Neuroscience and Biobehavioral Reviews 135 (2022) 104558

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review article

# At the intersection of anger, chronic pain, and the brain: A mini-review

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ARTICLE INFO

*Keywords:*
Chronic pain
Anger
Emotion regulation
Neuroimaging

ABSTRACT

Chronic pain remains one of the most persistent healthcare challenges in the world. To advance pain treatment, experts have recently introduced research-driven subtypes of chronic pain based on proposed underlying mechanisms. Nociplastic pain (e.g., nonspecific chronic low back or fibromyalgia) is one such subtype which may involve a greater etiologic role for brain plasticity, painful emotions induced by life stress and trauma, and unhealthy emotion regulation. In particular, correlational and behavioral data link anger and the ways anger is regulated with the presence and severity of nociplastic pain. Functional neuroimaging studies also suggest nociplastic pain and healthy anger regulation demonstrate inverse patterns of activity in the medial prefrontal cortex and amygdala; thus, improving anger regulation could normalize activity in these regions. In this Mini-Review, we summarize these findings and propose a unified, biobehavioral model called the Anger, Brain, and Nociplastic Pain (AB-NP) Model, which can be tested in future research and may advance pain care by informing new treatments that address anger, anger regulation, and brain plasticity for nociplastic pain.

## 1. Introduction

Chronic pain, defined as pain lasting more than 3 months, is a substantial healthcare challenge. Despite recent advances in the definition and classification of pain (Raja et al., 2020; Shraim et al., 2020) and increased attention to the safe and effective treatment of chronic pain connected to the recent "opioid crisis" (CDC, 2016; Services, 2019; VA/DoD,2017), chronic pain continues to be a leading source of burden to patients, healthcare systems, and society in the U.S. and around the world (Rice et al., 2016).

Chronic pain patients are often exposed to many medical investigations and treatments for their pain (Rustøen et al., 2005), and pain management protocols treat most types of chronic pain similarly (Lumley et al., 2021). Moreover, chronic pain is often viewed as permanent, requiring management, coping, or acceptance, rather than as a condition which is potentially malleable and able to be greatly reduced or even eliminated (Yarns et al., 2020). The fact that effective treatment to reduce chronic pain is elusive likely derives from the fact that the causes of chronic pain are still poorly understood.

While acute pain is caused by actual or potential tissue injury, the causes of chronic pain are less clear to pain management clinicians and experts alike. Recently, the International Association for the Study of Pain (IASP) has proposed that three subtypes of chronic pain may be differentiated based on unique causal mechanisms (IASP, 2017). Although other experts have proposed alternative classifications, definitions, and features of pain mechanism categories (Dewitte et al., 2018; Kolski et al., 2016), most do not differ substantially from the IASP definitions. In addition, categories are difficult to validate, difficult to assess in vivo, may be overinterpreted, and individual patients may experience more than one subtype of chronic pain, which may also change over time (Shraim et al., 2020). Yet, the IASP definitions are used here to illustrate how mechanisms of chronic pain can be delineated. First, nociceptive pain is characterized by ongoing injury to peripheral tissues and includes knee or hip osteoarthritis, rheumatoid arthritis, cancer pain, and other conditions. Second, neuropathic pain is characterized by ongoing injury to peripheral nerves, as in diabetic neuropathy. Third, nociplastic pain includes conditions without evidence of peripheral tissue or nervous system lesion or disease, or with poor correlation of such peripheral findings to the patient's subjective report of the locations of pain (Clauw, 2015; Raja et al., 2020; Shraim et al., 2020). Examples of nociplastic pain include fibromyalgia and "primary" musculoskeletal pain conditions, including chronic back, neck, leg, and pelvic pain; complex regional pain syndrome; temporomandibular joint disorders; irritable bowel syndrome; and tension headaches (Lumley et al., 2021). Thus, while tissue injury may play a role in the perpetuation of some types of chronic pain, it does not fully account for other types,

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https://doi.org/10.1016/j.neubiorev.2022.104558
Received 3 April 2021; Received in revised form 20 January 2022; Accepted 30 January 2022
Available online 2 February 2022
0149-7634/Published by Elsevier Ltd.

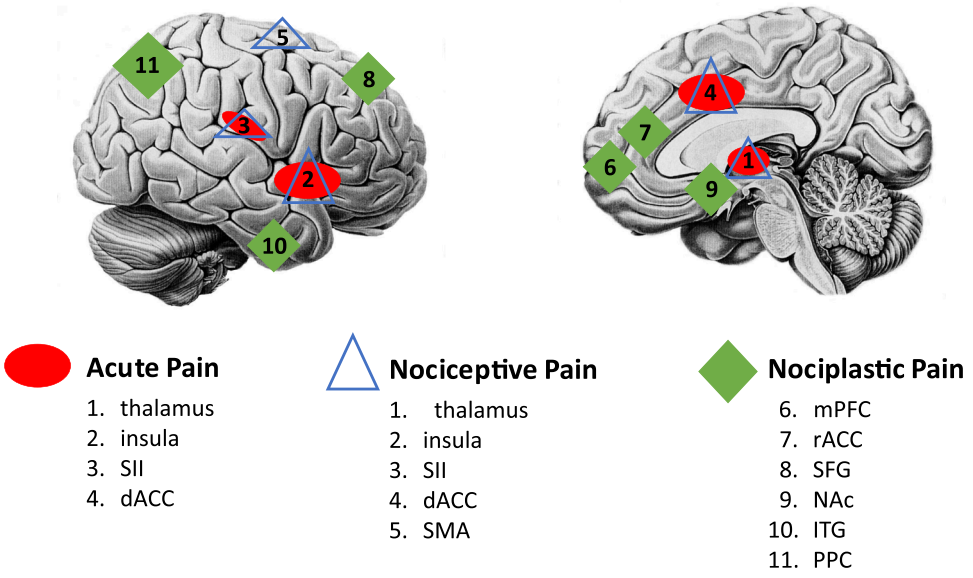


**Fig. 1.** Pain in the brain. Neural networks associated with three causally discrete types of pain: acute, nociceptive, and nociplastic. Note the high degree of overlap between the acute pain and nociceptive pain networks, which include both sensory and affective regions. In contrast, the nociplastic pain network includes relatively distinct affective regions. Abbreviations: SII, secondary somatosensory cortex; SMA, supplementary motor area; mPFC, medial prefrontal cortex; rACC, rostral anterior cingulate cortex; dACC, dorsal anterior cingulate cortex; SFG, superior frontal gyrus; NAc, nucleus accumbens; ITG, inferior temporal gyrus; PPC, posterior parietal cortex.

