



Published in final edited form as:

Pain. 2020 December ; 161(12): 2659–2666. doi:10.1097/j.pain.0000000000001988.

Psychosocial intervention and the reward system in pain and opioid misuse: new opportunities and directions

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Abstract

Clinicians and scientists have begun to recognize that chronic pain and its treatment with opioid analgesics may occasion *hedonic dysregulation*—a blunting of physiological and positive emotional responses to rewarding objects and events in the social environment. Conversely, pain relief can be rewarding [83,84]. Yet, this relation is not unidirectional; experimental manipulations and clinical observational studies demonstrate the analgesic effects of positive affect and reward [32,86]. Although positive emotions and rewarding experiences can produce analgesia, how might they be intentionally cultivated for their therapeutic value? To answer this research question, this topical review proposes a mechanistic model (Figure 1) for optimizing psychosocial interventions by leveraging positive affective/reward-related mechanisms as means of addressing chronic pain and opioid misuse.

Keywords

CBT; hedonic; Mindfulness-Oriented Recovery Enhancement; opioid; positive affect; reward

1. Conceptual and Empirical Background

In classical Western philosophy, pleasure and pain were considered opposites on a hedonic balance that propelled behavior [9]. Modern neurobiology complements this view by demonstrating that pain and pleasure operate through a common emotional currency in the brain [17] – mediated by mesocorticolimbic dopamine circuitry [23,72,92,95,105,116] and the endogenous opioid system [15,19,28,79,96,121] – the neural substrates of reward. This common neurobiological architecture underlying hedonic experience integrates pain and reward to motivate homeostatic goal attainment [7]. When the decision to avoid potential injury is outweighed by the motivation to pursue a conflicting goal (e.g., a significant

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Conflict of Interest: Eric Garland, PhD, LCSW is the Director of the Center on Mindfulness and Integrative Health Intervention Development. The Center provides Mindfulness-Oriented Recovery Enhancement (MORE), mindfulness-based therapy, and cognitive behavioral therapy in the context of research trials for no cost to research participants; however, Dr. Garland has received honoraria and payment for delivering seminars, lectures, and teaching engagements (related to training clinicians in mindfulness) sponsored by institutions of higher education, government agencies, academic teaching hospitals, and medical centers. Dr. Garland also receives royalties from the sale of books related to MORE.

reward), top-down processes in the brain inhibit nociception via release of opioid peptides; conversely, if the decision is to ignore the conflicting goal and instead to respond to the noxious stimulus, top-down facilitation of nociception occurs [31]. As a result of this motivational-decisional process, pain may subvert enjoyment of reward via multiple mechanisms. The attention-grabbing quality of pain can shift attentional resources away from reward processing [26]. Stress produced by pain can also result in reward devaluation [87]. Pain-induced reward devaluation is coupled with dampened neural responding during reward anticipation in the ventral striatum [100]. Furthermore, chronic pain may blunt the motivation to seek reward via neuroplasticity in dopamine neurons [91] and produce anhedonia by reducing endogenous opioid signaling [60,79] and opioid receptor availability [101] in reward-related brain regions. These neurobiological alterations may underlie impaired reward learning [3] and reduced reward responsiveness [30,66] observed among individuals with chronic pain.

Because exogenous opioids interact with endogenous opioid and dopamine systems [63,95] involved in the regulation of pain and reward, prolonged opioid use is theorized to blunt reward processing by modulating dopaminergic and opioidergic mechanisms integral to hedonic function [110]. Overuse and misuse of opioid analgesics can exacerbate pain-related hedonic dysregulation [46,68,94] by (a) producing neuroadaptations in corticostriatal reward systems and (b) by magnifying anti-reward processes instantiated by limbic systems (e.g., extended amygdala) that mediate release of signaling molecules including corticotropin-releasing factor (CRF), dynorphin, and substance P [29]—neuromolecular mediators of stress and inflammation implicated in pain chronification [12] and opioid-induced hyperalgesia [2]. As such, opioid-misusing chronic pain patients demonstrate increased pain sensitivity [27], increased anhedonia [54], and decreased autonomic and attentional responses to naturally rewarding stimuli [40,43] relative to medication-adherent pain patients and healthy controls.

