

## Accepted Manuscript

Title: Brain systems at the intersection of chronic pain and self-regulation

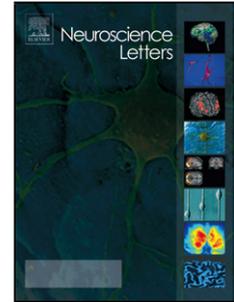
Authors: Marianne C. Reddan, Tor D. Wager

PII: S0304-3940(18)30833-4

DOI: <https://doi.org/10.1016/j.neulet.2018.11.047>

Reference: NSL 33965

To appear in: *Neuroscience Letters*



Please cite this article as: Reddan MC, Wager TD, Brain systems at the intersection of chronic pain and self-regulation, *Neuroscience Letters* (2018), <https://doi.org/10.1016/j.neulet.2018.11.047>

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

**Brain systems at the intersection of chronic pain and self-regulation**

Marianne C. Reddan<sup>1</sup>

Tor D. Wager<sup>1</sup>

<sup>1</sup> University of Colorado, Boulder

Running Head: SELF-REGULATION AND PAIN

Please address correspondence to:

Tor D. Wager

Department of Psychology and Neuroscience

University of Colorado, Boulder

345 UCB

Boulder, CO 80309

Email: tor.wager@colorado.edu

Telephone: (303) 895-8739

**Abstract**

Chronic pain is a multidimensional experience with cognitive, affective, and somatosensory components that can be modified by expectations and learning. Individual differences in cognitive and affective processing, as well as contextual aspects of the pain experience, render chronic pain an inherently personal experience. Such individual differences are supported by the heterogeneity of brain representations within and across chronic pain pathologies. In this review, we discuss the complexity of brain representations of pain, and, with respect to this complexity, identify common elements of brain network-level disruptions in chronic pain. Specifically, we identify prefrontal- limbic circuitry and the default mode network as key elements of functional disruption. We then discuss how these disrupted circuits can be targeted through self-regulation and related cognitive strategies to alleviate chronic pain. We conclude with a proposal for how to develop personalized multivariate models of pain representation in the brain and target them with real-time neurofeedback, so that patients can explore and practice self-regulatory techniques with maximal efficiency.

Pain is a multidimensional experience, often described in terms of sensory-discriminative, cognitive-evaluative, and affective-motivational components (Melzack 2001; Albe-Fessard et al. 1985). These three categories encompass a variety of processes, including nociception (Campbell and Meyer 2006), attention (Villemure and Bushnell 2002; Eccleston and Crombez 1999), learning (Mansour et al. 2014), memory (Sandkühler 2000; Mutso et al. 2012), expectation (Koyama et al. 2005; Atlas and Wager 2012), personality (Linton 2000), culture (Peacock and Patel 2008; Anderson and Reynolds Losin 2016; Losin et al. 2015), socioeconomic conditions (Christensen and Knardahl 2010; Katz 2006; Fuentes et al. 2007), and more. When peripheral nociceptive information enters the cortex the signal becomes integrated with complex multidimensional information from such domains and is modified via descending projections (Bräscher et al. 2016; Suzuki et al. 2004; Wager and Atlas 2015; Coghill 2010). Through this mechanism, the pain experience is not only heterogeneous, but personalized. Therefore, to understand pain, we must seek to understand the person in pain (Darnall 2018; Gatchel et al. 2007).

Broadening our conceptualization of pain to include dimensions outside of primary nociception and sensation complicates the task of neurobiological research, but it also expands the landscape of treatment possibilities. That is, when we reconceptualize pain as something *constructed in the brain*, rather than something that *happens to* the brain, we allow for the development and testing of noninvasive and nonpharmacological interventions, such as self-regulation—a family of cognitive strategies for managing thoughts, emotions, and actions that affects the brain’s activity and neurochemistry and alters neuroplasticity over the course of time (Karoly 1993; Boekaerts et al. 2005; Heatherton 2011; Mischel, Cantor, & Feldman, 1996).

The exploration of nonpharmacological treatments for chronic pain is important. Opioids, though effective in the short term, cannot provide long-term pain relief (Chu et al. 2008; Trescot et al. 2008; Collett 1998). Furthermore, opioids are prone to abuse (Compton and Volkow 2006; Ballantyne and LaForge 2007). Aberrant addiction-like behaviors develop in approximately 24% of cases of chronic back pain patients prescribed opioids (Martell et al. 2007; Salsitz 2016). There is also a growing epidemic of opioid abuse and opioid-related death in Western countries (Kolodny et al. 2015; Volkow and Collins 2017), which can sometimes be localized to neighborhoods surrounding opioid-prescribing physicians (Dhalla et al. 2011). Therefore, it is critical for scientists to prioritize investigations of non-opioid, or even nonpharmacological treatments for chronic pain, as they are not only limited in their effectiveness, but potentially deadly.

Compared to other treatments, opioids are not significantly advantageous. Their efficacy for short-term pain management (Furlan et al. 2006) is comparable to both cyclobenzaprine (a 5-HT<sub>2A</sub> antagonist, pro-adrenergic muscle relaxant; Tofferi et al. 2004) and antidepressants (Onghena and Van Houdenhove 1992). Furthermore, nonpharmacological treatments of chronic pain, such as mindfulness (Bawa et al. 2015), hypnosis (Devine 2003; Montgomery et al. 2000), yoga (Holtzman and Beggs 2013), and combinations of psychological and physical treatment programs (biopsychosocial multidisciplinary rehabilitation; Kamper et al. 2015) produce pain-reducing effects comparable to that of opioids (Figure 1). Self-regulatory treatments for chronic pain are therefore, a promising, albeit desirable, alternative to pharmacologic agents and are worthy of further research.

In this paper, we briefly discuss the heterogeneity of pain representations in the brain and identify several loci whose activity can be disrupted to alleviate chronic pain conditions through self-regulatory techniques. Specifically, we discuss (1) prefrontal-limbic circuitry and (2) resting state networks, which are altered during the chronification of pain. We propose that prefrontal-limbic circuitry alters the way pain is *valued* in individuals, while changes to default mode network (DMN) morphometry and connectivity may alter self-referential processes related to the pain experience. These systems can be targeted by self-regulatory strategies that alter evaluative (i.e., reappraisal-based strategies) and self-referential processes (i.e., acceptance-based strategies), respectfully.

### **The Heterogeneity of Pain Representations in the Brain**

The experience of chronic pain is different from that of acute pain. Critically, it is *appraised* differently; its perceived causes are understood differently, and it connotes different implications for future wellbeing. Acute pain is often appraised as self-limiting, with an identifiable cause and expected resolution. Conversely, chronic pain is appraised as something without a known end that is dissociated from its initial driver and a part of daily life (Grichnik and Ferrante 1991).

Likewise, different types of chronic pain are experienced and represented in unique ways. For example, chronic back pain disrupts activity in the mPFC more than post-herpetic neuralgia or knee osteoarthritis (Baliki et al., 2006). In post-herpetic neuralgia, the most prominent correlates of spontaneous pain are in the amygdala and accumbens, while knee osteoarthritis has greater correlations in the orbitofrontal cortex. Insula activity is central to brain changes associated with fibromyalgia (Kuchinad et al. 2007; Harris et al. 2009; López-Solà et al. 2017; Napadow et al. 2010). Migraine episodes evoke a distributed network of activity with a significant emphasis on subcortical circuitry— signal intensity in the red nucleus and substantia nigra as related to visually-triggered onset (Cao et al. 2002), and the pons as related to spontaneous migraine experiencing

(Afridi et al. 2005), migraine severity (Russo et al. 2012), and migraine-related changes in morphology (Chong et al. 2017). In phantom pain, pain may be best explained by persistent local cortical representations in S1 (Makin et al. 2013) or maladaptive cortical reorganization (Flor, Nikolajsen, and Jensen, 2006). To summarize, brain representations across chronic pain pathologies are unique, though they may implicate common circuitry that overlaps with acute pain at a broad level (Figure 2).