particularly nociplastic pain. Although this model does not account for neural mechanisms associated with chronic pain, findings from neuroimaging research can supplement our understanding. Importantly, such research increasingly points to the brain's plasticity as playing a role in the maintenance and generation of many chronic nociplastic pain conditions.

In addition, many emotional states, such as depression and anxiety, and emotional processes, such as emotional awareness and regulation, influence the presence and severity of nociplastic pain (Aaron et al., 2020; Lumley et al., 2021). Nociplastic pain patients have also been found to have higher rates of emotional trauma and mental health diagnoses such as post-traumatic stress disorder (PTSD) (Amir et al., 1997; Anda et al., 2010; Felitti et al., 1998; Sherman et al., 2000; Varinen et al., 2017). For at least 70 years, theorists have placed a special emphasis on the importance of anger and anger regulation to nociplastic pain conditions (Bruehl et al., 2006; Burns et al., 2008c; Coen and Sarno, 1989; De Ridder et al., 2021; Engel, 1959). Correlational and behavioral research indicate that state anger and unhealthy ways of regulating anger can lead to worsening pain in nociplastic pain conditions while, conversely, healthier anger regulation can lead to improvements in pain outcomes. Indeed, so much has been written on the topic that a recent systematic review found 16 different self-report assessments developed to measure anger in pain patients (Sommer et al., 2019).

In this targeted review we will briefly summarize and synthesize several areas of research. Our goal is to offer a biobehavioral model highlighting the critical roles of emotions (particularly anger), emotion regulation, and the brain in nociplastic pain that can be tested in future research toward advancing the diagnosis and treatment of nociplastic pain. In the following sections we first describe the neural correlates of pain. Second, we introduce a framework for understanding emotions and emotion regulation in the context of chronic pain. We then review anger as an important socioemotional construct with special relevance to pain and report behavioral and correlational studies highlighting the relationships between anger and nociplastic pain. We survey neuroimaging literature on anger and summarize findings that suggest healthy anger regulation and nociplastic pain exhibit opposing activation patterns in the medial prefrontal cortex (mPFC) and amygdala. To synthesize this literature, we propose a biobehavioral model that integrates these separate but related fields, namely nociplastic pain, emotion, especially anger, and the brain. Finally, we discuss the limitations of this review and the relevance of the possible inverse relationship between anger and nociplastic pain in the brain to the future of clinical pain management and research.

## 2. Pain and the brain

Neural activity of patients experiencing nociplastic pain is characterized by patterns distinct from acute pain and other types of chronic pain. According to a recent meta-analysis, the experimental induction of acute pain (e.g., with painful versus non-painful thermal stimuli) is generally associated with activations of both sensory (e.g., thalamus, secondary somatosensory cortices (SII), dorsal posterior insula) and affective (e.g., dorsal anterior cingulate cortex (ACC), anterior insula) brain regions in healthy adults and pain patients (Xu et al., 2020). Indeed, painful mechanical stimulation of the knee in patients with knee osteoarthritis—a nociceptive pain condition—is associated with similar activations of both sensory and affective regions when compared to the brain activity of those same patients during a visual attention task (Baliki et al., 2008b).

In contrast, nociplastic pain conditions, such as nonspecific chronic low back pain (cLBP), are associated with altered neural activation patterns in affective brain regions only, particularly the rostral ACC, mPFC, and amygdala (Apkarian et al., 2005; Denk et al., 2014). Several resting-state studies showed increased blood-oxygen-level-dependent (BOLD) response in the mPFC among nociplastic pain patients compared to controls (Baliki et al., 2011; Otti et al., 2013; Tagliazucchi et al., 2010). In addition, a complex pattern of abnormal resting-state functional connectivity has been observed between the mPFC and several brain networks in nociplastic pain patients. In particular, connectivity between the mPFC and other regions of the default mode network (DMN), including the posterior cingulate cortex, were found to be decreased, while connectivity between mPFC and regions of the salience network (SN), including the insula and ACC, were found to be increased among patients with nociplastic pain compared to controls (Tu et al., 2019). The DMN is thought to be associated with self-monitoring (Gusnard et al., 2001; Raichle et al., 2001), while the SN is associated with processing sensory input (Tu et al., 2019).

Importantly, these network-level changes are correlated with the severity of clinical symptoms (Kucyi et al., 2014; Tu et al., 2019). Greater resting-state connectivity during an episode of subacute back pain between the mPFC and nucleus accumbens (NAc), a region dealing with reward and reinforcement, is the strongest predictor of persistent back pain after 1 year (Baliki et al., 2012). Furthermore, mPFC-NAc connectivity strengthens over time in patients with persistent

compared to remitting back pain (Baliki et al., 2012; Hashmi et al., 2013), suggesting such brain plasticity is a primary driver of the development of nociplastic pain (McCarberg and Peppin, 2019). In the words of one group of pain neuroscientists, nociplastic pain results from "novel learning processes, which interact with the PFC and shift cortical activity from nociceptive perception to emotional suffering" (Mansour et al., 2014).