Despite basic science suggesting that chronic pain and opioid misuse are linked with a dearth of positive affect and undergirded by reward system dysfunction, current psychosocial pain treatments (e.g., cognitive-behavioral therapy – CBT) focus primarily on ameliorating negative affective reactions to pain. Though CBT is efficacious [16] and includes techniques that might affect reward mechanisms, few studies have gathered evidence on how CBT or other psychosocial interventions can modulate reward system function in ways that both reduce pain and opioid misuse. To address this gap we present a model that can guide efforts in this area.

2. Conceptual Model

Chronic pain is fueled by a habit loop of attentional bias towards pain, biased pain appraisals (e.g., catastrophizing), negative affect, and maladaptive coping behaviors (e.g., overuse of opioids—which in turn may further exacerbate pain chronicity via opioid-induced neuroadaptations). As shown in Figure 1, psychosocial interventions can be used to disrupt the habit loop by first re-orienting attention from pain sensations and decentering from catastrophic appraisals, and then activating three core positive affective/reward mechanisms: (1) *savoring natural rewards* by focusing on pleasant features of naturally rewarding stimuli

and the resulting positive emotions and bodily responses that occur while doing so; (2) *noticing and generating pleasant internal states* in spite of painful sensations by cultivating interoceptive awareness to delimit pain, increasing awareness of pleasurable sensations, and using imagination to superimpose pleasure on painful body sites; and (3) *cultivating meaning and self-transcendence* to disrupt cognitive biases by shifting patients' thinking from a narrowed focus on pain to a much broader awareness of how pleasant and painful life experiences interact to produce meaning in life. By virtue of their potential effects on cortico-limbic-striatal circuitry function, these three therapeutic mechanisms may alter the motivational-decisional balance via top-down modulatory processes to disengage from pain and engage salient life goals, thereby reducing pain experience and enhancing reward. Ultimately, this process may reduce the drive towards opioid dose escalation and opioid misuse.

Mechanism 1: Savoring Natural Rewards

Attention allocation to pain comes at the expense of processing non-painful stimuli [26], and in particular, diverts attentional resources from noticing and appreciating pleasant, naturally rewarding objects and events in the social environment. Similarly, by virtue of sensitization of the mesocorticolimbic dopamine system, repeated opioid use imbues opioid-related cues with incentive salience [11], resulting in an attentional bias towards opioid cues [47] that promotes opioid misuse [51] and diverts attention from natural rewards. Countering this process by re-orienting attention away from pain and opioid-related cues might be therapeutic. Diverting attention from chronic pain may be optimized by attending to motivationally-salient exteroceptive stimuli [107]. In that regard, attending to pleasant visual [115] and auditory stimuli [89] modulates nociception at spinal and supraspinal levels [88]; the analgesic effect of rewarding stimuli appears to be mediated by connectivity between nucleus accumbens and corticostriatal circuitry [93]. Among people with chronic pain, attending to pleasant visual stimuli reduces chronic pain intensity [102].

Decades ago, Fordyce made similar observations and clarified the role of operant conditioning and reward contingencies in the maintenance of chronic pain, and recommended leveraging natural rewards to reinforce behavioral activation as a treatment for chronic pain [34]. This approach is integrated into modern CBT approaches that emphasize behavioral activation and pleasant activity scheduling [102]. Insofar as these techniques increase motivation to engage in, and exposure to, naturally rewarding events, they may boost activation in brain reward circuitry [82]. Yet, merely being in the presence of a natural reinforcer may not be sufficient to overcome a chronic pain patient's negative attentional bias. A recent review found no evidence that behavioral activation (or CBT as a whole) can significantly improve anhedonia [65]. Additional psychosocial approaches may be needed to disrupt maladaptive cognitive-attentional styles and increase reward responsiveness.