For at least some types of pain—and chronic low back pain in particular—the transition from acute to chronic pain is thought to be supported by a shift in pain representation from nociceptive to ‘emotional’ circuits, that is, the limbic system and prefrontal cortex (Hashmi et al. 2013). This is supported by a pattern of dissociation between brain systems involved in immediate evoked pain experience and those that seem to track pain chronification. For example, the Neurologic Pain Signature (NPS; Wager et al. 2013), a brain pattern predictive of evoked experimental pain, includes a set of brain regions that overlap with those often considered to be in the ‘pain matrix’ by virtue of their responses to noxious stimuli and correlations with pain ratings (Apkarian, Bushnell, Treede, & Zubieta, 2005; Coghill, Sang, Maisog, & Iadarola, 1999; Melzack, 1999, 2001). Like the ‘pain matrix,’ in the NPS, activity in the anterior cingulate cortex (ACC), insula, secondary somatosensory cortex (S2), and thalamus is related to a greater pain experiencing, while increased activity in the ventromedial prefrontal cortex (vmPFC) and precuneus is related to *less* pain experiencing. Indeed, the regions that predict evoked pain as part of the NPS are not the regions that correlate with the intensity of spontaneous fluctuations in chronic back pain (Baliki et al., 2006) nor does activity in these regions predict back pain chronification (Baliki et al., 2012). The region most heavily implicated in pain chronification is the vmPFC, which changes from being anti-correlated with pain in healthy participants (Woo et al., 2017) to being positively associated with pain in several patient groups (Harris et al. 2009; López-Solà et al. 2017; Napadow et al, 2010).

One interpretation of this evidence is that there is a shift in the drivers of pain from systems that encode the immediate, sensory-discriminative aspects of pain experience to affective-motivational information relevant for pain avoidance, which requires linking actions and contexts with pain via associative learning mechanisms (Ingvar 2015; Mansour et al. 2014; Zaman et al. 2015; Roy et al. 2014). This is generally adaptive, as actions associated with pain should be avoided in order to prevent harm. However, avoidance can become maladaptive if a wide variety of actions and contexts become linked with pain—particularly if those actions are not harmful and the pain-avoidance system has over-generalized (Meulders, Vansteenwegen, & Vlaeyen, 2011).

For example, pain from an injury may be exacerbated by long periods of standing. If a patient is required to stand for long periods of time at work, they may learn to associate their work environment with pain. Indeed, conditioned increases in muscle tension are acquired more rapidly in subacute pain patients at high risk for chronification (Flor and Birbaumer 1994). That is, those at a higher risk of pain chronification demonstrate quicker associative learning between pain contexts and nociceptive responses. Furthermore, if the patient's community engages in movement-related hobbies, the patient may learn to expect pain during social events. This may promote social withdrawal and feelings of alienation (Smith and Osborn 2007; Hunfeld et al. 2001). One patient's testimony of their experience living with chronic pain elucidates this point:

"In my 10+ years of chronic pain I've done many regrettable things, but the thing I regret is something I had no clue I was doing. I began pushing everyone away so that they didn't have to deal with me or so that I could just quietly decay in my bed without bother. It starts small, you begin missing more and more things and then people stop trying to invite you because they think you'll say no. I wish I was stronger is the only phrase I want to tell my best friend and how I wish I could have been at your wedding to see you happy." (Anonymous user on the forum: [www.reddit.com/r/chronicpain](http://www.reddit.com/r/chronicpain)).

Depressed mood, negative pain beliefs, and early beliefs that the pain may be permanent are also predictive of the chronification of neck and back pain (Young Casey et al. 2008). In this way, various aspects of a person's life may become entangled with their pain experience, and a widening variety of activities that could promote recovery and wellbeing become threatening and are avoided. That is, chronic pain, unlike acute pain, is conceived as something inseparable from one's sense of *self*. This pathological interweaving of pain and self is therefore a promising target for treatment through self-regulatory techniques.

### **Pain Self-Regulation**

Self-regulation encompasses a wide variety of strategies for deploying conscious thought to shape attention, emotion, decision-making, and behavior (Karoly 1993; Boekaerts et al. 2005; Heatherton 2011; Mischel, Cantor, & Feldman, 1996). It has been proven to be effective for the attenuation of both experimental pain (Fernandez and Turk 1989) and chronic pain (Mann et al. 2013; Escolar-Reina et al. 2009; Perry et al. 2010; Hadjistavropoulos and Shymkiw 2007; Darnall, Sturgeon, Kao, Hah, and Mackey, 2014). Furthermore, it is a feasible option for long-term treatment because it is a free, learnable skill set that can be improved with practice (Boekaerts et al. 2005; Tang et al. 2007; Muraven et al. 1999). When practiced effectively, self-regulatory strategies can reduce reliance on drugs, surgery, and other high-cost and high-risk treatments (Bandura 2005; Kabat-Zinn

et al. 1986; Aspinwall and Taylor 1997). Self-regulatory interventions that induce learning or neuroplasticity in brain regions that undergo reorganization or functional connectivity changes during the chronification of pain may be able to slow down, mitigate, or reverse the effects of chronic pain pathologies (Flor 2003). Here we identify three categories of self-regulatory strategies with the potential to alter the neural substrate underlying chronic pain: (1) reappraisal-based (Gross 1998), (2) acceptance-based (Hayes et al. 2006), and (3) attention-based (Carver and Scheier 1983) strategies (Table 1).

Pain **reappraisal**, a type of cognitive reframing of the context and meaning of pain, is a part of a family of processes studied extensively in relation to emotion (Gross 2002; Buhle et al., 2014). Reappraisal involves changing an emotional experience by reinterpreting the meaning of the emotion-eliciting stimulus. During pain reappraisal, one's perceptions of pain and pain reactivity are consciously modified by changing the meaning of the pain (i.e., reinterpreting pain as non-dangerous, reminding oneself that it is time-limited and under control, affirming that 'suffering builds character,' and more; Tracey 2010; Turk and Genest 1979; Woo, Roy, Buhle, & Wager, 2015; Sturgeon, Kao, Hah, and Mackey, 2014). Through reappraisal, the value of pain is consciously altered to either down-weight its negative components or up-weight its positive components. It may remain salient, but its meaning is intentionally modified.

Pain **acceptance** is the process of learning to acknowledge pain's existence as neither positive nor negative. It requires one to stop resisting pain, but instead, to learn to live with it without judgment, and to notice and reduce fear and avoidance of pain. Acceptance-based therapies have been shown to decrease both pain experiencing and psychological distress (Lachapelle et al. 2008; McCracken and Eccleston 2005; Chamberlain 2001; Ceyhan and Ceyhan 2011). Through acceptance, the value of the pain is neutralized; it is no longer salient though it is still consciously accessible.

