain through a common final pathway, including overlapping endogenously driven and neural systems. While the cognitive modulation of pain is mediated through a host of endogenous

modulatory systems, including cannabinoid, serotonergic, dopaminergic, cholecystokinin, adrenergic, and other neurochemical systems (i.e., vasopressin), the endogenous opioidergic system is the most understood (and studied) pain modulatory system.[88] Endogenous opioidergic mechanisms have been repeatedly demonstrated to mediate analgesia produced by placebo,[89–93] conditioned pain modulation,[94] acupuncture,[95] hypnosis,[96] and attentional control.[97] Pain relief produced by these cognitive techniques are associated with significant reductions in pain-related brain activation (i.e., SI, SII, posterior insula, parietal operculum) and activation in higher-order brain regions, such as the ACC, PFC, and insula.[86, 89, 98–110] Importantly, the PFC, insula, and ACC contain high concentrations of opioid receptors and are associated with producing analgesia through descending inhibitory systems.[105, 111–115] The ACC and PFC project to the PAG,[116] a structure that can be directly activated by opioids. The PAG projects to the rostral ventral medulla,[117–119] which, in turn, projects to the spinal dorsal horn and can inhibit nociceptive processing through multiple neurotransmitter systems.[120]

Brain mechanisms supporting the modulation of pain by long-term meditators

A large proportion of mindfulness meditation–based experimental pain research has focused on examining the effects of meditation practice ranging from 8 weeks to multiple decades. In one of the first mindfulness meditation–focused experimental pain studies, Grant and Rainville found that long-term Zen meditation practitioners required significantly higher levels of noxious thermal stimulation to report paralleling levels of pain as age-matched controls.[121] In their follow-up study with an overlapping sample, the authors found that, in the presence of noxious thermal stimulation, long-term Zen practitioners showed significant activation of sensory processing–related brain regions (thalamus, insula) and reduced activation in brain areas that process the evaluation of pain (medial PFC (mPFC), OFC). There was also a significant relationship between greater deactivation of the mPFC/OFC, meditative experience, and lower pain reports.[18] Remarkably, these findings were exhibited during a non-meditative cognitive state, suggesting that long-term meditation training produces stabilized changes in the subjective evaluation of pain.

In addition, Lutz and colleagues examined the psychophysical and neural effects of meditation across 14 long-term mindfulness meditation practitioners (approximately 10,000 h of formal meditation practice in the Nyingma and Kagyu traditions of Tibetan Buddhism) during noxious heat stimulation compared to 14 non-meditating controls.[19] The control group was provided with guidelines to practice mindfulness meditation and instructed to practice at home for 30 min/day for 1 week. Surprisingly, there was no difference between long-term meditators and the novice meditation group on pain intensity ratings during samatha practice. Not surprisingly, open-monitoring meditation produced significant reductions in pain unpleasantness in the expert meditation group when compared to the controls.[19] This form of meditation was associated with reduced anticipatory (before the painful heat stimulus) activation in the anterior insula. Further, the reduced baseline activation in left anterior insula correlated with lifetime meditation experience. These

findings and others[16] indicate that reducing expectations of impending pain is at least one process/mechanism by which mindfulness meditation reduces pain.

In a study by Gard *et al.*, the neural mechanisms supporting mindfulness meditation–based analgesia were examined in 17 long-term vipassana practitioners (mean meditation practice experience = 5979 h) in response to noxious electrical stimulation compared to 17 age-, gender-, and education-matched non-meditating controls.[17] Similar to other studies,[16, 19, 122] the authors did not find a significant difference between the meditation and control groups in pain intensity ratings, but did find a significant reduction in pain unpleasantness ratings compared to the control group during the mediation state in the presence of noxious stimulation.[17] Greater activation of the contralateral SII/posterior insula was associated with meditation-induced pain unpleasantness ratings. The authors also found greater rACC and ventromedial PFC (vmPFC) activation during the prestimulus anticipatory phase, suggesting that cognitive control mechanisms were at play. However, meditation-induced analgesia was directly associated with greater deactivation of the PFC and increased activation of the posterior insula, which is consistent with the abovementioned work by Grant and Rainville.[18] Taken together, these findings are important because they demonstrate that the neural mechanisms involved in mindfulness-based pain relief are consistent with the postulated psychological expression/experience of mindfulness (i.e., greater sensory processing and parallel reductions in pain appraisal).