One novel approach consists of attentional retraining via *savoring* – the practice of attending to the pleasant sensory features of a naturally rewarding stimulus while cultivating meta-awareness of the positive emotions and pleasant sensations occasioned by that stimulus [42]. Savoring can be taught through instructions to focus attention on a generally pleasant or

personally meaningful object in the present. For instance, in savoring a flower, one might attend to its pleasant colors, textures, and scents, as well as the touch of its petals against the skin, and then appreciate the embodied pleasure and emotions of contentment and joy occasioned by this process. Or, in savoring the warmth and sense of connection from holding hands with a loved one, one might magnify the analgesia produced by affective touch [55]. Also, given that exposure to nature and other enriched environments can reduce pain and post-operative analgesic requirements [77,104], savoring pleasant sensory features of the environmental context may amplify positive affect [90] and thereby improve analgesia—for instance, when in pain, one could shift attention away from the body and towards a beautiful skyline view, focusing on the pleasing hues and contours of the open expanse while deepening awareness of awe and calm.

Mindfulness has been theorized to promote savoring by first stabilizing and reorienting attention from distraction onto the pleasant stimulus, and then by deepening meta-awareness of positive emotional and sensory responses to the stimulus [41]. In support of this contention, mindfulness increases pleasure derived from eating and thereby decreases caloric intake [4,62]. Given hedonic dysregulation of the reward system in opioid misuse, I previously proposed the *reward restructuring hypothesis* that posits that psychosocial interventions may increase responsiveness to natural rewards by shifting reward processing from valuing drug-related rewards back towards much greater valuing of natural rewards, and thereby reduce addictive behavior [36].

2.1. Mechanism 2: Noticing and Generating Pleasant Internal States

From the perspective of “pain perception as inference” [99,113], pain is shaped by inferences and predictions derived from past pain episodes [71,114]. Over time, pain episodes are associated with deeply held and biased ways of attending and viewing the world (cognitive schema) that may obscure patients’ interoceptive awareness of non-painful sensations [20,25,106,108] – including pleasant sensations [18]. Opioid craving may result from a similar inferential process; misinterpretations of interoceptive signals magnify the discrepancy between predicted versus actual internal states of the body (“Will this opioid make me feel better?”), resulting in reward prediction errors that drive craving and blunted responsivity to natural rewards [97].

In contrast, nuanced and fine-grained use of interoceptive attention to delimit pain (i.e., notice the precise location and boundary of pain sensations) may enable patients to become more aware of pleasant sensations occurring contemporaneously with painful ones. To test this hypothesis, we recently developed a digital sensation manikin capable of quantifying the spatial distribution of pleasant and unpleasant sensations, and found that chronic pain patients who reported a greater distribution of pleasant sensations relative to unpleasant sensations experienced less pain-related functional interference, even after controlling for pain severity [58] – suggesting that awareness of embodied pleasure might be therapeutic. These results are congruent with preclinical data demonstrating that sexual pleasure in the context of painful stimulation reduces pain sensitivity via endogenous opioid release [56,98], and data from humans showing that sexual pleasure [112] and affective touch [69] during painful stimulation modulates pain experience. Similarly, consumptive pleasure from

palatable sweet foods during painful stimulation increases pain tolerance [80]. Beyond externally-stimulated pleasant sensations, internally generated pleasant sensations produced by psychosocial pain interventions like hypnosis and mindfulness meditation [38] may also be analgesic and reduce the desire for opioids. In that regard, these mind-body therapies have been shown to reduce pain severity, opioid dose, and craving [39].

Hypothetically, activation in orbitofrontal, limbic, and striatal brain circuits [8,85,93,109,118] observed to mediate analgesia from reward and positive affect might underlie relief of pain and craving stemming from the use of psychosocial interventions to induce pleasant sensations. These circuit functions may be undergirded by increased endogenous dopamine and opioid release [78,83,121], and if so, inducing pleasant sensations might provide a non-drug means of reward and thereby reduce craving among opioid misusing chronic pain patients. That said, naloxone blockade studies indicate that that pain relief via pleasant imagery [10], hypnosis [81], and mindfulness [119] is not mediated by endogenous opioids, suggesting that at least among healthy individuals, non-opioid neurochemical mediators including dopamine, endocannabinoids, GABA, and serotonin may be at play.