Task-based functional magnetic resonance imaging (fMRI) paradigms have also shed light on nociplastic pain. For instance, during a "spontaneous pain" rating task, in which cLBP patients were asked to rate the amount of pain they are experiencing from moment to moment, periods of high compared to low pain was associated with increased activations in the rostral ACC, mPFC, amygdala, and ventral striatum (Baliki et al., 2006, 2008b; Etkin et al., 2011; Lindquist et al., 2012). In healthy adults, more complex cognitive tasks tend to show activations in cortical regions that are negatively correlated with activations in midline structures (i.e., deactivation of the DMN) (Raichle et al., 2001). However, during such tasks cLBP patients exhibit *reduced deactivations* of the mPFC and amygdala compared to healthy pain-free adults (Baliki et al., 2008a), suggesting nociplastic pain may be associated with a chronic inability to "turn off" these regions. Brain regions associated with acute pain, nociceptive pain, and nociplastic pain conditions are illustrated in Fig. 1.

## 3. Emotion, pain, and the brain

Findings from emotion research highlight three fundamental principles regarding emotions with relevance to nociplastic pain. First, emotional states can be regarded as either "primary/adaptive" or "secondary/reactive" (Lumley et al., 2021). Primary emotions are thought to occur in response to prototypical situations, such as sadness in response to loss, or fear in response to true danger, and guide an individual toward an adaptive behavioral response (Damasio and Carvalho, 2013). Secondary emotions, such as shame or embarrassment, inhibit getting one's needs met and may derive from an avoidance of one or more primary emotions (Lumley et al., 2021). Substantial research suggests that nociplastic pain is correlated with higher rates of secondary emotions (Aaron et al., 2020; Turner-Cobb et al., 2015).

Second, emotional states or experiences, such as joy, sadness, fear, or anger, are usually distinguished from emotion regulation (Lumley et al., 2021). Convergent literatures describe emotional states as comprised of at least three components: a cognitive label, physical sensations, and action tendencies (Damasio and Carvalho, 2013; Davanloo, 2000; Lindquist et al., 2015; MacCormack and Lindquist, 2017; Scherer, 2005, 2009). The cognitive label refers to the name or designation given to an emotional experience within a particular sociocultural context (Jackson et al., 2019; Lindquist et al., 2015). Prototypical physical sensations have been identified for different emotional experiences (e.g., warmth for love, nausea for disgust), along with changes in physiology that accompanies emotional activation (Hietanen et al., 2016; Nummenmaa et al., 2014; Pace-Schott et al., 2019; Volynets et al., 2019). Action tendencies represent thoughts and possibilities about various ways for a person to engage with the environment when experiencing a certain emotion (e.g., thoughts of running or hiding when feeling fear) (Damasio and Carvalho, 2013; Scherer, 2005, 2009).

Emotion regulation refers to processes governing the experience, expression, and modification of emotions (Braunstein et al., 2017; Lumley et al., 2021). While usually referring to strategies that "downregulate" secondary emotions in the context of chronic pain, emotion regulation can also refer to "upregulating" primary positive (e.g., joy) or even primary negative (e.g., anger) emotions through techniques such as emotional awareness, verbal or written disclosure of emotions, and emotion differentiation (Aaron et al., 2020). In addition, emotion regulation strategies can be either explicit (i.e., conscious) or implicit (i.e., automatic or nonconscious). Specific emotion regulation strategies have been shown to be more or less healthy and adaptive on various measures of well-being and clinical symptoms (Braunstein et al., 2017; Kelley et al., 2019). For instance, specific emotion regulation strategies such as emotional awareness and affect labeling—paying attention to emotions and naming them—may reduce chronic pain, whereas suppression or inhibition of emotions may exacerbate chronic pain (Aaron et al., 2020; Koechlin et al., 2018; Lumley et al., 2021; Ziadni et al., 2020).

Third, affective scientists point to an important distinction between the action tendencies of an emotion and actual behavioral expressions following an emotional experience (Scherer, 2009). Action tendencies, known in some literatures as impulses, are thought to provide important information to an individual about the range of behavioral responses available in reaction to an emotional experience and are thus generally considered advantageous for an individual to be aware of because they may guide an appropriate behavioral expression (Damasio and Carvalho, 2013; Lumley et al., 2021). In contrast, behavioral expressions are the actions people take in reality following an experience of an emotional state, are not generally considered part of the emotion itself, and may be constructive or destructive (Scherer, 2009). For instance, if a person is making a speech and feels embarrassed upon misstating a line, she may have an action tendency—or thought—to run off the stage but may or may not do so in reality; the actual behavioral expression may be to regulate her embarrassment and finish her speech. The relevance of this distinction for chronic pain is that psychological treatment programs that help nociplastic pain patients "upregulate" or increase awareness of the action tendencies of healthy, primary emotions have shown to reduce nociplastic pain (Slavin-Spenny et al., 2013; Yarns et al., 2020), whereas certain destructive and unregulated behavioral expressions of emotions, including both shouting when angry or suppressing anger, have been associated with worsening pain (Burns et al., 2015), suggesting differential effects on pain for action tendencies and behavioral expressions.

The key regions involved in nociplastic pain—the amygdala, rostral ACC, and mPFC—are also associated with emotional experiences and emotion regulation. The amygdala is frequently associated in the literature with specific experiences of fear, but has also been implicated more widely in emotion generation (Lindquist et al., 2012) and has shown to have increased activity in patients with emotional disorders such as anxiety and PTSD compared to healthy controls in a meta-analysis of functional neuroimaging studies (Etkin and Wager, 2007). Emotion regulation involves a wide range of large-scale brain networks that differ according to specific characteristics of the regulation strategy, such as whether it is implicit or explicit (Morawetz et al., 2020). Importantly, increased rostral ACC and mPFC activations are frequently associated with emotion suppression (Etkin et al., 2011), as well as resolving emotional conflict (Egner et al., 2008; Etkin et al., 2006). This hyperactivity in emotionally responsive regions led prior authors to suggest that nociplastic pain could be described as a form of emotional suffering and conflict, and persistent and chronic yet failed attempts to regulate this suffering (Egner et al., 2008; Mansour et al., 2014; McCarberg and Peppin, 2019).