**Attentional control** focuses on directing attention away from the pain experience (Miron et al., 1989; Eccleston 1995). Through attentional control, the actual value of the pain is not changed, instead its accessibility is changed. The redirection of attention can be very effective for evoked pain (Buhle and Wager 2010; Sprenger et al. 2012; Johnston et al. 2012); however, it may not be sustainable when pain is chronic (Suls and Fletcher 1985; Holmes and Stevenson 1990). Furthermore, there is evidence that distraction from chronic pain during pain-inducing activity has a paradoxical effect of increasing pain immediately after the task (Goubert et al. 2004). Therefore, we focus here on reappraisal- and acceptance-based strategies.

### Reappraisal-based strategies

*Behavioral Effectiveness.* A popular treatment that often utilizes reappraisal is cognitive-behavioral therapy (CBT), a psychotherapy that seeks to alleviate dysfunction through the modification of emotions, behaviors, and thoughts (Meichenbaum 1977; Beck 1979). CBT is reportedly efficacious for the treatment of pain and stress-related disorders (Morley et al. 1999; Fagerhaugh 1974; Turk et al. 1983; Hoffman et al. 2007; Darnall, Sturgeon, Kao, Hah, and Mackey, 2014) with treatment effects greater than some drugs and other education-based therapies (see Figure 1). For example, CBT has been shown to provide pain relief from headaches (Turner and Chapman, 1982; Holroyd et al. 1977), and its protective effects last through six- to nine-week follow up periods (Holroyd and Andrasik 1978; Mitchell and White 1977). CBT promotes general improvement in a variety of health-related outcomes in chronic pain patients, including pain experiencing, mood, physical activity, coping ability, and sociality (Morley et al. 1999). CBT also reduces the economic as well as societal impacts of chronic pain; in an investigation of 409 chronic low back pain patients, patients who had CBT in combination with usual care in a 3-week inpatient rehabilitation program had 5.4% fewer work absences six months later than those who received usual care alone (Schweikert et al. 2006).

Reappraisal therapies teach techniques to help endure or mitigate the current pain experience. They also teach ways in which a patient can alter environmental, cognitive, and affective factors that may trigger or exacerbate pain. In this way, CBT is a method of ‘unlearning’ pain (Shpaner et al. 2014; Hollander et al. 2010; Peuterl et al. 2011), which can change one’s expectations, beliefs, and cognitions about one’s pain. A cognitive component related to persistence and intensity of pain which can be targeted by CBT is catastrophizing (Wertli et al. 2014; Wertli et al. 2014; Vlaeyen et al. 1995; Darnall, Sturgeon, Kao, Hah, and Mackey, 2014). Pain catastrophizing is a key feature of the Fear-Avoidance Model of Pain, which describes two paths for patients after an injury (Gatchel et al. 2016; Leeuw et al. 2007; Vlaeyen et al. 2016; Lethem et al. 1983). Patients who develop chronic pain after an injury may begin to fear pain, associating negative affect, vigilance towards potential pain, and negative beliefs with their experience of pain. For example, an item on the Fear-Avoidance Components Scale is “*I believe that my pain will keep getting worse until I won’t be able to function at all.*” Such beliefs may lead to hypervigilance and generalized avoidance of physical and social activity — behaviors that may worsen musculoskeletal and central nervous system drivers of pain (i.e., disuse may increase disability), and also create socio-emotional distress (i.e., social withdrawal and feelings of isolation may lead to depression). In this model, if patients “confront” their pain

experience, they are more likely to recover. CBT is a tool patients can use to effectively “confront” their pain by understanding this vicious cycle of pain and fear, and changing their beliefs about their pain (Crombez et al. 2012; Gatchel et al. 2014; Gatchel and Okifuji 2006). Patients who interpret their pain as non-threatening are less likely to catastrophize or engage in pain-related fear-avoidance behaviors, and demonstrate quicker recovery times (Gatchel et al. 2016).

*Brain targets of Reappraisal Strategies.* The basal ganglia (BG) is a crucial structure for both valuation (for a review Hikosaka et al. 2014) and multisensory integration (Nagy et al. 2006; Reig and Silberberg 2014) implicated in both pain experiencing (Borsook et al. 2010) and emotion reappraisal (Wager et al, 2008). There is evidence that thalamo-cortico-BG loops integrate sensorimotor, affective, and cognitive information into the pain experience (Borsook et al. 2010; Chudler and Dong 1995; Bauer et al. 2012), indicating that plasticity in prefrontal-limbic circuitry changes the way nociceptive signals are appraised, evaluated, and associated with other types of processing. Indeed, pain chronification in humans (Baliki, Geha, Fields, & Apkarian, 2010) and rats (Metz, Yau, Centeno, Apkarian, & Martina, 2009; Schwartz et al., 2014) induces structural changes in the PFC and nucleus accumbens (NAc) that promote pain avoidance and depression-like behavior. In subacute back pain patients, the degree of functional connectivity between the mPFC and the NAc predicts transition to chronic pain (Baliki et al., 2012), and the strength of mPFC-NAc connectivity is correlated with a “shift” in the neural representation of back pain from primarily nociceptive to emotional processing brain regions (Hashmi et al. 2013).

In a rat model of neuropathic pain (Ren et al. 2016), peripheral nerve injury selectively sensitized an indirect pathway between the NAc shell and spiny projection neurons (which constitute ~95% of cells in the mammalian striatum; Plenz and Wickens 2017). This experimentally induced tactile pain sensitization was reversed when spiny projection neurons were inhibited and exacerbated when spiny projection neurons were excited. The authors interpret this finding as evidence that spiny projection neurons of the striatum not only participate in the central representation of pain, but gate activity in ascending nociceptive pathways (Ren et al. 2016). Drawing from this evidence, the PFC and NAc have been identified as part of a ‘gatekeeping’ system, which calculates a stimulus’ relevance (saliency) and affective value, and modulates information flow in the descending modulatory pain system (Rauschecker et al. 2015; Brischoux et al. 2009). Self-regulatory techniques which target evaluative processes may alter the pain experience through modulation of this circuitry.

In studies of emotion regulation, cognitive reappraisal increases activity in brain regions associated with the processing of affective meaning: the mPFC, anterior temporal cortices, and the

ventral striatum (Staudinger et al. 2009). It also decreases activity in limbic regions, particularly the amygdala (McRae et al. 2010; Ochsner et al. 2002; Ochsner et al. 2004; Buhle et al., 2012), which may be associated individual differences in rumination (Ray et al. 2005). Using a mediation analysis, Wager et al. (2008) found two independent pathways for cognitive reappraisal via the ventrolateral PFC (vlPFC): (1) a pathway between the vlPFC and amygdala which predicted greater negative emotion reports, that is, failures of reappraisal, and (2) a pathway between the vlPFC and NAc (and/or surrounding ventral striatum) that predicted greater positive emotion reports, that is, reappraisal success. Focusing on NAc as a seed, Wager et al. (2008) identified an additional pathway from the vmPFC to NAc supporting reappraisal success. Similarly, self-regulation of evoked heat pain can be explained by a pathway connecting the vmPFC and the NAc (Woo et al. 2015). In animals, stimulation of the PFC can inhibit both sensory and affective pain signals (Dale et al. 2018) via descending projections to the striatum (Lee et al. 2015; Martinez et al. 2017), amygdala (Ji and Neugebauer 2014), brainstem, and spinal cord (Fields et al. 1983). Through this mechanism, activation of the PFC during CBT may alter the valuation of the pain experience via its projections to limbic circuitry, and therefore, facilitate the reappraisal of pain beliefs.