2.2 Mechanism 3: Cultivating Meaning and Self-Transcendence

The ability to generate positive meaning might be an important protective factor against the adverse sequelae of pain [61] and opioid misuse [42]. According to the Mindfulness-to-Meaning Theory [41], meaning can arise from mindful acceptance of painful life experiences, which disrupts negative, self-relevant appraisals (e.g., “Pain and opioids ruined my life”) and broadens awareness to encompass an expanded set of contextual information from which adaptive reappraisals can be generated. Integrating a widened array of pleasant, neutral, and painful situational features within a broadened scope of awareness can reconfigure appraisals within working memory, leading to a shift in perspective on difficult life circumstances that promotes positive meaning in the face of adversity (“Pain has taught me to be more compassionate and to appreciate the good things in my life”).

On the psychological level, cultivating meaning may foster resilience to pain and addiction in much the same way that it fosters resilience to other stressors – by reappraising adversity as a source of personal growth [1,31,98]. To that point, meaning in life predicts lower levels of pain intensity, depressive symptoms, and analgesic medication use [21], and less attenuation of positive affect among people with chronic pain [57]. On a neural level, reappraisal recruits corticostriatal and limbic circuitry to produce lasting changes in amygdala reactivity to negative experiences [111] and activates nodes of the corticostriatal reward circuit, including ventral striatum and mPFC [22]. Such neural-functional effects are also evident when attributing positive meaning to pain; in a recent experiment, experiencing increased pain for the benefit of one’s romantic partner increased mPFC activation coupled with decreased neural pain processing and reduced pain unpleasantness [74]. Similarly, reappraising the meaning of drug-related stimuli decreases craving by modulating corticostriatal circuitry function [67].

Ultimately, meaning-making may reach its zenith in the experience of *self-transcendence* – the profound sense of connection or oneness with something greater than the self. Though

self-transcendence can emerge naturally during intense experiences of awe, flow, and other peak experiences [117], it might also be induced by psychosocial interventions, like mindfulness meditation. Indeed, the original purpose of mindfulness and other contemplative practices was to foster self-transcendence through the emergence of a form of *non-dual awareness* [24]— a temporary experiential unification of the subject-object dichotomy that structures ordinary human consciousness. During meditation practices focused on self-transcendence, neural activity in nodes of the default mode network (DMN) decreases [13] while DMN connectivity increases with neural networks involved in exteroceptive stimulus processing [64], including the dorsal attentional and salience networks [35]. In view of the central role of the DMN in pain chronification [5,6,70] and opioid addiction [73,75,76], modulating default mode processing by evoking self-transcendence might transform the maladaptive cognitive-affective habits underlying chronic pain and opioid misuse.

3. MORE as an Example

How might behavioral treatment development research leverage these therapeutic mechanisms to generate novel psychosocial interventions? As one example, here I briefly describe how Mindfulness-Oriented Recovery Enhancement (MORE), a therapy I developed that has been shown to significantly decrease chronic pain, opioid misuse, and craving in several RCTs [48,49,53], integrates all three therapeutic mechanisms. Research on MORE advances prior work in this area by being theory-based and programmatic, with a focus on examining mechanisms, and findings to date that support proposed conceptual model (Fig. 1).

