



# Neurophysiological Mechanisms Supporting Mindfulness Meditation–Based Pain Relief: an Updated Review

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## Abstract

**Purpose of Review** This review examines recent (2016 onwards) neuroscientific findings on the mechanisms supporting mindfulness-associated pain relief. To date, it is clear that mindfulness lowers pain by engaging brain processes that are distinct from placebo and vary across meditative training level. Due to rapid developments in the field of contemplative neuroscience, an update review on the neuroimaging studies focused on mindfulness, and pain is merited.

**Recent Findings** Mindfulness-based therapies produce reliable reductions in a spectrum of chronic pain conditions through psychological, physiological, and neural mechanisms supporting the modulation of evaluation and appraisal of innocuous and noxious sensory events.

**Summary** Neuroimaging and randomized control studies confirm that mindfulness meditation reliably reduces experimentally induced and clinical pain by engaging multiple, unique, non-opioidergic mechanisms that are distinct from placebo and which vary across meditative training level. These promising findings underscore the potential of mindfulness-based approaches to produce long-lasting improvements in pain-related symptomatology.

**Keywords** Pain · Mindfulness · Meditation · Analgesia

## Introduction

Despite the wealth of empirical physiological, psychological, and neuroscientific evidence, the affective, cognitive, and sensory mechanisms that modulate pain remain difficult to disentangle, forming an obstacle to the effective treatment of a wide number of chronic pain conditions. Chronic pain affects over

116 million Americans [1] and 1.5 billion people worldwide [2], impacting women disproportionately [3], and with an annually increasing prevalence [4]. Many qualify chronic pain as having reached epidemic proportions [5].

Under the mistaken belief that the risk for developing opioid use disorder was low when opioids are taken for the purpose of analgesia [6], the rate of opioid prescriptions markedly increased over the past two decades [7]. In 2012 alone, 259 million opioid prescriptions were given in the USA [8]. The repeated use of opioids produces physiological adaptations that lead to tolerance and physical dependence [7], driving a downward spiral of maladaptive cognitive-affective sequelae [9] that have led to an increased rate of opioid misuse and opioid use disorder among chronic pain patients [10].

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## Shortcomings of Pharmacological Pain Therapies

The use of opioids as frontline analgesics has been further called into question by a recent wave of evidence

demonstrating that opioid-based treatments provide little benefit and actually exacerbate chronic pain. A recent randomized clinical trial (RCT) examined 12 months of opioid vs. non-opioid treatment for chronic back, hip, or knee pain and found that individuals taking opioids reported no pain-related improvements when compared with non-opioid therapies [11]. In contrast, opioid-treated patients exhibited significantly higher pain intensity and medication-related adverse effects. A number of cohort-based studies and systematic reviews report similar results—small or no beneficial effects of opioids in treating polyneuropathy, chronic low back pain, musculoskeletal, and chronic non-cancer pain, alongside higher risks of all-cause mortality, opioid dependency, and overdose [12–16].

The shortcomings of other chronic pain treatments like spinal cord stimulation [17], intrathecal pumps [18], and nerve ablations [19, 20] to produce long-term pain relief have inspired a wave of cognitive therapies that integrate components of contemplative practices to strengthen self-regulation of affective processes and target the etiological factors of chronic pain, rather than the physical source of injury. Yet, the degree to which complex psychosocial factors underlie many of these conditions has made the efficacious treatment of chronic pain a slow and difficult approach. Enhancing self-regulation of arising sensory and affective experiences is a potential mechanism in promoting long-lasting reductions in pain and corresponding comorbidities [21]. To this end, self-regulatory practices such as mindfulness-based meditation reliably reduce affective pain when compared with sensory pain by targeting moment-to-moment appraisals of self and environment [22–27].