Understanding the extent of distinct patterns of activations for different emotions is of great relevance to advancing the neuroscience of pain, since "upregulating" or "downregulating" different emotional states likely has differential effects on nociplastic pain based on previous research (Aaron et al., 2020). Considerable controversy remains about whether discrete emotions—such as anger—are associated with activations of unique and specific neural networks or whether most or all emotions activate the same or similar neural networks (Jackson et al., 2019; Lindquist et al., 2012). Results from several meta-analyses indicate that while some brain regions may be involved more generally in emotional experience—such as the consistent association of the periaqueductal gray with action tendencies of emotions—some distinct patterns of activations for different emotions have been observed (Kober et al., 2008; Murphy et al., 2003; Phan et al., 2002; Vytal and Hamann, 2010). Indeed, subtle but significant differences in patterns of activation

have even been noted for the experimental induction of similar emotions using emotion-provoking scripts, such as shame conditions contrasted with guilt conditions (Michl et al., 2014), guilt conditions contrasted with embarrassment conditions (Takahashi et al., 2004), or differences in contrasts between disgust or indignation versus neutral conditions (Moll et al., 2002). Anger also appears to have distinct neural correlates from other discrete emotions and, specifically, different effects on the mPFC and amygdala.

## 4. Anger and nociplastic pain

State anger has often been associated with greater pain severity among nociplastic pain patients (Burns, 2006; Burns et al., 2008b; Quartana and Burns, 2007). Affective scientists often—but not always—regard anger as a primary emotion in response to injustice or violation and important for assertiveness, setting boundaries, and saying "no" (Ekman, 1992; Lumley et al., 2021; Panksepp, 1998; Tangney et al., 1996b). Qualitative and quantitative research demonstrate that anger, in healthy adults, includes prototypical physical sensations, namely a sensation of rising heat or energy moving upward from the pelvis and abdomen to the chest, arms, and jaw and down the legs (Davanloo, 2000; MacCormack et al., 2019; Nummenmaa et al., 2014; Tangney et al., 1996a; Volynets et al., 2019). However, one important study indicated that cLBP patients have a different, more tense, physical experience of anger from healthy pain-free controls and the degree of tension with anger was positively correlated with pain severity (Burns, 2006). Patients—but not controls—experienced greater low back muscle tension during anger induction compared to neutral or sadness conditions, as recorded on electromyography (EMG). Furthermore, the amount of muscle tension in response to anger positively correlated with everyday pain severity in patients. These findings suggest that nociplastic pain patients—such as cLBP patients—may have a uniquely tense physical experience of anger that is associated with the severity of their pain. The tense, painful experience of anger in nociplastic pain patients is likely why several pain studies show an association between greater state anger and greater pain severity (Burns, 2006; Burns et al., 2008b; Quartana and Burns, 2007).

In addition to physical sensations, anger has been associated with many action tendencies as well as behavioral expressions in the literature, which exhibit a complex relationship with nociplastic pain (Tangney et al., 1996a, 1996b). Some examples of action tendencies with anger include direct, indirect, or displaced physical or verbal aggression; escapist responses such as minimizing or leaving the anger-provoking situation; cognitive reappraisals; and adaptive behaviors such as discussing with the target or corrective action (Tangney et al., 1996a). Researchers have classified these into either "constructive" or "destructive" and evaluated the frequencies of these action tendencies and their corresponding behavioral responses in daily episodes of anger in healthy adults (Averill, 1983; Tangney et al., 1996a).

Because of its perceived association with aggressive behavioral expressions, views on anger among some scientists and the public often skew negative (Berkowitz, 2012). However, survey research indicates that aggressive behavior in response to anger occurs in no more than 10% of cases of daily anger in healthy adults (Averill, 1983). Action tendencies toward physical aggression (e.g., *feeling like* punching or kicking an instigator) are common—occurring in as many as 40% of cases of daily anger in healthy adults—and do not share an association with aggressive actions (Averill, 1983). Moreover, a series of behavioral experiments demonstrated that people automatically hold back aggressive behaviors when they become aware of aggressive action tendencies, suggesting that "upregulating" aggressive thoughts by becoming aware of them may serve as an important mechanism of "downregulating" aggressive behaviors (Berkowitz, 1990). Other research has shown that suppressing or inhibiting aggressive thoughts is associated with poorer health, including worse pain (Burns et al., 2008c).

Problems with anger regulation are among the most replicated emotion regulation findings in nociplastic pain. Some types of anger inhibition (e.g., suppressing the experience or expression of anger) and unhealthy expressions of anger to others (e.g., shouting or hitting) have been associated with worse pain outcomes (Bruehl et al., 2006; Burns et al., 2008c). There are two types of anger inhibition: trait and state. Trait anger inhibition (i.e., "anger-in") is the general tendency to avoid experiencing or expressing anger, usually evaluated with self-report questionnaires such as Spielberger's Trait Anger Expression Inventory (Spielberger, 1999). State anger inhibition refers to inhibiting the experience or expression of anger in particular situations and is ideally assessed through behavioral experiments (Burns et al., 2008c).