These findings have advanced our knowledge of the mechanisms supporting the stabilized psychological and neural changes associated with long-term meditation practice. Yet, the utility of meditation for treating pain remains limited because of the assumption that the benefits of meditation require lengthy training regimens.[15, 27] Specifically, extensive class time requirements[123] and overall length of meditation training regimens have been cited as leading barriers to the clinical utility of meditation interventions.[124] Furthermore, the aforementioned studies employed cross-sectional and/or case control designs, consequently limiting their generalizability because of the wide spectrum of potential between-group differences (e.g., demographics, demand characteristics, and meditative tradition) that may exist.[15] Thus, random assignment and longitudinal designs are encouraged for meditation-focused studies.[27] In light of these findings, we postulate that if the benefits of meditation can be elicited by brief mindfulness-based mental training regimens, then meditation may be more feasible to apply in clinical settings.

Mindfulness meditation after brief training reduces pain through unique mechanisms

Recent studies from our laboratory have focused on disentangling the specific analgesic behavioral, neural, and pharmacologic mechanisms involved in mindfulness meditation–related pain relief. In 2011, we examined the effects of mindfulness meditation in 15 healthy pain-free subjects after participation in a brief (four sessions; 20 min/session) mindfulness meditation–based intervention on experimentally induced (ten 12-s plateaus of 49 °C) pain, using arterial spin labeling (ASL) functional magnetic resonance imaging (fMRI). ASL is a neuroimaging technique that provides a direct quantifiable measurement of global cerebral

blood flow, an important consideration for breathing-focused cognitive practices, such as meditation.[21] During meditation training, subjects were instructed to close their eyes, sit with a straight posture and focus on the breath sensations, acknowledge distracting thoughts and feelings, and to simply let go of arising sensory events without judgment. Participants were taught that perceived sensory and affective events are momentary and fleeting and do not require further evaluation. In the first two meditation training sessions, subjects were instructed to focus on the breath sensations occurring at the tip of the nose and full flow of the breath. Meditation, after the four-session intervention, during noxious heat produced a mean 40% reduction in pain intensity and 57% reduction in pain unpleasantness ratings. Greater activation of the subgenual ACC (sgACC), OFC, and right anterior insula (Fig. 1) was associated with mindfulness meditation–based analgesia. The sgACC is critically involved in the cognitive and affective control of pain.[83, 86, 99, 125, 126] The OFC has been implicated in altering the contextual evaluation of arising sensory events,[127–130] and the right anterior insula is associated with the modulation of afferent nociceptive processing,[74, 75, 80, 100, 131] and processing interoceptive awareness.[132–134]. We also found that mindfulness meditation–based pain relief was associated with greater bilateral thalamic deactivation (Fig. 1) [21]. Thus, meditation may reduce pain by fine-tuning the amplification of nociceptive sensory events through top-down control processes,[15, 21, 23] potentially reflected by the significant attenuation of SI activation corresponding to the stimulation site when subjects meditated during noxious heat when compared to rest (right leg).[21] We postulated that mindfulness meditation attenuates pain through engagement of top-down (OFC to thalamus) inhibition of ascending nociceptive information.[15, 20, 21, 23] Thus, the cognitive state of mindfulness meditation–based analgesia does not reduce pain through one avenue but rather multiple, unique neural mechanisms. Although this study employed a longitudinal design, a control group was not included. However, our follow-up studies addressed this caveat.[20, 23]

Does mindfulness meditation engage mechanisms consistent with placebo analgesia?

While mindfulness meditation practice can improve health and well-being, the active mechanisms supporting mindfulness meditation have yet to be fully characterized. Importantly, a wide range of nonspecific placebo-related effects are likely involved during meditation training. Here, we define the placebo response as benefits or effects driven by nonspecific and/or inert dimensions of a drug, intervention, or manipulation. Nonspecific and potentially confounding variables, such as conditioning effects, psychosocial contexts, facilitator attention, intervention setting, body posture, and/or demand characteristics associated with the belief that one is practicing meditation,[15, 27, 135] could mediate mindfulness meditation–related health improvements.[136, 137] Randomized, placebo-controlled studies are the gold-standard approach to identify the effectiveness and specific mechanisms supporting the modulation of pain by mindfulness meditation. Yet, placebo-controlled meditation studies have been limited, which is problematic when considering that meditation is arguably highly susceptible to placebo-type effects.