Recent advances on the unique modulatory mechanisms supporting mindfulness-based analgesia have begun to shed light on *how* the affective-motivational and sensory-discriminative components of pain interact. Previous reviews have outlined the neuroimaging-based evidence of the distinct mechanisms supporting brief and long-term mindfulness training-induced pain relief discovered up to 2016 [28–31]. The present review presents a short synopsis of such work and delineates recently discovered (>2016) neuroscientific evidence that elucidates pain relief mechanisms and the manner in which interventions promote health across a broad range of disease points in greater detail. It is worth nothing that this review focuses on mindfulness meditation, one among thousands of distinct meditation techniques.

## Brief Synopsis of Neurophysiology and Non-pharmacological Pain Modulation

Pain is constructed and modulated through a myriad of interactions between peripheral nociceptive sensory afferents (A-delta and C-fibers), ascending nociceptive signals in the spinal

cord, and a distributed network of subcortical and cortical brain areas. Nociceptive information originates in sensory primary afferents that synapse in the dorsal horn before ascending contralaterally, largely through the spinothalamic pathway, to a feedback network of lower level sensory regions, including the periaqueductal gray matter (PAG), thalamus, and primary somatosensory (SI) and secondary somatosensory (SII) cortices [32–38]. The anterior and posterior insular cortices then fine-tune the ascending nociceptive signal before higher order brain regions, including the dorsal anterior cingulate cortex (dACC) and prefrontal cortex (PFC), enrich it with contextual meaning [39–42].

Cognitive techniques that manipulate mood [43], expectations [40, 44], and attention [45] reduce pain via a common descending inhibitory pathway. To this extent, the endogenous opioidergic system mediates cognitively modulated pain relief engaged by placebo [46–51], conditioned pain modulation [52], acupuncture [53], hypnosis [54], and attentional control [55]. Specifically, the cognitive modulation of pain is associated with reductions of neural activity in pain-related brain regions and activation of the PAG to facilitate descending inhibition of pain at the level of the spinal cord [56–59]. In contrast, growing evidence demonstrates that mindfulness meditation reduces pain through mechanisms that may bypass PAG-mediated descending inhibition [23, 31].

## Mindfulness and Mindfulness-Based Therapies

Mindfulness meditation originated 4500 years ago in Southeast Asia and is, in its modern instantiation, a loose construct whose precise definition remains a matter of debate. In the secular scientific context within which mindfulness-based therapies are studied, it refers to a self-regulated attentional state based on non-judgmental awareness of the present moment [60]. Mindfulness can be cultivated by a variety of meditation routines or can be practiced without formal training. Within the wide variety of mindfulness meditation techniques, two operationalized approaches stand out: focused attention [61] and choiceless awareness [62].

Focused attention involves narrowing attention to the dynamic moment-to-moment quality of a sensory, emotional, or cognitive event, such as the breath, and re-orienting attention from distractors so as to sustain attention on the chosen object [31, 61]. Choiceless awareness, on the other hand, involves the wide non-reactive monitoring of moment-by-moment sensory, cognitive, or affective states occurring in one's experience. The focused attention practitioner tends to naturally transition into a choiceless awareness state in which the internal sensory and cognitive milieu are monitored without evaluation [31, 61]. As choiceless awareness practice further

develops, awareness may reflect back upon itself, resulting in a profound reduction of self-referential processing during a state known as non-dual awareness that limits evaluation of object from the perspective of self [63]. The large number of operational variations even within each of these techniques, however, requires that scientific studies reference the precise technique being evaluated.

Mindfulness-based stress reduction (MBSR) [64] is one of the most promising mindfulness-based therapies to demonstrate clinical efficacy across a range of health outcomes. MBSR is an 8-week course that combines a range of sitting and moving meditation practices integrated with some behavioral therapy, daily “homework,” and a silent 2-day retreat. Other more-tailored mindfulness-based interventions evolved from MBSR to target different disease points: mindfulness-based cognitive therapy (MBCT) to treat depression [65–68], mindfulness-oriented recovery enhancement (MORE) to target opioid misuse and chronic pain [69], and mindfulness-based relapse prevention, a therapy that reliably alleviates addiction and long-term recovery [70].