Results are mixed on whether there is a relationship between trait anger inhibition and nociplastic pain (Burns et al., 2008c; Kerns et al., 1994). In one study of patients with mixed musculoskeletal pain conditions, trait anger inhibition was the strongest predictor of pain intensity and pain behavior compared to demographics, depression, state anger intensity, and other trait anger expression styles (Kerns et al., 1994). However, these results have not been replicated, and some report that a limitation of trait anger inhibition is its overlap with general negative affect, which may be less correlated with pain outcomes (Burns et al., 2008c). Therefore, more research is necessary to determine whether trait anger inhibition is consistently associated with the presence or severity of nociplastic pain.

However, state anger inhibition is highly associated with greater pain among nociplastic pain patients in numerous studies. In four anger induction experiments with cLBP patients, patients were instructed either to suppress their emotional experience or behavioral expressions (i.e., inhibition conditions) or allow their emotions to flow freely when asking patients to perform challenging mental arithmetic or play a computer maze game undergoing harassment from a confederate (Burns et al., 2008a, 2008b, 2007; Quartana and Burns, 2007). In all experiments, state anger inhibition led both to greater anger and greater pain intensity. Patients who were told to inhibit anger also showed greater behaviors associated with pain (e.g., wincing) and greater low back muscle tension as measured by EMG in the studies that assessed these parameters (Burns et al., 2008a, 2008b). In addition, a longitudinal study of married couples showed that suppressing or inhibiting anger during episodes of marital conflict predicted increases in musculoskeletal pain over 20 years of follow-up (Haase et al., 2016).

One experiment by Burns and colleagues highlighted how both state anger inhibition and episodes of unhealthy anger expression can precipitate worse pain in nociplastic pain patients (Burns et al., 2015). Patients with cLBP and their spouses completed electronic diaries and assessments of state anger, anger inhibition, unhealthy anger expressions, and pain metrics in 3-hour blocks 5 times a day for 14 days. During blocks when patients reported state anger inhibition, they reported concurrent increases in pain interference and disability. However, after reporting an unhealthy anger expression such as shouting, worse pain intensity and pain interference occurred at the *next* assessment point 3 h later, suggesting patients had a subsequent painful reaction to their aggressive behavior.

Other studies demonstrate that improved anger regulation and healthier, less tense experiences of anger can improve pain. Assuming a powerful, "dominant" posture (rather than an inhibited, tense one) (Bohns and Wiltermuth, 2012) and private verbal expressions of anger, such as swearing to oneself (Stephens et al., 2009; Stephens and Umland, 2011), have shown to increase pain thresholds in non-clinical populations without destructive interpersonal effects (Tangney et al., 1996b). An anger awareness and expression training program improved the severity and frequency of tension headaches by guiding headache patients through experiential exercises like privately verbalizing anger and practicing angry facial expressions and postures, and engaging in assertive, effective, and well-regulated communication of anger to others (Slavin-Spenny et al., 2013). These techniques have also been incorporated—to good effect—into emotional awareness and expression

**Table 1a**
Representative task-based pain studies.

| Sample | Sample Size | Task | Key Contrasts | Method | Brain Activity | Citation |
|---|---|---|---|---|---|---|
| Acute Pain | | | | | | |
| Healthy adults | K = 200 | Pain rating task | Experimentally-induced acute pain vs. contrast (e.g. rest or innocuous stimuli) | fMRI Meta-Analysis | ↑ SII, mid-cingulate cortex, insula & thalamus (core pain network)<br>↑ lateral PFC, SI, M1, SMA, amygdala, brainstem and cerebellum (additional regions, less consistent associations) | Xu et al., 2020 |
| Nociceptive Pain | | | | | | |
| Knee osteoarthritis patients | N = 5 | Pain rating task | Mechanical knee stimulation vs. visual attention task | fMRI | ↑ bilateral SII, cingulate cortex, insula & thalamus. Unilateral putamen & amydala | Baliki et al., 2008b |
| Nociplastic Pain | | | | | | |
| Chronic back pain patients | N = 8 | Pain rating task | Spontaneous back pain vs. visual attention task | fMRI | ↑ mPFC & rACC | Baliki et al., 2008b |
| Chronic back pain patients | N = 13 | Pain rating task | Sustained high vs. low levels of spontaneous pain | fMRI | ↑ mPFC, rACC, PPC, ventral striatum, amygdala & bilateral posterior thalamus | Baliki et al., 2006 |
| Chronic back pain patients vs. healthy adults | CBP N = 15<br>HA N = 15 | Visual attention task | Task vs. rest | fMRI | ↓ mPFC, posterior cingulate cortex/cuneus & amygdala (significantly less deactivation compared to healthy adults) | Baliki et al., 2008a |

therapy (EAET), which targets processing of multiple emotions including anger for patients with nociplastic pain (Lumley and Schubiner, 2019; Yarns et al., 2020).

## 5. A possible inverse relationship of anger and nociplastic pain in the brain

Nociplastic pain conditions are associated with activations of brain regions dealing with emotional experience and emotion regulation—most notably the rostral ACC, mPFC, and amygdala—that are distinct from the activations found in experiments that induce acute pain or in studies of nociceptive pain conditions. In addition, nociplastic pain patients have exhibited a failure to deactivate these regions during cognitive tasks, as typically seen in healthy adults.

No study has evaluated the neural correlates of anger in nociplastic pain patients, but a variety of positron emission tomography (PET) and fMRI paradigms have been used to evaluate the neural correlates of anger in healthy adults and patients with non-pain clinical conditions such as depression. Interestingly, the neural correlates of anger intersect with key regions involved in nociplastic pain, and findings suggest that rigorous anger imaging paradigms result in the inverse of activation patterns found in nociplastic pain in these regions.

Neuroimaging studies have evaluated constructs related to anger using paradigms which may be loosely categorized as anger perception and anger induction. A recent meta-analysis of whole brain imaging studies identified several regions that are consistently activated by each of these (Sorella et al., 2021). Specifically, anger perception is associated with activations of the right superior temporal gyrus, right fusiform gyrus, right inferior frontal gyrus, and amygdala. Additionally, some studies have found positive-going activation in the mPFC/ACC (Blair et al., 1999; Pichon et al., 2008) for anger perception, compared to neutral conditions in healthy adults.