3.1 Savoring natural rewards.

MORE, which integrates training in mindfulness and savoring, has been shown in opioid-treated chronic pain patients to increase autonomic [44] and neurophysiological responses [45] to natural reward stimuli which were associated with improvements in pain severity and pain catastrophizing, and predicted less pain interference at 3-month follow-up [50], suggesting that training attention towards natural rewards may decrease pain experience. MORE's effects on increasing autonomic and neurophysiological responsiveness to natural reward were also associated with decreased opioid craving [44,45]. Further, minutes of savoring practice predicted decreases in opioid dose following treatment with MORE [52]. More recently, using EEG we found that MORE decreased opioid cue-reactivity while simultaneously increasing the capacity to upregulate neurophysiological reward responses during savoring; and increased responsivity to natural rewards mediated the effect of MORE on decreasing opioid misuse by 3-month follow-up [37] (Figure 2a). Taken together, these data provide robust support for my aforementioned *restructuring reward hypothesis*.

3.2 Noticing and generating pleasant internal states.

In MORE, patients are taught unique mindful breathing and body scan meditations designed to decompose pain experience into its constituent sensations (e.g., heat, tightness, tingling), as well as to increase awareness of the center, edges, and permeability (versus solidity) of these sensations, and any adjacent or distal pleasant sensations. In a RCT using the digital

sensation manikin described above [58], after intervention, chronic pain patients participating in MORE reported a 7.5 fold increase in the ratio of pleasant to unpleasant sensations over the course of treatment (Figure 2b). No such increase in pleasant sensations was observed in the social support control condition, suggesting that these effects were not due to non-specific therapeutic factors, but rather stemmed from specific cognitive training provided in MORE.

3.3. Cultivating meaning.

In MORE, patients use mindfulness to encourage psychological flexibility and perspective shifting, facilitating reappraisal as a means of generating positive meaning in the face of adversity. Also, mindfulness training in MORE involves instructions to foster self-transcendence by cultivating non-dual awareness of the field of consciousness in which mental contents are experienced [59]. In a RCT of opioid-treated chronic pain patients in primary care (N=95), MORE significantly improved a latent positive psychological functioning variable comprised of positive affect, savoring, meaning in life, and self-transcendence measures. Importantly changes in this measure over the course of treatment predicted decreases in pain severity and opioid misuse risk [49] (Figure 2c). Among the factors included in the positive psychological functioning variable, increases in self-transcendence showed the largest effect size on reductions in pain severity.

4. Conclusion

Studies have taken important first steps to test the proposed model. Though MORE has been shown to modulate the three mechanisms delineated above in RCTs, extant investigations are subject to limitations including the (a) absence of a sham mindfulness condition [120] to provide a formal placebo control; (b) inability to identify the neural mechanisms undergirding the observed effects; (c) uncertainty regarding the duration of these effects, in light of hedonic adaptation/habituation [14]; and (d) use of a multi-modal treatment approach that combines mindfulness, reappraisal, and savoring skills, precluding dismantling of the independent contributions of these techniques on positive affect and reward-related processes. To remediate these limitations and advance the field, specific research recommendations are presented in Table 1.

Ultimately, rigorous scientific pursuit of a multifaceted research program into these domains of inquiry may generate a “fourth wave” of CBT and boost the known efficacy of mind-body therapies [39] to help stem the tide of the opioid crisis.

Acknowledgements:

E.L.G. was supported by R01DA042033 (PI: Garland) from the National Institute on Drug Abuse during the preparation of this manuscript. The content is solely the responsibility of the author and does not necessarily represent the official views of the National Institutes of Health. I would like to thank Francis J. Keefe for his comments on a previous version of this manuscript. I would also like to thank Mathias Sanyer for his artistic rendering of scientific data in Figure 3.