Mindfulness-based therapies improve pain-related symptoms across a range of conditions including fibromyalgia, migraine, and irritable bowel syndrome [69, 71–82], with recent meta-analyses on chronic pain [83], rheumatoid arthritis [84], and cancer-related pain [85] confirming earlier findings. Of the different interventions, the 8-week MBSR program is the most studied. Multiple randomized control trials report post-MBSR improvements in pain-related symptoms and quality of life for patients with a spectrum of chronic pain conditions [86] including chronic low back pain [71, 87] and, in some one case, with sustained effects after 3 years [88]. Mindfulness meditation-based pain relief has also been studied in healthy, pain-free subjects via experimentally induced pain, with results showing that bouts of training briefer than 8 weeks are efficacious. One such study using noxious heat found that after a four-session (20 min/session) mindfulness meditation-based intervention, meditation resulted in a significant 40% reduction in pain intensity and 57% reduction in pain unpleasantness ratings [22].

Importantly, across studies, the most salient effects of mindfulness-based therapies are related to the significant improvements in affective factors that accompany and often complicate pain conditions, such as pain acceptance [89], stress [90, 91], depression [68, 92–95], and catastrophizing [96]. Across most to all studies of mindfulness and pain, mindfulness practice leads to significant improvements in affective pain when compared with sensory pain [22–27]. Mindfulness-based therapies thus appear particularly effective at targeting the affective component of pain and constitute a promising avenue toward better understanding and mitigating the psychosocial components of chronic pain. Until recently, however, the specific neural mechanisms responsible for mindfulness-based analgesia remained largely unknown.

## The Neuroscience of Mindfulness-Based Pain Reduction up to 2016

The advent of neuroimaging techniques such as functional magnetic resonance imaging (fMRI) opened the doors for researchers to investigate the neural mechanisms active in mindfulness meditation-based pain relief and is associated with the surge in research on mindfulness [97]. Up to 2016, a number of studies identified multiple unique neuromodulatory mechanisms for both brief and long-term mental training.

In the context of brief mental training, two studies [22, 98] found mindfulness-based pain reductions in response to painful heat that were associated with activation in three cortical areas: the subgenual ACC (sgACC) (associated with cognitive and affective pain control), the orbitofrontal cortex (OFC) (supporting contextual evaluation of sensory events), and the right anterior insula (associated with afferent nociceptive signal modulation and interoceptive awareness). In addition, they found that effortful cognitive processes mediated by executive attention downregulate ascending nociceptive signals in the thalamus through a mechanistically unique cortico-thalamic-cortical pathway that may have also facilitated lower SI corresponding to the stimulation site. Taken together, these mechanisms may relieve pain by recontextualizing pain as innocuous sensory information rather than an affectively laden threat to bodily integrity—a type of “mindful” *reappraisal* of the meaning of nociceptive input. Researchers showed mindfulness-related pain relief to be mechanistically distinct from placebo-based pain relief by comparing experimentally induced pain during mindfulness meditation and sham mindfulness, an intervention identical to genuine mindfulness training except omitting mindfulness-based instructions (e.g., non-judgmental attention to the breath) [98]. Instead, participants are instructed to “take deep breaths” every 2–3 min “as we sit here in mindfulness meditation.” This novel pain modulatory pathway was found to be non-opioidergically mediated [23••] and thus distinct from those of placebo-based pain relief [31, 98].

On the other hand, long-term training elicits reductions in affective pain alongside greater activation in somatosensory regions and deactivation of appraisal-related regions like vmPFC [24, 25]. This decoupling between frontal, appraisal-related areas and sensory areas may reflect a distinct *non-appraisal* mechanism, reflecting the ability of expert meditators to separate the sensory experience of pain from the corresponding contextualization, thereby removing the need for OFC-mediated top-down inhibitory control [24, 25, 31, 99]. That is, experienced meditators have developed the capacity to sense noxious stimuli as frankly painful without the evaluation of unpleasantness/affect that traditionally accompanies painful experiences. Needless to say, there is great potential therapeutic value of both brief and long-term mindfulness practice to treat chronic pain patients for whom pharmacological analgesia has proven ineffective.