A separate set of neuroimaging studies have attempted to induce anger in participants in real time. The meta-analysis by Sorella and colleagues included a wide range of paradigms and found evidence for consistent activation in the bilateral ventrolateral PFC and the insula for anger induction. Given the heterogeneity of the findings and paradigms used, further consideration of two of the specific paradigms commonly used is warranted. Several studies have used paradigms that involve autobiographical recall of a personal anger eliciting episode, some with explicit instructions to "re-experience" anger during the scan. These studies tend to implicate mPFC/ACC; however, the pattern of activation in these regions tends to vary. For example, positive-going activations of the mPFC/ACC compared to neutral conditions have been found in healthy adults (Dougherty et al., 1999; Kimbrell et al., 1999) and patients with depression (Dougherty et al., 2004). However, another study in healthy adults showed greater negative-going deactivation of the mPFC/ACC during the anger compared to neutral condition (Damasio et al., 2000). Some of the variability in the findings may be due to subtle differences in the paradigms used, either because the tasks produce automatic suppression of the anger (Dougherty et al., 2004; Pietrini et al., 2000) or because they may produce multiple feelings in addition to anger, such as sadness and guilt, which may have different neural correlates (Shin et al., 2000). In one study that induced greater deactivation in mPFC/ACC (Damasio et al., 2000), it could be that their specific instructions, coupled with an absence of extraneous visual or auditory affective stimuli, resulted in an upregulation of anger via increased anger awareness thus likely resulting in more successful induction of anger and demonstrating the neural correlates of the actual experience of anger.

A final set of paradigms have used an innovative approach to anger induction. These "imaginal aggression" paradigms involve imagining an anger-inducing situation, such as an instigator trying to rob the subject, with instructions to imagine or view images of inflicting retaliatory harm on the instigator (i.e., upregulating the aggressive action tendencies of anger via increased awareness of them). These studies have also been associated with strong negative-going deactivations of the ACC, mPFC, and amygdala compared to emotionally neutral imaginal scenarios in healthy adults (Decety and Porges, 2011; Pietrini et al., 2000) and adolescents (Strenziok et al., 2011). In addition, in one of the studies (Pietrini et al., 2000), a condition with instructions to explicitly suppress the anger resulted in reduced deactivations of the ACC, mPFC, and amygdala compared to the non-suppression condition. A summary of task-based pain and anger neuroimaging studies and meta-analyses is listed in Tables 1a, 1b, respectively.

Based on these findings, we conclude that anger induction via increased anger awareness resulting in the actual experience of anger—especially in imaginal aggression—is associated with deactivation of the ACC, mPFC, and amygdala. This is the opposite of the pattern found in patients during experience of nociplastic pain, in which we find evidence for reduced deactivation and positive-going activation in these same regions. Peak activations and deactivations in key neuroimaging studies of nociplastic pain and imaginal aggression are shown in Fig. 2.

## 6. The anger, brain, and nociplastic pain (AB-NP) model and future research

Based on our review, we propose a biobehavioral model that integrates nociplastic pain, emotion and emotion regulation highlighting the special importance of anger, and the brain. To summarize, state

**Table 1b**
Representative task-based anger studies.

| Sample | Sample Size | Task | Key Contrasts | Method | Brain Activity | Citation |
|---|---|---|---|---|---|---|
| Anger Perception | | | | | | |
| Healthy adults | N = 21 | Affect matching task | Anger vs. neutral | fMRI | ↑ dmPFC, left IFG, bilateral fusiform gyri & right lateral occipital gyrus | Kesler-West et al., 2001 |
| Healthy adults | N = 16 | Emotion matching task with whole-body stimuli | Anger vs. neutral | fMRI | ↑ lateral OFC, vmPFC, amygdala, premotor cortex, temporal poles & Hypothalamus | Pichon et al., 2008 |
| Healthy adults | K = 35 | Visual or auditory cues | Anger vs. neutral | Functional Neuroimaging Meta-analyses | ↑ right superior temporal gyrus, right fusiform gyrus and right IFG & amygdala | Sorella et all., 2021 |
| Anger Induction | | | | | | |
| Healthy adults | K = 26 | Social interation games, recollection/imagination of autobiographic memories or imagined scenarios | Anger vs. neutral and/or provocative vs. non-provovative | Functional Neuroimaging Meta-analyses | ↑ bilateral vlPFC (lateral OFC), IFG & insula | Sorella et all., 2021 |
| Anger Induction - Imaginal Aggression | | | | | | |
| Healthy adults | N = 15 | Imagined aggression-evoking scenario | Unrestrained aggression vs. neutral | PET | ↑ limbic regions, primary/association visual cortex & cerebellum<br>↓ vmPFC, left medial frontal gyrus & right rostral SFG | Pietrini et al., 2000 |
| Healthy men | N = 22 | Short visual scenarios | Instructions to imagine harming another vs. being harmed | fMRI | ↓ mOFC | Decety and Porges, 2011 |
| Male adolescents | N = 20 | Imagined aggression-evoking scenario | Instructions to imagine acting with aggression vs. without aggression | fMRI | ↑ left primary visual cortex<br>↓ left vmPFC | Strenziok et al., 2011 |

Abbreviations: ↑, positive-going brain activation; ↓, negative-going deactivation; SII, secondary somatosensory cortex; M1, primary motor cortex; SMA, supplementary motor area; mPFC, medial prefrontal cortex; vmPFC, ventro-medial prefrontal cortex; vlPFC, ventro-lateral prefrontal cortex; dmPFC, dorso-medial prefrontal cortex; dlPFC, dorso-lateral prefrontal cortex; OFC, orbitofrontal cortex; ACC, anterior cingulate cortex; rACC, rostral anterior cingulate cortex; IFG, inferior frontal gyrus; SFG, superior frontal gyrus; PPC, posterior parietal cortex.

anger, anger inhibition, and unhealthy anger expressions are positively correlated with nociplastic pain and associated muscle tension as measured by EMG. Nociplastic pain, in turn, is associated with increased mPFC and amygdala activation, decreased mPFC deactivation, and disrupted mPFC resting-state connectivity. Conversely, improved anger awareness and reduced state anger are associated with decreased nociplastic pain and muscle tension along with lower mPFC and amygdala activation and greater mPFC deactivation. This AB-NP Model is depicted in Fig. 3.