### **Acceptance-based strategies**

*Behavioral Effectiveness.* Acceptance-based strategies for the regulation of pain and negative affect are rising in popularity, and hold promise for long-term pain management (Baer 2003; Rosenzweig et al. 2010; Cherkin et al. 2016). One favored form of acceptance-based therapy is mindfulness meditation. Mindfulness meditation is the act of focusing attention on bodily sensations on a moment-by-moment basis, and removing judgement attached to these sensations (Zeidan and Vago 2016). Thus, to be mindful of pain, one focuses on the experience of it unfolding through time but removes appraisals of what the experience means (i.e. a signifier of tissue damage). The psychological processes involved in mindfulness would suggest that it does not directly attenuate nociceptive signals or pain sensations, but acts by manipulating non-nociceptive qualities of pain. Indeed, experienced meditators report similar levels of pain intensity as non-meditators, but report reduced levels of pain unpleasantness (Lutz et al. 2013; Brown and Jones 2010; Perlman et al. 2010). Compared to rest, however, the act of meditation can reduce both pain unpleasantness and intensity ratings to acute noxious stimulations (Zeidan et al. 2011).

Mindfulness interventions have been effective for patients with fibromyalgia (Astin et al. 2003; Sephton et al. 2007; Cash et al. 2015), musculoskeletal pain (Plews-Ogan et al. 2005; Morone et al. 2008), rheumatoid arthritis (Pradhan et al. 2007; Zautra et al. 2008), and headache (Nash-McFeron 2005); though these effects are often estimated by comparing the treatment group to no-

treatment wait-listed controls, and thus include a wider variety of ‘non-specific’ effects of engagement in treatment and positive expectancy than most drug trials (Chiesa and Serretti 2011). Still, mindfulness is reported to have a significant impact on distress, depression, and other more affective dimensions of the pain experience (Gardner-Nix 2009), and in some cases it is more effective for long-term pain management than CBT or usual care (Cherkin et al. 2016). Mindfulness may work by reducing distracting and ruminative thoughts (Jain et al. 2007). Other potential psychological mechanisms are meta-awareness, the bringing to consciousness of feelings of fear and anxiety surrounding pain, and de-identification with both emotions and pain (i.e., “pain is an experience passing through me temporarily; it is not me and does not define me.”). Increasing awareness of the ‘vicious cycle’ of fear and avoidance may in turn help increase engagement in activities and break the cycle. Indeed, Schütze et al. (2010) found that patients who were practiced in mindfulness had lower rates of pain catastrophizing, as well as lower pain intensity, negative affect, and functional disability.

*Brain targets of Acceptance-based Strategies.* Experienced meditators can attenuate elements of pain by deactivating areas of the brain that process the meaning of pain (i.e., PFC), while leaving the sensory experience of it intact or even enhanced (Grant and Rainville 2009; Gard et al. 2012). Strikingly, several studies have failed to find any decreases in activity in correlates of evoked pain (e.g., posterior insula, SII, mid-insula, medial thalamus), and instead find increases in somatosensory processing regions including SII (Kerr et al. 2013; Gard et al. 2012; Grant et al. 2010; Zeidan et al. 2011). Experienced mindfulness meditators also demonstrate differences in default mode network (DMN) activity (Brewer et al., 2011). Core regions of the DMN include the mPFC, PCC, angular gyrus, lateral temporal cortex, hippocampus, parahippocampus, and inferior parietal lobule (IPL; Buckner et al. 2008). The DMN is active when an individual is engaged in internally directed thought—thinking about themselves or others, remembering the past, or imagining future events (Andrews-Hanna 2012; Buckner et al. 2008). It becomes deactivated when an individual’s attention is directed toward external tasks (Fox et al. 2005). Accumulating evidence suggests that the DMN is critical for self-referential processing (Davey et al. 2016; Andrews-Hanna et al. 2014; Denny et al. 2012; Northoff et al. 2006).

The DMN has been shown to interact with the PAG to support analgesia when one “mind-wanders away from pain” in healthy adults experiencing *acute* pain, a finding which suggests that one’s ability to switch between resting state networks may underlie individual differences in pain disengagement (Kucyi et al. 2013). However, for many chronic pain patients, “mind-wandering away from pain” is not viable long-term, and the more self-referential processing they engage in during their pain experience, the more their disease progresses (Aldrich et al. 2000; Campbell et al. 2003).

Indeed, increased DMN activity in chronic pain is correlated with increased rumination and pain-related depression (Kucyi et al. 2014; Kucyi et al. 2013; Erpelding and Davis 2013). Meditation, therefore, may help to reduce the frequency of mind-wandering and self-referential processing which may help to dissociate the experience of pain from one's concept of self.

Various chronic pain pathologies are marked by abnormalities of resting-state functional connectivity networks including the DMN, salience network, and sensorimotor network (Table 2). Many of the regions that encode immediate pain experience are included in the 'salience' and 'sensorimotor' networks. A putative function of the salience network (or 'ventral attention' network) is to identify the most relevant internal and external stimuli (Menon and Uddin 2010). It is comprised of the ventrolateral PFC, anterior insula, ACC (Bressler and Menon 2010), as well as subcortical structures including the amygdala and BG (Menon 2015; Seeley et al. 2007). The 'salience network' may influence activation in the DMN by aiding in the 'switching' between intrinsic and extrinsic loci of attention (Goulden et al. 2014). Greater connectivity between the DMN and the salience network may be related to increased disease activity and clinical pain in chronic pain patients (Hemington et al. 2016). The 'sensorimotor' or 'somatomotor' network primarily integrates information about bodily action and sensation, and involves the primary somatosensory and motor cortices (Bressler and Menon 2010; Damoiseaux et al. 2006). Connectivity between the DMN and the sensorimotor network may be related to physical functioning in chronic pain patients, where increased connectivity between M1 and the PCC predicts functional impairment (Hemington et al. 2016).

Normally, the DMN is anti-correlated with the 'salience network,' and has no strong relationship with the 'sensorimotor network' (Fox et al. 2005; Fox et al. 2009). In chronic pain, DMN and the 'sensorimotor network' demonstrate 'hyperconnectivity,' while DMN and the 'salience network' reduce in their anti-correlation, or in some cases, become positively correlated (Hemington et al. 2018; Hemington et al. 2016). Hemington et al. (2018) propose that the experience of pain initially evokes the 'salience' and 'sensorimotor' networks, as one must attend to their pain and potentially take action to escape it. However, during the chronification of pain, as the pain persists and becomes a part of daily functioning, people will naturally engage in self-referential processing while enduring pain. Therefore, pain-related processing in the salience network may no longer serve to suppress DMN activity, and 'sensorimotor' network activity may become correlated with DMN as the person begins to integrate their experience of pain with their sense of self (Otti et al. 2013). In this way, the pain signal becomes integrated with "non-nociceptive" self-referential processing streams. Acceptance-based self-regulation strategies may work to prevent or undo this pathological

association between one's sense of self and one's experience of chronic pain by preserving or enhancing anti-correlation between nociceptive and self-referential processing systems.

Overall, research on the self-regulation of pain indicates that pain regulation techniques interact with pain signaling to promote relief. Attention-based techniques such as distraction engage the descending pain modulatory system; reappraisal can influence pain by changing its valuation, or what it means to the self; and acceptance-based strategies such as mindfulness can reduce pain either by diminishing or manipulating pain-related self-referential processes. Together, this evidence supports the idea that that pain can be modified in meaningful ways by non-somatic interventions, that is, interventions that do not treat bodily tissue, but which target the *experience* of pain.