Some recent studies have successfully disentangled the processes by which meditation affects health. For example, Creswell and colleagues examined the behavioral and inflammatory stress markers (i.e., interleukin-6 (IL-6) and neural mechanisms related to participating in an intensive 3-day mindfulness meditation intervention compared to a 3-day health enhancement relaxation program in unemployed and clinically stressed adults.[138] The researchers matched all aspects of the relaxation program to the meditation intervention, including sitting in silence, meals, stretching exercises, slow walking, facilitator interviews, and even the location of the intervention. Both groups reported significant differences in perceived stress. However, increases were shown in pre- to post-meditation intervention functional neural connectivity between a central node of the default fault mode network (i.e., posterior cingulate cortex (PCC) and the dorsolateral PFC (dlPFC), a brain region implicated in cognitive and affective control. Furthermore, the dlPFC–PCC connectivity mediated reductions in circulating IL-6 from baseline to the 4-month follow-up. In contrast, the relaxation intervention group exhibited mild increases in IL-6 after the intervention. These findings provide supplementary evidence that mindfulness meditation employs unique mechanisms to improve health in clinically relevant populations.

Another research group developed an active comparison intervention, referred to as a health enhancement program (HEP), to specifically isolate and control for the effects of MBSR.[139–141] The HEP was postulated to control for facilitator allegiance, time spent providing instruction/therapy, social support, and other components related to participating in an MBSR program.[139] Although the HEP and MBSR program were effective at reducing self-reports of anxiety, distress, hostility,[139] and attentional stability,[140] there were no significant differences between groups. However, the MBSR program was more effective at reducing inflammatory responses following social stress[141] and experimentally-induced pain ratings.[139] These studies demonstrated the unique health-promoting properties supporting mindfulness-based health promotion. However, the question arises as to whether it is possible that the benefits of meditation may simply be related to the belief that one is practicing mindfulness meditation.

A recent study[23] examined whether mindfulness meditation–based pain relief engages neural mechanisms that are distinct from placebo analgesia and sham mindfulness meditation–related analgesia. Similar pain-evoking thermal stimulation paradigms and neuroimaging methods (ASL MRI) were employed as described previously.[21] Seventy-five healthy, pain-free subjects were randomly assigned to one of four 4-session (20 min/session) regimens: (1) a brief mindfulness meditation intervention similar to an intervention described previously;[21, 31, 36, 46, 142] (2) placebo conditioning; (3) sham mindfulness meditation; and (4) a book-listening intervention. Participants in the placebo-conditioning group were led to believe that the effects of an experimental form of lidocaine was being tested, in which the analgesic effects of the cream (placebo cream was petroleum jelly) progressively increase as a function of repeated applications. To enhance placebo conditioning, the stimulus temperatures delivered to the treated skin were covertly reduced, from 49 °C, in a progressive fashion across sessions (placebo conditioning session 1: 48 °C; sessions 2 and 3: 47 °C; session 4: 46.5 °C). The 49 °C stimulus was administered after applying/removing the placebo cream in the post-intervention MRI session to measure the efficacy of the placebo conditioning regimen. The sham mindfulness meditation intervention

was designed so that the only difference in training between the mindfulness and sham mindfulness meditation groups was the explicit mindfulness-based instructions (e.g., non-judgmental attention to the breath) given to the mindfulness meditation group. Subjects were first informed that they were randomly assigned to the mindfulness meditation intervention. Across four 20-min sessions, participants were trained to take deep breaths "as we sit here in mindfulness meditation." The control group listened to the *Natural History of Selborne*[143] across four sessions.