It will be important to test this model, which highlights the need for several important avenues for future research. First, to fully understand the neural correlates of nociplastic pain and how they interact with the neural correlates of anger, anger induction paradigms should be performed in these patients. Because of the reduced deactivations in the mPFC found in nociplastic pain patients using cognitive tasks (Baliki et al., 2008a), we hypothesize that nociplastic pain patients will also demonstrate reduced mPFC deactivation even when they are experiencing anger. These anger induction studies should use rigorous paradigms that have been effective to induce anger, such as the "imaginal aggression" paradigm. Other paradigms, such as those relying solely on autobiographical recall, have failed to induce anger in healthy controls and patients with non-pain clinical conditions, such as depression. Another hypothesis is that neural activation patterns relate to clinical outcomes in nociplastic pain patients. Therefore, future research could examine whether the magnitude of mPFC deactivations during experiences of anger is correlated with daily pain intensity and the degree of muscle tension patients experience in the location of their pain.

Once the overlap in the neural correlates of anger and pain is established, additional research should evaluate whether the neural patterns might be malleable and responsive to interventions. Repeating the "imaginal aggression" paradigm longitudinally or before and after treatment could evaluate whether patients with clinical improvement demonstrate greater mPFC deactivations during "imaginal aggression" over time. Changes in activation patterns in response to "imaginal aggression" could then be used as a biomarker to evaluate the efficacy of a variety of behavioral and biological treatments for nociplastic pain.

An important clinical implication of this model is that improving anger regulation—including increasing anger awareness and awareness of aggressive action tendencies; learning how to express healthy anger (e.g., in setting boundaries or saying "no"); and better distinguishing anger from the physical experiences and action tendencies of tension, anxiety, and shame—is a critical treatment strategy to improve nociplastic pain. These strategies may act by decreasing and thus normalizing heightened and persistent activity in the mPFC and amygdala during nociplastic pain. For example, emotional awareness and expression therapy (EAET) is an intervention that aims to reduce or eliminate nociplastic pain by employing techniques to improve patients' emotional awareness, emotion regulation, and healthy expression of adaptive emotions (Lumley and Schubiner, 2019). Some EAET techniques focus specifically on anger (Lumley and Schubiner, 2012; Yarns et al., 2020). For instance, patients are provided with psychoeducation about the physical sensations (e.g., rising heat or energy) and healthy action tendencies (e.g., assertiveness, boundary setting) that accompany anger. Patients then identify situations in which they felt angry and practice feeling adaptive anger during EAET sessions. During these exercises, the therapist also helps patients differentiate the physical experience and action tendencies of anger from pain and other emotions, such as shame and guilt. Healthy shame and healthy guilt are taught as painful physical experiences that are sometimes accompanied by tears. Healthy shame occurs in response to one not living up to one's own expectations and is accompanied by a desire to want to improve oneself. Healthy guilt occurs when one has wronged another and is associated with a tendency toward confession, apology, and repair. Patients also learn and practice healthy anger expression in EAET, including learning how to use the energy of healthy anger to appropriately assert oneself, set boundaries, or say "no." The therapist asks for patients' pain levels

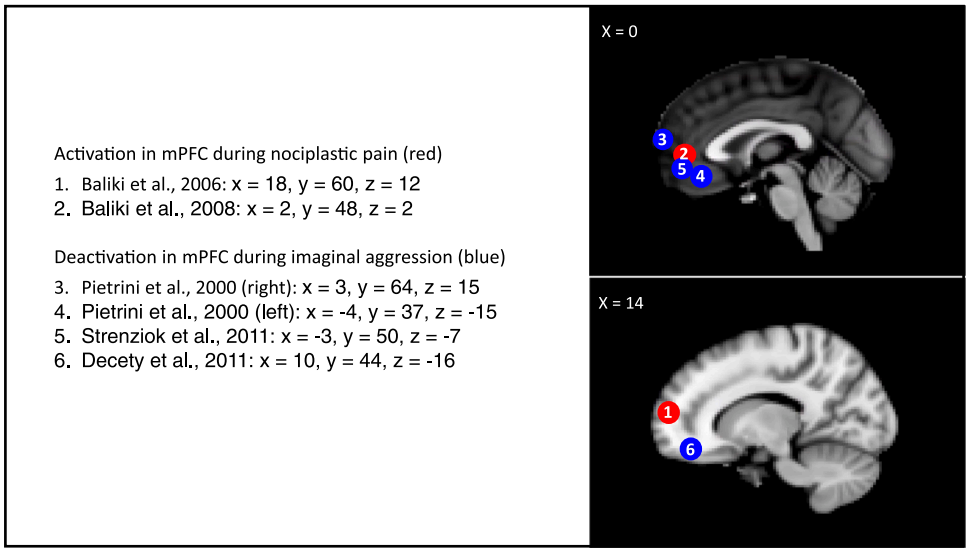


**Fig. 2.** Location of peak activation across studies, showing neural activation and deactivation in medial prefrontal cortex (mPFC) associated with nociplastic pain and imaginal aggression, respectively. Coordinates listed in MNI standard space.