### **Towards Personalized Models of Pain Experience**

The earlier discussion of the heterogeneity of pain experiencing suggests that no chronic pain conditions are alike, and that even within pathologies, pain is a personal experience. Therefore, despite commonalities in network dysfunction across a wide range of chronic pain disorders, the neural representation supporting any individual's experience of pain will necessarily reflect that person's unique integration of self-relevant information into their own pain experience. This is because the volume and content of information processed in these cortical regions is diverse and expansive, so when pain signaling is integrated into distributed cortical processing streams, it becomes much more complex than the peripheral input from which it originated. It is therefore possible that the pain experience itself *emerges* from the complex interactions occurring throughout these recurrent processing streams (Schneider and Karoly 1983; Auksztulewicz et al. 2012; Mansour et al., 2016) and therefore, depends upon diverse neurobiological processes in the context of one's daily life.

To understand the complexity of the pain experience, we propose that future research be devoted to the development of personalized neuroimaging models of pain experiencing. Using pattern-based multivariate modelling of whole brain activity during spontaneous pain experiencing in chronic pain patients, researchers can develop biomarkers sensitive and specific to pain within individual patients (Reddan and Wager 2018). An individual's brain-based biomarker could then be applied to their subsequent brain activity in order to predict the level of pain they are experiencing at any given moment (see Figure 3 for an illustration). If this is applied in real-time, a patient could receive immediate feedback on their neural representation of pain. This is most useful when a patient is learning how to self-regulate their pain experience. For example, a patient who is interested in

mindfulness but is having trouble learning which strategies work best for them, could try different strategies in the fMRI scanner while receiving feedback on their ability to downregulate their personal pain signature (similar frameworks have been attempted for fear-regulation see Taschereau-Dumouchel et al. 2018). In this way, a patient could learn through trial and error what self-regulation strategies work best for them.

## **Conclusion**

In this paper we ask: Can self-regulation impact the biological mechanisms that generate and perpetuate chronic pain? To answer this question, we first accepted and defended two premises: (1) that pain is a multidimensional experience, instantiated by emotional and cognitive systems in conjunction with primary nociception, and (2) that self-regulation is a cognitive process that affects affective-motivational processing and behavior. What may link these two processes, so that they can effectively influence one another, is their involvement of emotional and cognitive systems. If self-regulation affects emotional and cognitive brain mechanisms that directly contribute to chronic pain it is likely to be neurobiologically meaningful for patient recovery. Therefore, we sought to establish where in the brain these two experiences, that of chronic pain and that of self-regulation, interact neurobiologically. We propose that prefrontal-striatal circuitry and DMN functioning are critical entry points by which self-regulation can directly influence the chronification of pain.

Self-regulation is a cost-effective and scalable treatment available immediately to large populations, via clinics, educational programs, and even smartphone apps (Bakker et al. 2016). Furthermore, self-regulation works safely in conjunction with currently prescribed drug regimens, allowing any patient to simply and effectively supplement their ongoing treatment. Finally, self-regulation a continuous and preventative measure for healthy populations to minimize the risk of developing chronic pain in the first place. Pain self-regulation therapies holds great promise for people suffering from chronic pain. Through continued study of the neurological underpinnings of self-regulation and how it impacts learning and neural plasticity, we will be able to optimize and personalize self-regulation training, understand how it can augment drug treatments, and accelerate its integration into therapeutic treatment programs.

## References

- Afridi, S. K., Giffin, N. J., Kaube, H., Friston, K. J., Ward, N. S., Frackowiak, R. S. J., & Goadsby, P. J. (2005). A positron emission tomographic study in spontaneous migraine. *Archives of Neurology*, *62*(8), 1270–1275.
- Albe-Fessard, D., Berkley, K. J., Kruger, L., Ralston, H. J., 3rd, & Willis, W. D., Jr. (1985). Diencephalic mechanisms of pain sensation. *Brain Research*, *356*(3), 217–296.
- Aldrich, S., Eccleston, C., & Crombez, G. (2000). Worrying about chronic pain: vigilance to threat and misdirected problem solving. *Behaviour Research and Therapy*, *38*(5), 457–470.
- Anderson, S. R., & Reynolds Losin, E. A. (2016). A sociocultural neuroscience approach to pain. *Culture and Brain*, *5*(1), 14–35.
- Andrews-Hanna, J. R. (2012). The brain's default network and its adaptive role in internal mentation. *The Neuroscientist: A Review Journal Bringing Neurobiology, Neurology and Psychiatry*, *18*(3), 251–270.
- Andrews-Hanna, J. R., Smallwood, J., & Spreng, R. N. (2014). The default network and self-generated thought: component processes, dynamic control, and clinical relevance. *Annals of the New York Academy of Sciences*, *1316*, 29–52.
- Apkarian, A. V., Bushnell, M. C., Treede, R.-D., & Zubieta, J.-K. (2005). Human brain mechanisms of pain perception and regulation in health and disease. *European Journal of Pain*, *9*(4), 463–484.
- Aspinwall, L. G., & Taylor, S. E. (1997). A stitch in time: self-regulation and proactive coping. *Psychological Bulletin*, *121*(3), 417–436.
- Astin, J. A., Berman, B. M., Bausell, B., Lee, W.-L., Hochberg, M., & Forays, K. L. (2003). The efficacy of mindfulness meditation plus Qigong movement therapy in the treatment of fibromyalgia: a randomized controlled trial. *The Journal of Rheumatology*, *30*(10), 2257–2262.
- Atlas, L. Y., & Wager, T. D. (2012). How expectations shape pain. *Neuroscience Letters*, *520*(2), 140–148.
- Auksztulewicz, R., Spitzer, B., & Blankenburg, F. (2012). Recurrent neural processing and somatosensory awareness. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *32*(3), 799–805.
- Azqueta-Gavaldon, M., Schulte-Göcking, H., Storz, C., Azad, S., Reiners, A., Borsook, D., ... Kraft, E. (2017). Basal ganglia dysfunction in complex regional pain syndrome - A valid hypothesis? *European Journal of Pain*, *21*(3), 415–424.
- Baer, R. A. (2003). Mindfulness training as a clinical intervention: A conceptual and empirical review. *Clinical Psychology: Science and Practice*, *10*(2), 125–143.
- Bakker, D., Kazantzis, N., Rickwood, D., & Rickard, N. (2016). Mental Health Smartphone Apps: Review and Evidence-Based Recommendations for Future Developments. *JMIR Mental Health*, *3*(1), e7.
- Baliki, M. N., Chialvo, D. R., Geha, P. Y., Levy, R. M., Harden, R. N., Parrish, T. B., & Apkarian, A. V. (2006). Chronic pain and the emotional brain: specific brain activity associated with spontaneous fluctuations of intensity of chronic back pain. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *26*(47), 12165–12173.
- Baliki, M. N., Geha, P. Y., Apkarian, A. V., & Chialvo, D. R. (2008). Beyond feeling: chronic pain hurts the brain, disrupting the default-mode network dynamics. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *28*(6), 1398–1403.
- Baliki, M. N., Mansour, A. R., Baria, A. T., & Apkarian, A. V. (2014). Functional reorganization of the default mode network across chronic pain conditions. *PloS One*, *9*(9), e106133.