## Recent Discoveries in the Neurophysiological Mechanisms Supporting Mindfulness-Based Pain Relief

Since 2016, evidence has continued to accumulate demonstrating that mindfulness-based pain relief is modulated through multiple unique neural mechanisms that are largely insensitive to opioidergic antagonism. As the role of pain's affective dimension in chronic disease etiology has grown in importance, so too has the accumulation of evidence demonstrating that mindfulness uniquely impacts affective pain to promote well-being. These new findings remarkably parallel recent findings suggesting that mindfulness meditation engages a novel modulatory pathway to reduce pain.

### Unique Neurophysiological Mechanisms Supporting Mindfulness Meditation-Induced Pain Relief: an Update from 2016

Recent mechanistically focused clinical trials examining the effects of brief mindfulness-based mental training provide converging evidence that meditation bypasses the body's endogenous opioid system and operates via multiple unique neural pathways. The mechanisms supporting pain relief by mindfulness meditation are postulated to be disparate across training level and experience. Yet, recent evidence demonstrates that long-term meditation practitioners reliably reduce pain via non-opioidergic mechanisms. May and colleagues [100] recorded subjects' pain ratings in response to painful electrical stimulation, before and during choiceless awareness meditation during intravenous administration of saline or naloxone (the opioid antagonist) in a double-blind, randomized, cross-over design. Naloxone infusion not only failed to antagonize meditation-induced pain relief but actually enhanced pain relief—an unexpected result. It was suggested that the opioid blockage may have upregulated a non-opioid pathway.

In order to disentangle the specific role of other underlying components of mindfulness for pain relief, Wells and colleagues [101] conducted a double-blind, placebo-controlled crossover naloxone and saline infusion study. Healthy subjects were randomized into mindfulness meditation, sham mindfulness meditation, and slow-paced breathing groups and administered noxious 49 °C heat to the back of the calf. As expected, naloxone did not reverse pain relief associated with mindfulness meditation. Surprisingly, slow-paced breathing significantly reduced pain during opioidergic antagonism. Importantly, naloxone infusion reversed analgesia produced by sham mindfulness meditation, providing supplementary evidence that mindfulness is mechanistically distinct from placebo. Since all techniques significantly lowered breathing rates, the independent pain-relieving role of slow breathing from endogenous opioids could not be ruled out. However, the authors found that self-reported “attention to

the breath” was absent only from sham mindfulness practice. The shifting of executive attention between breath sensations, appraising distractions, and reorienting back to breath was hypothesized to modulate pain before nociceptive information can be elaborated into a subjective sensory experience, a phenomenon corroborated by post-hoc qualitative assessments in which greater pain relief was associated with self-reported attention to the breath [101]. Thus, the authors postulated that attending to the breath, independently of mindfulness-based reappraisal, reduces pain by bypassing opioidergically mediated descending inhibition. Crucially, since slow-paced breathing is easier to perform than mindful attention to the breath, slow attentive breathing may be a critically valuable therapy for patients seeking a less cognitively demanding, non-opioidergic, self-administered pain therapy. Taken together, three separate studies now demonstrate that mindfulness reduces pain via non-opioidergic processes independent of meditation expertise.

Mindfulness meditation involves a number of components such as choiceless awareness, attention to the breath, body awareness, and relaxation, which might underlie its effects on pain. A number of recent studies have begun to elucidate which specific components drive these effects, showing, for example, that the relaxation component alone is not the driver behind mindfulness-based pain relief [102] but that attention to breathing is a potential mechanism of action [101]. Moreover, it has been shown that the autonomic nervous system plays a unique role in mindfulness-associated affective pain relief.