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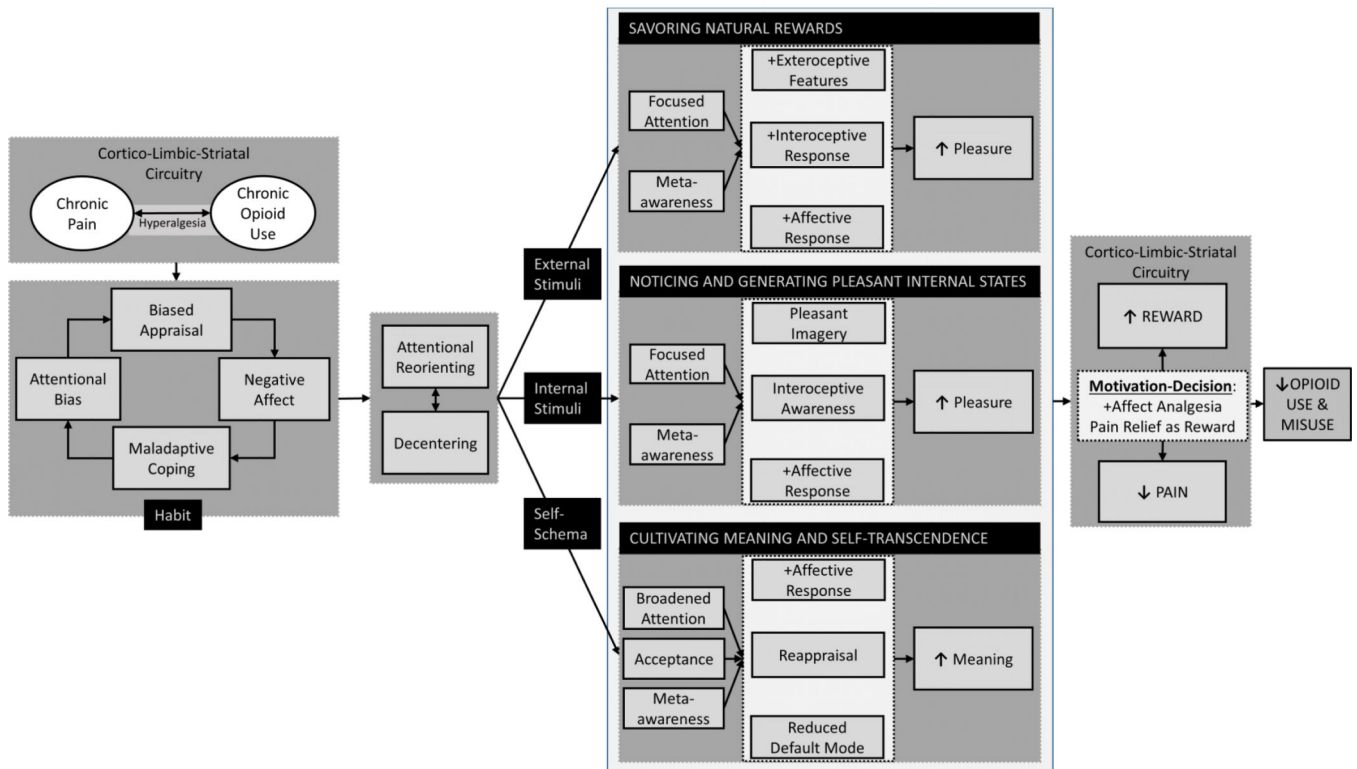


Figure 1. Conceptual model depicting positive affective/reward-related processes to be targeted by psychosocial interventions for chronic pain and opioid misuse.

Chronic pain and chronic opioid use/misuse amplify one another through reward/antireward processes kindled by opioid-induced neuroplasticity in cortico-limbic-striatal circuitry. Psychosocial interventions may leverage positive affective/reward-related processes to ameliorate chronic pain and opioid misuse. Standard CBT techniques are well-suited to interrupt the habit loop of attentional bias and hypervigilance towards pain, reducing biased pain appraisals (e.g., pain catastrophizing) and thereby decreasing negative affect and maladaptive coping behaviors (e.g., avoidance). Mindfulness techniques can then be used to decenter from dysfunctional pain-related cognitive processing and re-orient attention from pain sensations and catastrophic appraisals to focus on three therapeutic targets: positive external stimuli, positive internal stimuli, or self-schemas. Focused attention and meta-awareness facilitates the practice of *savoring natural rewards*, involving attending the pleasant exteroceptive (i.e., perceptual) features of a naturally rewarding stimulus while cultivating meta-awareness of the positive emotions and pleasant interoceptive sensations occasioned by that stimulus. Through focused attention and meta-awareness, one may *notice and generate pleasant internal states* (e.g., positive affect and pleasurable sensations) in spite of painful sensations. This process may be accomplished by fine-grained interoceptive awareness to delimit pain and increase appreciation of pleasure, as well as the use of imagination to superimpose pleasure on body sites proximal and distal to the painful body part. Finally, meta-awareness and acceptance may disrupt biased appraisals and allow one to integrate a widened array of pleasant, neutral, and painful life experiences within the broadened scope of attention, thereby attenuating default model processing and fueling