- Baliki, M. N., Petre, B., Torbey, S., Herrmann, K. M., Huang, L., Schnitzer, T. J., ... Apkarian, A. V. (2012). Corticostriatal functional connectivity predicts transition to chronic back pain. *Nature Neuroscience*, 15(8), 1117–1119.
- Baliki, M. N., Schnitzer, T. J., Bauer, W. R., & Apkarian, A. V. (2011). Brain morphological signatures for chronic pain. *PloS One*, 6(10), e26010.
- Ballantyne, J. C., & LaForge, K. S. (2007). Opioid dependence and addiction during opioid treatment of chronic pain. *Pain*, 129(3), 235–255.
- Bandura, A. (2005). The Primacy of Self-Regulation in Health Promotion. *Applied Psychology = Psychologie Appliquee*, 54(2), 245–254.
- Bauer, C. C. C., Pasaye, E. H., Romero-Romo, J. I., & Barrios, F. A. (2012). The Integrative Role of the Basal Ganglia. *BASAL GANGLIA--AN INTEGRATIVE VIEW*, 87.
- Bawa, F. L. M., Mercer, S. W., Atherton, R. J., Clague, F., Keen, A., Scott, N. W., & Bond, C. M. (2015). Does mindfulness improve outcomes in patients with chronic pain? Systematic review and meta-analysis. *The British Journal of General Practice: The Journal of the Royal College of General Practitioners*, 65(635), e387–e400.
- Beck, A. T. (1979). *Cognitive Therapy and the Emotional Disorders*. Penguin.
- Boekaerts, M., Pintrich, P. R., & Zeidner, M. (2005). *Handbook of Self-Regulation*. Academic Press.
- Bolwerk, A., Seifert, F., & Maihöfner, C. (2013). Altered resting-state functional connectivity in complex regional pain syndrome. *The Journal of Pain: Official Journal of the American Pain Society*, 14(10), 1107–1115.e8.
- Borsook, D., Upadhyay, J., Chudler, E. H., & Becerra, L. (2010). A key role of the basal ganglia in pain and analgesia--insights gained through human functional imaging. *Molecular Pain*, 6, 27.
- Bräscher, A.-K., Becker, S., Hoeppli, M.-E., & Schweinhardt, P. (2016). Different Brain Circuitries Mediating Controllable and Uncontrollable Pain. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, 36(18), 5013–5025.
- Bressler, S. L., & Menon, V. (2010). Large-scale brain networks in cognition: emerging methods and principles. *Trends in Cognitive Sciences*, 14(6), 277–290.
- Brewer, J. A., Worhunsky, P. D., Gray, J. R., Tang, Y.-Y., Weber, J., & Kober, H. (2011). Meditation experience is associated with differences in default mode network activity and connectivity. *Proceedings of the National Academy of Sciences of the United States of America*, 108(50), 20254–20259.
- Brischoux, F., Chakraborty, S., Brierley, D. I., & Ungless, M. A. (2009). Phasic excitation of dopamine neurons in ventral VTA by noxious stimuli. *Proceedings of the National Academy of Sciences of the United States of America*, 106(12), 4894–4899.
- Brown, C. A., & Jones, A. K. P. (2010). Meditation experience predicts less negative appraisal of pain: Electrophysiological evidence for the involvement of anticipatory neural responses. *Pain*, 150(3), 428–438.
- Buckner, R. L., Andrews-Hanna, J. R., & Schacter, D. L. (2008) The brain's default network: anatomy, function, and relevance to disease *Ann NY Acad Sci*; 1124: 1-38.
- Buhle, J. T., Silvers, J. A., Wager, T. D., Lopez, R., Onyemekwu, C., Kober, H., ... Ochsner, K. N. (2014). Cognitive reappraisal of emotion: a meta-analysis of human neuroimaging studies. *Cerebral Cortex*, 24(11), 2981–2990.
- Buhle, J., & Wager, T. D. (2010). Performance-dependent inhibition of pain by an executive working memory task. *Pain*, 149(1), 19–26.

- Callan, D., Mills, L., Nott, C., England, R., & England, S. (2014). A tool for classifying individuals with chronic back pain: using multivariate pattern analysis with functional magnetic resonance imaging data. *PLoS One*, 9(6), e98007.
- Campbell, J. N., & Meyer, R. A. (2006). Mechanisms of neuropathic pain. *Neuron*, 52(1), 77–92.
- Campbell, L. C., Clauw, D. J., & Keefe, F. J. (2003). Persistent pain and depression: a biopsychosocial perspective. *Biological Psychiatry*, 54(3), 399–409.
- Cao, Y., Aurora, S. K., Nagesh, V., Patel, S. C., & Welch, K. M. A. (2002). Functional MRI-BOLD of brainstem structures during visually triggered migraine. *Neurology*, 59(1), 72–78.
- Carver, C. S., & Scheier, M. F. (1983). A Control-Theory Approach to Human Behavior, and Implications for Problems in Self-Management. In P. C. Kendall (Ed.), *Advances in Cognitive-Behavioral Research and Therapy* (pp. 127–194). Academic Press.
- Cash, E., Salmon, P., Weissbecker, I., Rebholz, W. N., Bayley-Veloso, R., Zimmaro, L. A., ... Sephton, S. E. (2015). Mindfulness meditation alleviates fibromyalgia symptoms in women: results of a randomized clinical trial. *Annals of Behavioral Medicine: A Publication of the Society of Behavioral Medicine*, 49(3), 319–330.
- Cauda, F., D'Agata, F., Sacco, K., Duca, S., Cocito, D., Paolasso, I., ... Geminiani, G. (2010). Altered resting state attentional networks in diabetic neuropathic pain. *Journal of Neurology, Neurosurgery, and Psychiatry*, 81(7), 806–811.
- Ceyhan, A. A., & Ceyhan, E. (2011). Investigation of university students' self-acceptance and learned resourcefulness: a longitudinal study. *Higher Education*, 61(6), 649–661.
- Chamberlain, J. M., & Haaga, D. A. F. (2001). Unconditional Self-Acceptance and Responses to Negative Feedback. *Journal of Rational-Emotive and Cognitive-Behavior Therapy: RET*, 19(3), 177–189.
- Cherkin, D. C., Sherman, K. J., Balderson, B. H., Cook, A. J., Anderson, M. L., Hawkes, R. J., ... Turner, J. A. (2016). Effect of Mindfulness-Based Stress Reduction vs Cognitive Behavioral Therapy or Usual Care on Back Pain and Functional Limitations in Adults With Chronic Low Back Pain: A Randomized Clinical Trial. *JAMA: The Journal of the American Medical Association*, 315(12), 1240–1249.
- Chiesa, A., & Serretti, A. (2011). Mindfulness-based interventions for chronic pain: a systematic review of the evidence. *Journal of Alternative and Complementary Medicine*, 17(1), 83–93.
- Chong, C. D., Plasencia, J. D., Frakes, D. H., & Schwedt, T. J. (2017). Structural alterations of the brainstem in migraine. *NeuroImage. Clinical*, 13, 223–227.
- Christensen, J. O., & Knardahl, S. (2010). Work and neck pain: A prospective study of psychological, social, and mechanical risk factors. *Pain*, 151(1), 162–173.
- Chudler, E. H., & Dong, W. K. (1995). The role of the basal ganglia in nociception and pain. *Pain*, 60(1), 3–38.
- Chu, L. F., Angst, M. S., & Clark, D. (2008). Opioid-induced hyperalgesia in humans: molecular mechanisms and clinical considerations. *The Clinical Journal of Pain*, 24(6), 479–496.
- Coghill, R. C. (2010). Individual differences in the subjective experience of pain: new insights into mechanisms and models. *Headache*, 50(9), 1531–1535.
- Coghill, R. C., Sang, C. N., Maisog, J. M., & Iadarola, M. J. (1999). Pain intensity processing within the human brain: a bilateral, distributed mechanism. *Journal of Neurophysiology*, 82(4), 1934–1943.
- Collett, B. J. (1998). Opioid tolerance: the clinical perspective. *British Journal of Anaesthesia*, 81(1), 58–68.