All cognitive manipulations (mindfulness meditation, placebo cream, sham mindfulness meditation) reduced pain intensity and unpleasantness ratings compared to the control group. Importantly, mindfulness meditation was significantly more effective at reducing pain than both placebo groups. Mindfulness meditation–based pain relief was associated with similar brain activation as in our previous neuroimaging study,[21] including greater activation of the OFC, pregenual ACC (pgACC), and right anterior insula. Placebo-cream analgesia was associated with significant reductions in pain-related brain activation (posterior insula/parietal operculum; secondary somatosensory cortices) and produced greater activation in the thalamus and PAG compared to mindfulness meditation. Interestingly, the main effects of mindfulness meditation and sham mindfulness meditation significantly overlapped in activation of the bilateral putamen, SI corresponding to the nose/mouth, and the dACC, suggesting that the two breathing-focused practices engage similar mechanisms (Fig. 2). However, the two techniques were associated with significantly distinct neural processes when the analyses were focused on the pain-related MRI series. In contrast to mindfulness meditation, sham mindfulness meditation produced greater activation in the thalamus and deactivation of the rostral ACC. Importantly, sham mindfulness meditation–related analgesia was associated with greater reductions in respiration rate, demonstrating a mechanistic difference between sham and mindfulness meditation. That is, mindfulness meditation–related pain relief was associated with greater executive-level modulation of pain and, in contrast, sham mindfulness meditation–induced analgesia was driven by bottom-up processes consistent with placebo and relaxation.[144]

While the endogenous pain modulatory systems supporting mindfulness-based analgesia remain unknown, it is well established that the cognitive modulation of pain, including manipulations such as placebo[89, 91–93, 105, 145], conditioned pain modulation,[94] and attentional control,[97] is partially dependent on descending pain control systems[98, 146] and can be reversed by the opioid antagonist naloxone.[90, 91, 97, 147] Interestingly, meditation reduces pain by engaging brain regions (sgACC, OFC, anterior insula) that contain high concentrations of opioid receptors.[92, 111, 113, 148] On the other hand, mindfulness meditation also reduces activation in the PAG, a brain region involved in facilitating opioid-mediated descending pain inhibition.[72, 149] Thus, a recent double-blind psychophysical study tested whether mindfulness meditation–based analgesia was mediated by endogenous opioids; 78 healthy pain-free subjects were randomized to one of four 4-session intervention groups (meditation + naloxone, book-listening control + naloxone, meditation + saline, book-listening control + saline) to determine if intravenous administration of high doses of naloxone would reverse meditation-induced analgesia. Surprisingly, it was found that, independent of naloxone or placebo-saline administration, meditation significantly reduced pain intensity and unpleasantness ratings compared to rest and the control groups (Fig. 3)[20].

These findings provide supplementary evidence that mindfulness meditation engages mechanisms that are distinct from placebo to reduce pain and are of critical importance to the millions of chronic-pain patients seeking a fast-acting non-opioid pain therapy. Specifically, it was proposed that the combination of mindfulness-based and pharmacologic/nonpharmacologic analgesic strategies may be particularly effective in the treatment of pain.

Conclusion

Mindfulness meditation engages multiple unique brain mechanisms that attenuate the subjective experience of pain. Yet, analgesic mechanisms supporting mindfulness-based meditation change as a function of increasing meditative experience/training. While meditation after brief training (less than 1 week) produces significant reductions in pain intensity and unpleasantness ratings,[20, 21, 23, 122, 142] long-term meditation does not produce changes/differences in pain intensity but rather influences the unpleasantness dimension of self-reported pain.[17, 121, 122] This proposed change in the subjective experience is likely attributable to a shift in approach to meditating in the context of incoming sensory information between novice and adept practitioners. For instance, a shift in meta-awareness has been proposed,[45] in which adept meditators can engage an invasive sensation (e.g., pain) without appraising/evaluating the event. It remains unclear how this shift changes as a function of greater practice.[51, 52, 150] Nevertheless, it is not surprising that a decoupling between sensory and appraisal-related brain regions is exhibited in adept meditators in the presence of noxious stimulation.[17, 18] In contrast, novice meditators engage more effortful reappraisal processes to reduce pain, and adept meditators employ no-appraisal mechanisms.