adaptive reappraisals of pain-laden self-schemas. This process ultimately results in *cultivating meaning and self-transcendence* in the face of adversity. By virtue of their effects on corticostriatal circuitry function, these three processes in turn shift the motivation-decision balance to disengage from pain and engage salient life goals, resulting in enhanced reward and reduced pain experience. Ultimately, this process may reduce the drive towards opioid dose escalation and opioid misuse.

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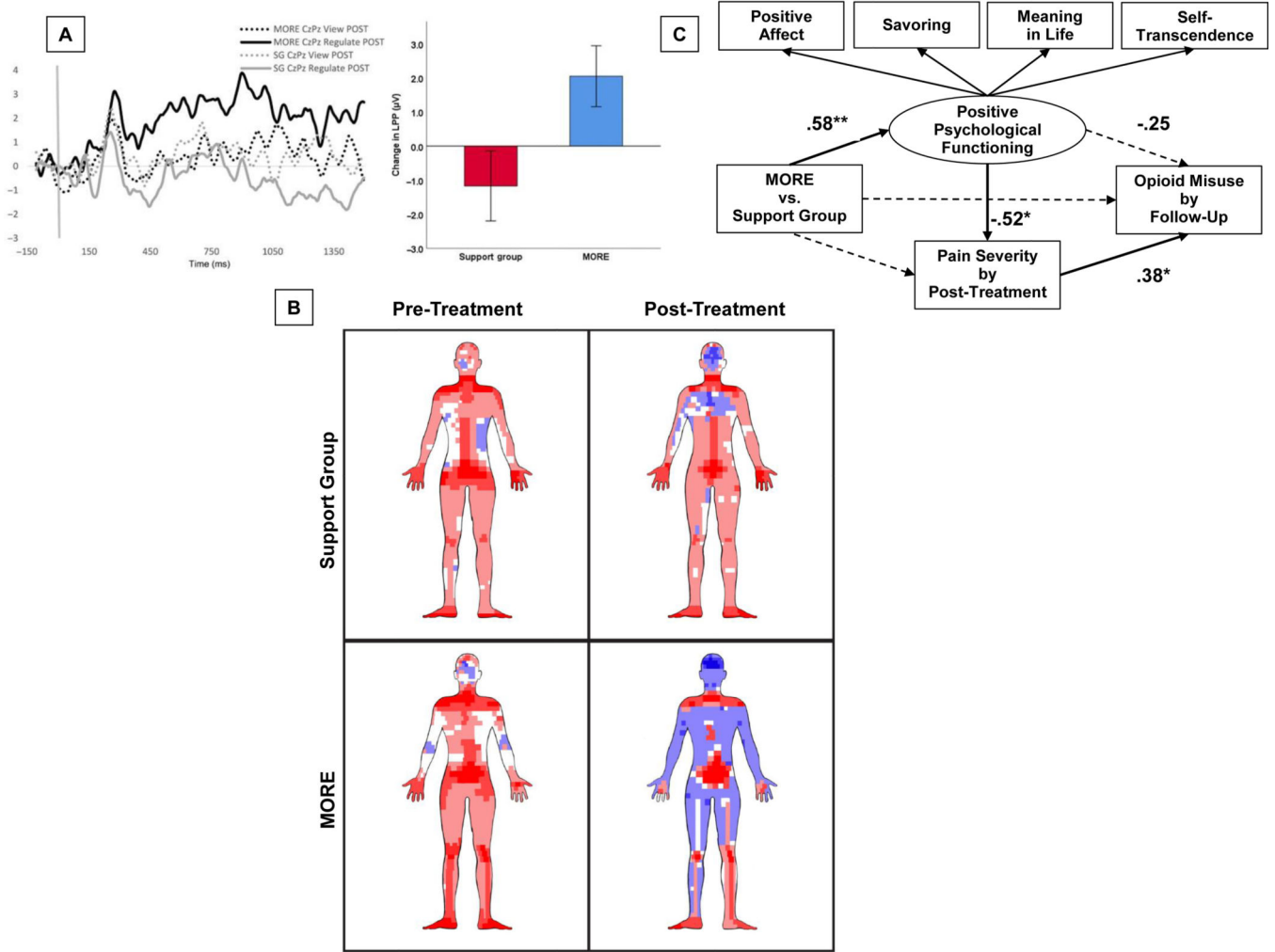