- Compton, W. M., & Volkow, N. D. (2006). Major increases in opioid analgesic abuse in the United States: concerns and strategies. *Drug and Alcohol Dependence*, 81(2), 103–107.
- Crombez, G., Eccleston, C., Van Damme, S., Vlaeyen, J. W. S., & Karoly, P. (2012). Fear-avoidance model of chronic pain: the next generation. *The Clinical Journal of Pain*, 28(6), 475–483.
- Dale, J., Zhou, H., Zhang, Q., Martinez, E., Hu, S., Liu, K., ... Wang, J. (2018). Scaling Up Cortical Control Inhibits Pain. *Cell Reports*, 23(5), 1301–1313.
- Damoiseaux, J. S., Rombouts, S. A. R. B., Barkhof, F., Scheltens, P., Stam, C. J., Smith, S. M., & Beckmann, C. F. (2006). Consistent resting-state networks across healthy subjects. *Proceedings of the National Academy of Sciences of the United States of America*, 103(37), 13848–13853.
- Darnall, B. (2018). To treat pain, study people in all their complexity. *Nature*, 557(7703), 7.
- Darnall, BD., Sturgeon, JA., Kao, MC, Hah, JM, & Mackey, SC (2014) From Catastrophizing to Recovery: a pilot study of a single-session treatment for pain catastrophizing. *J Pain Res.* 7:219-26.
- Davey, C. G., Pujol, J., & Harrison, B. J. (2016). Mapping the self in the brain's default mode network. *NeuroImage*, 132, 390–397.
- Davis, K. D., Pope, G., Chen, J., Kwan, C. L., Crawley, A. P., & Diamant, N. E. (2008). Cortical thinning in IBS: implications for homeostatic, attention, and pain processing. *Neurology*, 70(2), 153–154.
- Denny, B. T., Kober, H., Wager, T. D., & Ochsner, K. N. (2012). A meta-analysis of functional neuroimaging studies of self- and other judgments reveals a spatial gradient for mentalizing in medial prefrontal cortex. *Journal of Cognitive Neuroscience*, 24(8), 1742–1752.
- Devine, E. C. (2003). Meta-analysis of the effect of psychoeducational interventions on pain in adults with cancer. *Oncology Nursing Forum*, 30(1), 75–89.
- Dhalla, I. A., Mamdani, M. M., Gomes, T., & Juurlink, D. N. (2011). Clustering of opioid prescribing and opioid-related mortality among family physicians in Ontario. *Canadian Family Physician Medecin de Famille Canadien*, 57(3), e92–e96.
- Eccleston, C. (1995). Chronic pain and distraction: an experimental investigation into the role of sustained and shifting attention in the processing of chronic persistent pain. *Behaviour Research and Therapy*, 33(4), 391–405.
- Eccleston, C., & Crombez, G. (1999). Pain demands attention: a cognitive-affective model of the interruptive function of pain. *Psychological Bulletin*, 125(3), 356–366.
- Erpelding, N., & Davis, K. D. (2013). Neural underpinnings of behavioural strategies that prioritize either cognitive task performance or pain. *Pain*, 154(10), 2060–2071.
- Escolar-Reina, P., Medina-Mirapeix, F., Gascón-Cánovas, J. J., Montilla-Herrador, J., Valera-Garrido, J. F., & Collins, S. M. (2009). Self-management of chronic neck and low back pain and relevance of information provided during clinical encounters: an observational study. *Archives of Physical Medicine and Rehabilitation*, 90(10), 1734–1739.
- Fagerhaugh, S. Y. (1974). Pain expression and control on a burn care unit. *Nursing Outlook*, 22(10), 645–650.
- Fernandez, E., & Turk, D. C. (1989). The utility of cognitive coping strategies for altering pain perception: a meta-analysis. *Pain*, 38(2), 123–135.
- Fields, H. L., Bry, J., Hentall, I., & Zorman, G. (1983). The activity of neurons in the rostral medulla of the rat during withdrawal from noxious heat. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, 3(12), 2545–2552.

- Flodin, P., Martinsen, S., Altawil, R., Waldheim, E., Lampa, J., Kosek, E., & Fransson, P. (2016). Intrinsic Brain Connectivity in Chronic Pain: A Resting-State fMRI Study in Patients with Rheumatoid Arthritis. *Frontiers in Human Neuroscience*, 10, 107.
- Flor, H. (2003). Cortical reorganisation and chronic pain: implications for rehabilitation. *Journal of Rehabilitation Medicine: Official Journal of the UEMS European Board of Physical and Rehabilitation Medicine*, (41 Suppl), 66–72.
- Flor, H., & Birbaumer, N. (1994). Acquisition of chronic pain: Psychophysiological mechanisms. *APS Journal*, 3(2), 119–127.
- Flor, H., Nikolajsen, L., Jensen, T.S. (2006). Phantom limb pain: a case of maladaptive CNS plasticity? *Nat Rev Neurosci*. 7(11):873-81.
- Fox, M. D., Snyder, A. Z., Vincent, J. L., Corbetta, M., Van Essen, D. C., & Raichle, M. E. (2005). The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proceedings of the National Academy of Sciences of the United States of America*, 102(27), 9673–9678.
- Fox, M. D., Zhang, D., Snyder, A. Z., & Raichle, M. E. (2009). The global signal and observed anticorrelated resting state brain networks. *Journal of Neurophysiology*, 101(6), 3270–3283.
- Fuentes, M., Hart-Johnson, T., & Green, C. R. (2007). The association among neighborhood socioeconomic status, race and chronic pain in black and white older adults. *Journal of the National Medical Association*, 99(10), 1160–1169.
- Furlan, A. D., Sandoval, J. A., Mailis-Gagnon, A., & Tunks, E. (2006). Opioids for chronic noncancer pain: a meta-analysis of effectiveness and side effects. *CMAJ: Canadian Medical Association Journal = Journal de l'Association Medicale Canadienne*, 174(11), 1589–1594.
- Gardner-Nix, J. (2009). Mindfulness-Based Stress Reduction for Chronic Pain Management. In F. Didonna (Ed.), *Clinical Handbook of Mindfulness* (pp. 369–381). New York, NY: Springer New York.
- Gard, T., Hölzel, B. K., Sack, A. T., Hempel, H., Lazar, S. W., Vaitl, D., & Ott, U. (2012). Pain attenuation through mindfulness is associated with decreased cognitive control and increased sensory processing in the brain. *Cerebral Cortex*, 22(11), 2692–2702.
- Gatchel, R. J., McGeary, D. D., McGeary, C. A., & Lippe, B. (2014). Interdisciplinary chronic pain management: past, present, and future. *The American Psychologist*, 69(2), 119–130.
- Gatchel, R. J., Neblett, R., Kishino, N., & Ray, C. T. (2016). Fear-Avoidance Beliefs and Chronic Pain. *The Journal of Orthopaedic and Sports Physical Therapy*, 46(2), 38–43.
- Gatchel, R. J., & Okifuji, A. (2006). Evidence-based scientific data documenting the treatment and cost-effectiveness of comprehensive pain programs for chronic nonmalignant pain. *The Journal of Pain: Official Journal of the American Pain Society*, 7(11), 779–793.
- Gatchel, R. J., Peng, Y. B., Peters, M. L., Fuchs, P. N., & Turk, D. C. (2007). The biopsychosocial approach to chronic pain: scientific advances and future directions. *Psychological Bulletin*, 133(4), 581–624.
- Geha, P. Y., Baliki, M. N., Chialvo, D. R., Harden, R. N., Paice, J. A., & Apkarian, A. V. (2007). Brain activity for spontaneous pain of postherpetic neuralgia and its modulation by lidocaine patch therapy. *Pain*, 128(1-2), 88–100.
- Goubert, L., Crombez, G., Eccleston, C., & Devulder, J. (2004). Distraction from chronic pain during a pain-inducing activity is associated with greater post-activity pain. *Pain*, 110(1-2), 220–227.
- Goulden, N., Khusnulina, A., Davis, N. J., Bracewell, R. M., Bokde, A. L., McNulty, J. P., & Mullins, P. G. (2014). The salience network is responsible for switching between the default mode network and the central executive network: replication from DCM. *NeuroImage*, 99, 180–190.