### Greater Granularity on Unique Mechanisms Underlying Affective Pain Relief

There is an established relationship between increased activity in the parasympathetic autonomic nervous system and pain relief. However, until recently, it was unknown to what extent mindfulness meditation-induced pain relief is associated with parasympathetic activity. A study examined high-frequency heart rate variability (HF HRV), a robust marker of parasympathetic activation, during noxious heat and mindfulness and sham mindfulness meditation to determine the role of the parasympathetic system [103]. Higher HF HRV was more strongly associated with lower pain unpleasantness (though not with pain intensity) ratings during genuine mindfulness than during sham mindfulness. Further mechanistic research is needed to characterize the precise role of the autonomic nervous system in mindfulness-based pain relief, but these results point toward a unique parasympathetic activation pattern engaged by mindfulness to relieve pain.

The neuroscientific basis for affective pain relief associated with mindfulness meditation has benefited from randomized control studies combining different forms of experimentally induced pain and pain-eliciting stimuli. In one study,

meditation-naïve participants received 30 min of mindfulness training before either maintaining a mindset of mindful acceptance or reacting naturally to a series of aversive vs. neutral images and individually calibrated noxious vs. innocuous heat stimuli [104]. After each trial, participants reported subjective pain and negative emotion levels. Mindful acceptance led to lower self-reported pain, less emotional reactivity to negative images as registered in the amygdala and PFC, and lower pain-related activity in the neurological pain signature (NPS)—a machine learning-based regression technique that can reliably predict self-reported pain [105]. These findings provide novel evidence that a single mindfulness training session produces significant pain relief and engages modulatory brain mechanisms that support the evaluation of negative affect.

Mindfulness meditation may also reduce social pain. In a study by Laneri et al. [106], long-term meditators and non-meditators were presented with images of people in neutral and in socially embarrassing situations after either a choiceless awareness mindfulness meditation or rest. All subjects exhibited greater ACC, anterior insula, and mPFC activation in response to embarrassing images, a typical pattern associated with the negative affect of experiencing another's distressing mental state [107]. Compared with the subjects who did not meditate prior to the task, long-term meditation practitioners exhibited lower anterior insula activation during the presentation of embarrassing images, and these effects were associated with higher compassion scores. These data provide supplementary evidence that the anterior insula is strongly associated with cultivating interoceptive processes and compassion, an effect that may be developed after longer bouts of training. Previous studies had shown social pain from vicarious embarrassment to be significantly associated with anterior insula activation [107–109], while others had shown that mindfulness decreases reactivity to affective experiences, with associated lower anterior insula activation [110, 111]. Therefore, these results suggest that meditation may reduce affective distress not only in response to one's own pain but also to someone else's. Moreover, this attenuation of empathic distress—feeling of another's pain—is in line with studies showing different brain activation patterns for empathic distress and empathic care [112], with the latter associated to compassion. Thus, converging lines of evidence suggest that mindfulness meditation may also attenuate social pain, an additional health benefit [113]. Remarkably, the degree of decreased anterior insular activation was contingent on the frequency of daily practice, adding to growing evidence that compassion cultivation is a trainable skill.

### Growing Therapeutic Usefulness

The studies reviewed above, conducted in healthy, pain-free individuals, have elucidated the specific pain-relieving

mechanisms that may now allow for the design of more effective mindfulness-based therapies to target specific chronic pain conditions.

The neural mechanisms supporting the direct alleviation of clinical pain have been brought into sharp focus by a seminal study by Seminowicz et al. [114••], which assessed the behavioral efficacy and neural mechanisms supporting enhanced MBSR (MBSR+) on episodic migraine, a severe and disabling neurological pain disorder. The 98-participant randomized clinical trial compared a 12-session 4-month-long MBSR+ (doubling the duration of the original MBSR) intervention to a time-matched stress management for headache (SMH) program. Both groups showed reductions in the number of headache days per month from baseline to 20 weeks, with 23% of the SMH group responding to treatment compared with 52% of the MBSR+ group, a response rate comparable with that of first-line pharmacologic treatment. Moreover, fMRI data showed the MBSR+ group had weaker resting-state connectivity between dorsal anterior insula and both superior parietal lobule and cuneus, an effect the authors interpreted as evidence of increased cognitive efficiency from mindfulness-based training. Promising therapeutic results like these highlight the potential of mindfulness-based pain relief to reshape the chronic pain experience without the need for lengthy or cognitively demanding interventions. In the final section, the potential of mindfulness-based interventions to reduce the risk of opioid misuse among opioid-treated chronic pain patients will be discussed.

