



# Mindfulness Meditation Modulates Pain Through Endogenous Opioids

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## ABSTRACT

**BACKGROUND:** Recent evidence supports the beneficial effects of mindfulness meditation on pain. However, the neural mechanisms underlying this effect remain poorly understood. We used an opioid blocker to examine whether mindfulness meditation-induced analgesia involves endogenous opioids.

**METHODS:** Fifteen healthy experienced mindfulness meditation practitioners participated in a double-blind, randomized, placebo-controlled, crossover study. Participants rated the pain and unpleasantness of a cold stimulus prior to and after a mindfulness meditation session. Participants were then randomized to receive either intravenous naloxone or saline, after which they meditated again, and rated the same stimulus.

**RESULTS:** A  $(3) \times (2)$  repeated-measurements analysis of variance revealed a significant time effect for pain and unpleasantness scores (both  $P < .001$ ) as well as a significant condition effect for pain and unpleasantness (both  $P < .2$ ). Post hoc comparisons revealed that pain and unpleasantness scores were significantly reduced after natural mindfulness meditation and after placebo, but not after naloxone. Furthermore, there was a positive correlation between the pain scores following naloxone vs placebo and participants' mindfulness meditation experience.

**CONCLUSIONS:** These findings show, for the first time, that meditation involves endogenous opioid pathways, mediating its analgesic effect and growing resilient with increasing practice to external suggestion. This finding could hold promising therapeutic implications and further elucidate the fine mechanisms involved in human pain modulation.

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**KEYWORDS:** Analgesia; Meditation; Opioids; Pain

Pain is a complex and multifaceted phenomenon involving sensory, cognitive, and emotional brain processes.<sup>1</sup> In recent years, a growing body of research has provided support for the beneficial effects of mindfulness meditation on acute and

chronic pain.<sup>2,3</sup> Because mindfulness meditation has been shown to enhance cognitive control and improve emotion regulation,<sup>4-6</sup> a placebo-like mechanism of top-down control involving suggestion and expectation has been proposed as enabling such meditation-induced analgesia.<sup>7</sup> However, the neurofunctional and neurochemical mechanisms underlying this analgesic effect remain poorly understood. By using an opioid blocker during mindfulness-meditation modulation of a painful stimulus, we aimed to examine whether mindfulness meditation-induced analgesia is mediated via endogenous opioids, and if so, whether it is susceptible to manipulation by suggestion/expectation.

## METHODS

Fifteen healthy mindfulness-meditation practitioners participated in 30 sessions of a double-blind, randomized,

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placebo-controlled, crossover study. All participants were recruited from the same meditation practice center in Tel Aviv and had over a year's experience of at least one hour of practice a day at least 3 times a week. All practiced sitting mindfulness meditation and referred to the type of practice that they perform as Shamatha or Vipassana meditation.<sup>5</sup> All participants had no previous or current neurological or psychiatric disorders, and did not suffer from any chronic pain (constant or episodic syndromes). One subject was excluded from the analysis due to technical difficulties with the intravenous line; thus, the final analyses included 14 subjects. Participants were asked to rate the pain and unpleasantness of a cold stimulus (immersing their hand in icy water, 2°C-4°C, for 10 seconds) using a visual analog scale score prior to and after a normal mindfulness-meditation session (nonmanipulation condition). Participants were then randomized to receive either 0.1 mg/kg of intravenous naloxone, an opioid antagonist, or intravenous saline, after which they meditated again, and then rated the same painful stimulus. On a different date (a mean of 7 days apart), each participant underwent the same procedure in a crossover-counterbalanced design. The study was reviewed and approved by the Tel Aviv Medical Center Ethics Committee.