We propose that, at the early stages of training, mindfulness meditation alters the evaluation and meaning of pain as a function of self-referential processing. Subject testimonials from our previous studies[20, 21, 23, 142] provide supplementary support for this hypothesis. Study subjects routinely stated that the experience of noxious heat stimulation during meditation was "shorter," "softer," and accompanied with "less dwelling" and a greater ability to "fully embrace the feeling of pain," but to simply "let go" of the appraisal of what the pain meant to them. These reports are remarkably consistent with the mindfulness principles that were instilled during their meditation training. Neuroimaging data provide supplementary support for these experiences. Novice meditators recruit higher-order brain regions (OFC, sgACC, anterior insula) to downregulate ascending nociceptive input at the level of the thalamus through shifts in executive attention.[21,23] Thus, meditation after brief mental training affects sensory and affective pain-related responses. The comprehensive modulation of both the intensity- and unpleasantness-related dimensions of pain is hypothetically facilitated through changes in executive attention. Activation of the OFC may facilitate inhibitory connections of the thalamic reticular nuclei (TRN) to further reduce the elaboration of nociceptive information throughout the cortex (evidenced by reductions in thalamic, PAG, and SI activation).[21, 23] Thus, brief mental training in mindfulness meditation engages cortico–thalamic–cortical interactions to reduce pain through mechanisms such as inhibitory control[45] or reappraisal (or "re-perceiving"[151]) to essentially "close the gate" on ascending nociceptive information. In contrast, the neural mechanisms involved in long-term meditation practice are associated with significantly greater activation in somatosensory regions and deactivation of appraisal-related brain regions (vmPFC).[17, 18] The decoupling

between the sensory experience and the meaning and/or contextualization of what the pain means to the self, in long-term meditation practitioners, provides evidence that the analgesic effects of meditation can be developed and enhanced through greater practice, a critical consideration for those seeking long-lasting narcotic-free pain relief.

When taking into consideration the current chronic pain[152] and opioid epidemic,[153, 154] the use of mind–body approaches, such as mindfulness meditation, may prove to be an important resource to teach patients to self-regulate their respective experience of pain directly with a present-centered and acceptance-based focus. Converging lines of evidence demonstrate that mindfulness meditation significantly attenuates pain across clinical and experimental settings. In contrast to other health outcomes, the health-promoting effects of meditation are most pronounced for pain and pain-related comorbidities, including opioid addiction and misuse,[155–158] stress,[37, 138] depression,[159–161] and anxiety.[31, 162, 163] Some recent studies of fibromyalgia[22] and chronic low back pain[54] patients who received mindfulness training also see a similar decoupling of sensory and affective pain, such that pain intensity or frequency does not necessarily decrease, but coping with the pain does improve. Furthermore, across almost all mindfulness/pain–focused experiments, the unpleasantness dimension of pain was significantly more attenuated with respect to pain intensity,[16–21, 23, 121, 122] which is a critically important effect when considering the use of meditation for clinical pain. For instance, the experience of chronic pain is dramatically influenced by the context in which it occurs. One example of this comes from studies assessing pain in patients and in women giving birth.[164] The pain of labor was rated as significantly higher on sensory aspects compared to the affective dimension. In contrast, cancer pain was rated significantly higher on pain unpleasantness than pain intensity.[165] The suggestion here is that the contextual evaluation of welcoming a new baby into the world when compared to facing one's own death has profound implications for what might have otherwise been very similar experiences. We suggest that mindfulness, in a similar, albeit less profound manner than giving birth or dying, also alters the meaning, interpretation, and appraisal of nociceptive information, an important consideration for producing stabilized and long-lasting improvements in chronic pain symptomology, and can potentially serve as a mechanism to buffer against the chronification of pain.