### Role of Mindfulness-Based Therapies for Opioid-Treated Chronic Pain Recovery

So far, mindfulness-based interventions have been discussed in light of their therapeutic potential to modulate pain. Important recent research also suggests that these interventions may also mitigate the risk factors causing opioid-treated chronic pain patients to develop opioid use disorder, a valuable role in light of the current opioid crisis.

Evidence suggests that prolonged opioid use may cause hedonic dysregulation, a sensitization to aversive experiences and concurrent reduction in responsiveness to natural rewards, which decreases positive affect and drives a downward spiral linking chronic pain to opioid misuse [9, 115]. In order to counteract this negative spiral and promote hedonic well-being, MORE, an intervention based on Garland et al.'s mindfulness-to-meaning theory [116], unites training in mindfulness, reappraisal, and savoring skills to simultaneously address chronic pain and addictive behavior. In two stage 2 RCTs, MORE was shown to decrease prescription opioid misuse and pain severity. In the first of these trials, in a sample of 115 chronic pain patients who had taken prescription opioids for more than 10 years, MORE reduced the occurrence of opioid misuse by 63% while decreasing opioid craving, pain

severity, and pain interference [75]. The effects of MORE on pain were statistically mediated by the capacity to reappraise pain as innocuous sensory information, again suggesting that mindfulness training modifies contextual evaluations of nociceptive information. In a second RCT, MORE was evaluated as a prophylactic intervention for long-term opioid-treated chronic pain patients at risk of developing opioid misuse [117]. Ninety-five patients were randomized to 8 weeks of MORE or to a support group intervention, after which MORE-treated patients reported significantly greater improvements in an array of positive psychological functions and reductions in pain severity and opioid misuse risk than support group patients at 3-month follow-up. The effects of MORE on reducing pain severity were statistically mediated by increases in positive psychological functioning and, most notably, by mindfulness-induced mental states and enhanced capacity to savor positive experiences. These clinical effects parallel recent EEG data from a series of randomized controlled experiments demonstrating that MORE increases neurophysiological responsivity to naturally rewarding, positive stimuli and decreases neurophysiological reactivity to opioid-related cues [118]. However, the underlying neural mechanisms supporting the effect of MORE on reducing pain and opioid misuse remain unknown. While more research is needed to confirm the precise neural mechanisms that modulate these processes, the ability of mindfulness meditation to not only target pain via multiple unique non-opioidergic modulatory pathways but to also mitigate the psychological risks of developing opioid use disease makes it an important candidate for further research.

### Future Directions for Mindfulness-Based Pain Therapies

The neuroscience of mindfulness-based pain relief is in its infancy, and yet it has already proven capable of expanding the repertoire of known neural modulatory pain pathways and of shedding light on the complex affective and psychosocial components of chronic pain. The vast number of global chronic pain sufferers as well as the health and social risks of opioid use disorder underscores the potential value of developing validated self-administrable mind-body therapies that target pain multidimensionally via several unique neuromodulatory pathways. The great variability within mindfulness meditation techniques as well as the biopsychosocial complexity of chronic pain conditions, however, requires researchers to continue to apply the highest experimental standards to find and fine-tune the clinically relevant tools we need to produce long-lasting improvements in chronic pain management. By altering the meaning, interpretation, and appraisal of nociceptive information on its way to constructing the subjective experience of pain, mindfulness-based approaches may play an

important role in the integrative therapeutic regimens capable of stemming the rising tide of chronic pain.

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### Compliance with Ethical Standards

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

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

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