## RESULTS

A (3) × (2) repeated-measurements analysis of variance was performed separately for both pain and unpleasantness scores for the within-subjects factors of time (prior to/after meditation) and condition (no treatment, naloxone or placebo injection). Both analyses revealed a significant time effect [ $F(1, 13) = 19.01$  for pain ratings;  $F(1, 13) = 22.85$  for unpleasantness, both  $P < .001$ ], as well as a significant condition effect [ $F(2, 26) = 4.62$  for pain ratings;  $F(2, 26) = 9.01$  for unpleasantness, both  $P < .2$ ]. Both measurements further revealed a significant interaction between time and condition [ $F(2, 26) = 3.68$ , for pain ratings;  $F(2, 26) = 4.61$  for unpleasantness, both  $P < .04$ ]. Tukey honest significant difference post hoc comparisons revealed that pain and unpleasantness scores were significantly reduced after natural mindfulness meditation, compared with baseline (from  $6.11 \pm 0.46$  to  $4.21 \pm 0.5$ , and from  $5.8 \pm 0.47$  to  $3.4 \pm 0.44$ , both  $P < 3E-5$ ), as well as after placebo administration (from  $6.14 \pm 0.48$  to  $5 \pm 0.66$ , and from  $5.71 \pm 0.48$  to  $4.28 \pm 0.58$ , both  $P < .01$ ), but not after naloxone administration (from  $6 \pm 0.47$  to  $5.2 \pm 0.56$ ,  $P = 0.1$ , and from  $5.9 \pm 0.5$  to  $4.78 \pm 0.5$ ,  $P = 0.07$ , respectively) (Figure, top panel).

To further explore the development of mindfulness-meditation analgesia, we tested the correlation between the

differences in pain scores following naloxone vs placebo and participants' mindfulness-meditation experience. Interestingly, a significant correlation was found ( $r = 0.67$ ,  $P < .01$ ; Figure, bottom panel) suggesting reduced response to placebo with increasing experience.

## CLINICAL SIGNIFICANCE

- Meditation-induced analgesia involves endogenous opioids that mitigate its beneficial effect on pain.
- Our results suggest that with increasing experience this process becomes unaffected by cognitive manipulation.
- These observations support the notion that cultivating a long-term practice of meditation in chronic pain patients may have potential therapeutic effects.

## CONCLUSIONS

In line with previous reports, we found that mindfulness meditation induces a significant analgesic effect. However, we found that this effect was reversed by the administration of an opioid antagonist, indicating the recruitment of the endogenous opioid system during meditation.

Interestingly, in this study there was a significant correlation between the differential response to naloxone vs saline and participants' meditation experience, with saline being more likely to reverse

the mindfulness meditation-induced analgesic effect in less-experienced practitioners. This sensitivity to placebo in less-experienced meditators implies the contribution of cognitive-emotional top-down mechanisms that are still susceptible to expectation. Such mechanisms do not appear to be as sensitive to manipulation in more experienced meditation practitioners. This finding supports the growing recent evidence from brain imaging studies indicating that the neural mechanisms underlying mindfulness meditation-induced analgesia are different from those that underlie placebo analgesia.<sup>8</sup> Moreover, it suggests that mindfulness meditation-induced analgesia is shaped by a dynamic neural process that evolves with time and experience — while in early stages it seems to rely mostly on mechanisms related to suggestion, it later becomes a dedicated opioid-mediated process that is less susceptible to external psychological manipulation. This observation also echoes findings of macroanatomical changes in gray matter density among long-term meditators, which also suggest a robust and ongoing modulation of brain function.<sup>4,7</sup> Interestingly, a recent study has also shown a similar principle for placebo — for example, in migraine patients taking placebo medications that were explicitly labeled “placebo” and experiencing significant pain relief compared with no treatment,<sup>9</sup> suggesting that a learned association between pill taking and a beneficial effect makes the very habit of pill taking beneficial in itself over time, regardless of explicit external suggestion. Our results further support recent proposals<sup>10</sup> that future study of mindfulness meditation-induced analgesia should explore its temporal dynamics, as well as its delineation from other cognitive-emotional means of modulating pain in humans, by using integrated structural and functional neuroimaging techniques in meditators with varying levels of experience or in

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