Figure 2. Effects of MORE on positive affective and reward-related processes.
2A. Evidence in support of mechanism 1: savoring natural rewards. Findings from [21] depicting effects of Mindfulness-Oriented Recovery Enhancement (MORE) vs. a social support group control condition on pre-post treatment change in event-related potentials of the EEG during savoring (i.e., up-regulating) vs. viewing of natural reward cues. 2B. Evidence in support of mechanism 2: noticing and self-generating pleasant internal states. Rendering of sensation reports on a computerized sensation manikin for participants treated with Mindfulness-Oriented Recovery Enhancement (MORE) or a social support group control condition in [35]. Blue represents pleasant sensations and red represents unpleasant sensations. The density of the hue reflects the frequency of pleasant or unpleasant sensation reports at a given sensation pixel. 2C. Evidence in support of mechanism 3: cultivating meaning and self-transcendence. Findings from [31] indicating that the effect of MORE on reducing pain severity and opioid misuse risk was associated with increases in these positive affective/reward-related psychological functions.

Table 1.

Recommendations to advance research on the positive affective/reward mechanisms of psychosocial interventions for chronic pain and opioid misuse.

Recommendation	Detail
<u><i>Dismantle effects of various techniques</i></u>	Studies should optimize the next generation of psychosocial pain therapies by using micro RCTs and factorial designs (e.g., multiphase optimization strategy) to determine the independent and interactive effects of an array of techniques for stimulating the reward system.
<u><i>Quantify the phenomenological and physiological experience of pleasure as a mediator of treatment outcomes</i></u>	Studies should quantify and examine interoceptive awareness of pleasure elicited by psychosocial interventions as a mediator of treatment outcomes.
<u><i>Employ biobehavioral measures of reward processing</i></u>	Studies should employ behavioral (e.g., eye-tracking) and neuroimaging (e.g., fMRI) measures to assess effects of psychosocial intervention on reward processing of exteroceptive stimuli, and whether increased reward responsiveness predicts reduced pain and opioid (mis)use.
<u><i>Decipher intervention-induced dynamics of change</i></u>	Studies should employ high-density ecological momentary assessments (EMA) of positive emotions, savoring, reappraisal, and other processes to analyze complex chains of causes and effects that synergistically emerge during chronic pain treatment.
<u><i>Use placebo controls</i></u>	Studies should use sham intervention arms (e.g., sham mindfulness [112]) to parse effects of expectancy and social desirability from mechanisms of action.
<u><i>Determine the duration of effects on reward system function</i></u>	Studies should collect longitudinal data to ascertain the duration of psychosocial intervention effects on reward-related mechanisms, and to determine whether such interventions can overcome the hedonic treadmill effect [12] to produce trait-like changes in the propensity towards positive affective states.
<u><i>Experimentally stimulate meaning and self-transcendence</i></u>	With the re-emergence of psychedelic research, pharmacological probes to reliably stimulate meaning and self-transcendent states are becoming available [49]. Studies with psychedelics, alone or in combination with psychosocial interventions like MBIs, may test whether self-transcendent experiences produce relief of pain and opioid craving by modulating reward system function.