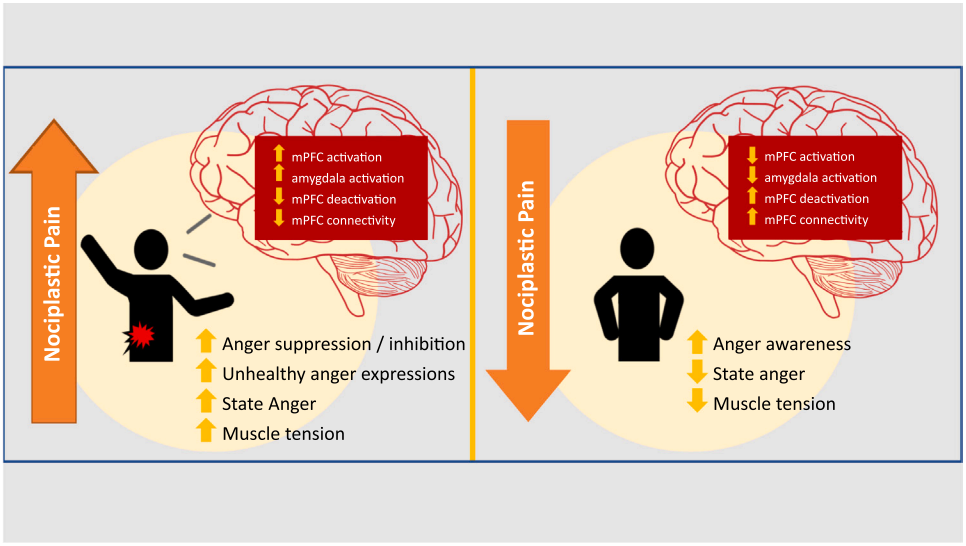


**Fig. 3.** The anger, brain, and nociplastic pain (AB-NP) model. This biobehavioral model illustrates the inverse relationship between nociplastic pain and anger in the brain. Increases in unhealthy anger suppression and expression are associated with a corresponding increase in nociplastic pain, along with mPFC and amygdala activation. Conversely, increased anger awareness and reduced state anger is associated with reduced nociplastic pain along with reduced mPFC and amygdala activation.

(on a 0–10 scale) before and after experiential exercise to determine the effects of healthy anger on pain. All in all, the goal of EAET is to move toward differentiated, healthy, adaptive emotional experiences and expressions and away from pain. In nociplastic pain patients, including those with fibromyalgia and chronic musculoskeletal pain, EAET has demonstrated large effect size reductions in pain severity, pain interference, and other symptoms like anxiety, that are greater than control interventions and cognitive-behavioral therapy (Lumley et al., 2017; Yarns et al., 2020). In fact, EAET has recently been referred to as a treatment of choice for nociplastic pain (Lazaridou et al., 2020). EAET practitioners hypothesize that the large improvements from EAET are achieved because the emotion regulation techniques normalize activity in the neural networks involved both in emotion and nociplastic pain (Lumley and Schubiner, 2019). Future research should leverage effective anger induction paradigms to determine whether this is, in fact, the case.

## 7. Limitations

The goal of this review was to integrate clinical pain, pain neuroscience, and emotion research toward an integrated biobehavioral model of pain and emotion that can improve and expand treatment options for patients living with pain. However, the review is not without several limitations. Most prominently, the terminology used in the reviewed studies is heterogenous and comes from different disciplines, including clinical fields, emotion research, and neuroscience. We have attempted to synthesize the research, which has been challenging with differences in terminology. Applying this research to our model at times required us to use our own framework that was different from that of the original authors. Still, we believe our interpretations are supported by the reported data. In addition, this review aims to report patterns of neuroimaging data, but we are limited to what the authors reported. In some studies, there could have been regions, especially showing deactivation, that were not reported, which could affect our interpretations. Peak activation coordinates were also not included in every paper, which has limited our synthesis of the literature in some cases. The included articles were also not acquired in a systematic process. In well-established fields, such as neuroimaging studies of acute pain, we collected representative articles and recent meta-analyses in the current review. For more nascent fields such as imaginal aggression studies, we

feel confident we have comprehensively reviewed the literature. Finally, no study has evaluated the neural correlates of emotion induction or emotion regulation in nociplastic pain patients. In particular, the most effective paradigms for inducing anger, such as the "imaginal aggression" paradigms, have not been tested in pain patients. Therefore, the activation patterns in relevant networks in response to anger induction may be different in nociplastic pain patients. This is an important area for future research. Moreover, there is some indication that neural activation patterns in nociplastic pain patients may be malleable or responsive to interventions (Baliki et al., 2008b); however, as highlighted above, this has not yet been thoroughly investigated.

## 8. Conclusions

Nociplastic pain likely develops through complex biobehavioral learning processes (McCarberg and Peppin, 2019). However, the experience and regulation of anger especially influence outcomes in nociplastic pain. Nociplastic pain is associated with overactivation of the mPFC and amygdala and reduced mPFC deactivation during cognitive tasks, while carefully upregulating anger and its aggressive action tendencies using emotional awareness are associated with the inverse. Assessment of patients' experience of anger and anger regulation patterns—and intervening to improve them through behavioral programs such as EAET—should become increasingly important to address the pandemic of chronic pain.

## Funding

Dr. Yarns was supported by the U.S. Department of Veterans Affairs [grant number IK2CX001884]. Dr. Jimenez was supported by the U.S. Department of Veterans Affairs [grant number IK2CX001607]. The U.S. Department of Veterans Affairs had no role in any study design, collection, analysis, and interpretation of any data; in the development of concepts or writing of the report; or in the decision to submit the article for publication.

## Declarations of Interest

None.

## Acknowledgements

The authors wish to thank our mentors, particularly Drs. David L. Sultzer, Rebecca J. Melrose, and Michael F. Green, for their support of this work.

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