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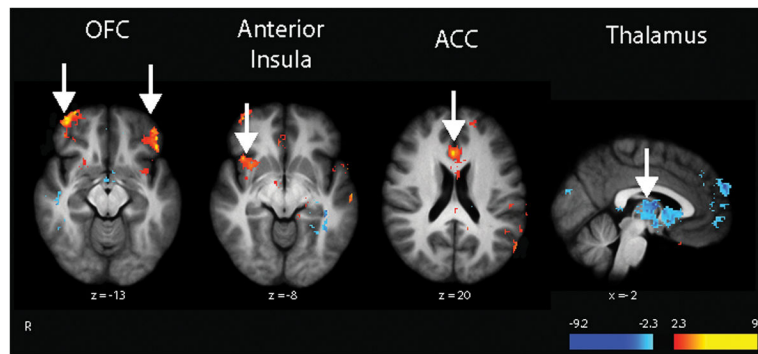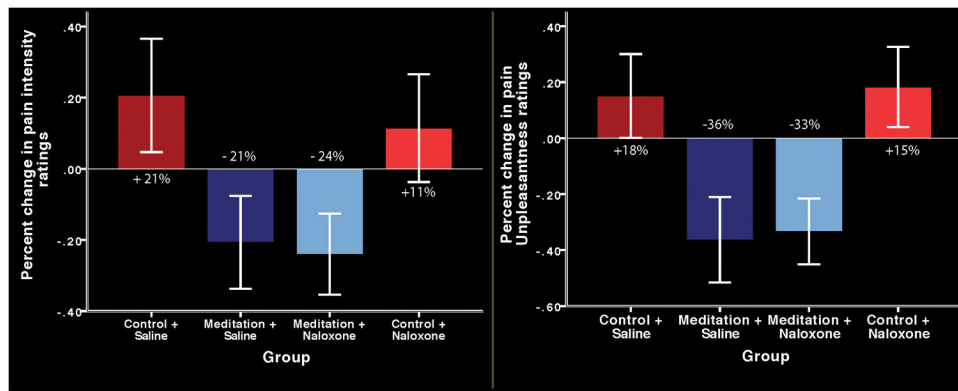
Figure 1.
Mindfulness meditation–based pain relief is associated with multiple brain mechanisms. Regression analyses corresponding to those in Zeidan *et al.*[21] revealed that reductions in mindfulness meditation–induced pain intensity were associated with greater activation (depicted in red) in the right anterior insula and rostral aspects of the anterior cingulate cortex (ACC). Greater reductions in pain unpleasantness ratings were associated with greater activation of the orbitofrontal cortex (OFC) and thalamic deactivation (depicted in blue).
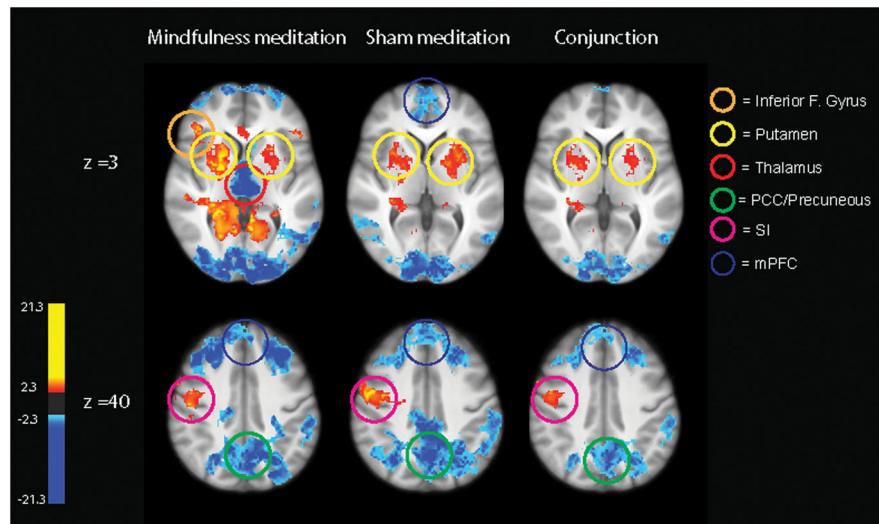
Figure 2.
The main effects of mindfulness meditation and sham mindfulness meditation involve similar neural processes. Mindfulness meditation and sham mindfulness meditation produced activation (red) in the bilateral putamen and primary somatosensory cortex (SI) corresponding to the nose/face regions and deactivation (blue) of the medial prefrontal cortex (mPFC) and precuneous/poster cingulate cortex (PCC). Mindfulness meditation also activated the right inferior frontal gyrus and produced deactivation of the bilateral thalamus. Conjunction analyses revealed significant overlapping activation in the bilateral putamen, SI representation of the nose/face, and deactivation of the PCC and mPFC.

Figure 3.
Psychophysical pain intensity (left graph) and unpleasantness (right graph) ratings (95% confidence intervals). Meditation during saline (meditation + saline) infusion significantly ($P < 0.001$) reduced pain intensity and unpleasantness ratings compared with rest and the control and saline (control + saline) group. Naloxone did not reverse meditation-induced pain relief. Meditation during naloxone administration (meditation + naloxone) significantly ($P < 0.001$) reduced pain intensity and unpleasantness ratings compared with rest, the control + saline group, and the control and naloxone (control + naloxone) groups. There were also no significant differences in pain intensity or unpleasantness ratings between the meditation + saline and the meditation + naloxone groups ($P > 0.69$).