- Grant, J. A., Courtemanche, J., Duerden, E. G., Duncan, G. H., & Rainville, P. (2010). Cortical thickness and pain sensitivity in zen meditators. *Emotion*, 10(1), 43–53.
- Grant, J. A., & Rainville, P. (2009). Pain Sensitivity and Analgesic Effects of Mindful States in Zen Meditators: A Cross-Sectional Study. *Psychosomatic Medicine*, 71(1), 106–114.
- Grichnik, K. P., & Ferrante, F. M. (1991). The difference between acute and chronic pain. *The Mount Sinai Journal of Medicine, New York*, 58(3), 217–220.
- Gross, J. J. (1998). Antecedent- and response-focused emotion regulation: divergent consequences for experience, expression, and physiology. *Journal of Personality and Social Psychology*, 74(1), 224–237.
- Gross, J. J. (2002). Emotion regulation: affective, cognitive, and social consequences. *Psychophysiology*, 39(3), 281–291.
- Hadjistavropoulos, H., & Shymkiw, J. (2007). Predicting readiness to self-manage pain. *The Clinical Journal of Pain*, 23(3), 259–266.
- Harris, R. E., Sundgren, P. C., Craig, A. D., Kirshenbaum, E., Sen, A., Napadow, V., & Clauw, D. J. (2009). Elevated insular glutamate in fibromyalgia is associated with experimental pain. *Arthritis and Rheumatism*, 60(10), 3146–3152.
- Hashmi, J. A., Baliki, M. N., Huang, L., Baria, A. T., Torbey, S., Hermann, K. M., ... Apkarian, A. V. (2013). Shape shifting pain: chronification of back pain shifts brain representation from nociceptive to emotional circuits. *Brain: A Journal of Neurology*, 136(Pt 9), 2751–2768.
- Hayes, S. C., Luoma, J. B., Bond, F. W., Masuda, A., & Lillis, J. (2006). Acceptance and commitment therapy: model, processes and outcomes. *Behaviour Research and Therapy*, 44(1), 1–25.
- Heatherton, T. F. (2011). Neuroscience of self and self-regulation. *Annual Review of Psychology*, 62, 363–390.
- Hemington, K. S., Rogachov, A., Cheng, J. C., Bosma, R. L., Kim, J. A., Osborne, N. R., ... Davis, K. D. (2018). Patients with chronic pain exhibit a complex relationship triad between pain, resilience, and within- and cross-network functional connectivity of the default mode network. *Pain*. <https://doi.org/10.1097/j.pain.0000000000001252>
- Hemington, K. S., Wu, Q., Kucyi, A., Inman, R. D., & Davis, K. D. (2016). Abnormal cross-network functional connectivity in chronic pain and its association with clinical symptoms. *Brain Structure & Function*, 221(8), 4203–4219.
- Hikosaka, O., Kim, H. F., Yasuda, M., & Yamamoto, S. (2014). Basal Ganglia Circuits for Reward Value-Guided Behavior. *Annual Review of Neuroscience*, 37(1), 289–306.
- Hoffman, B. M., Papas, R. K., Chatkoff, D. K., & Kerns, R. D. (2007). Meta-analysis of psychological interventions for chronic low back pain. *Health Psychology: Official Journal of the Division of Health Psychology, American Psychological Association*, 26(1), 1–9.
- Hollander, M. D., de Jong, J. R., Volders, S., Goossens, M. E., Smeets, R. J., & Vlaeyen, J. W. S. (2010). Fear reduction in patients with chronic pain: a learning theory perspective. *Expert Review of Neurotherapeutics*, 10(11), 1733–1745.
- Holmes, J. A., & Stevenson, C. A. (1990). Differential effects of avoidant and attentional coping strategies on adaptation to chronic and recent-onset pain. *Health Psychology: Official Journal of the Division of Health Psychology, American Psychological Association*, 9(5), 577–584.
- Holroyd, K. A., & Andrasik, F. (1978). Coping and the self-control of chronic tension headache. *Journal of Consulting and Clinical Psychology*, 46(5), 1036–1045.

- Holroyd, K. A., Andrasik, F., & Westbrook, T. (1977). Cognitive control of tension headache. *Cognitive Therapy and Research*, 1(2), 121–133.
- Holtzman, S., & Beggs, R. T. (2013). Yoga for chronic low back pain: a meta-analysis of randomized controlled trials. *Pain Research & Management: The Journal of the Canadian Pain Society = Journal de La Societe Canadienne Pour Le Traitement de La Douleur*, 18(5), 267–272.
- Hunfeld, J. A., Perquin, C. W., Duivenvoorden, H. J., Hazebroek-Kampschreur, A. A., Passchier, J., van Suijlekom-Smit, L. W., & van der Wouden, J. C. (2001). Chronic pain and its impact on quality of life in adolescents and their families. *Journal of Pediatric Psychology*, 26(3), 145–153.
- Ichesco, E., Schmidt-Wilcke, T., Bhavsar, R., Clauw, D. J., Peltier, S. J., Kim, J., ... Harris, R. E. (2014). Altered resting state connectivity of the insular cortex in individuals with fibromyalgia. *The Journal of Pain: Official Journal of the American Pain Society*, 15(8), 815–826.e1.
- Ingvar, M. (2015). Learning mechanisms in pain chronification--teachings from placebo research. *Pain*, 156 Suppl 1, S18–S23.
- Jain, S., Shapiro, S. L., Swanick, S., Roesch, S. C., Mills, P. J., Bell, I., & Schwartz, G. E. R. (2007). A randomized controlled trial of mindfulness meditation versus relaxation training: effects on distress, positive states of mind, rumination, and distraction. *Annals of Behavioral Medicine: A Publication of the Society of Behavioral Medicine*, 33(1), 11–21.
- Ji, G., & Neugebauer, V. (2014). CB1 augments mGluR5 function in medial prefrontal cortical neurons to inhibit amygdala hyperactivity in an arthritis pain model. *The European Journal of Neuroscience*, 39(3), 455–466.
- Johnston, N. E., Atlas, L. Y., & Wager, T. D. (2012). Opposing effects of expectancy and somatic focus on pain. *PloS One*, 7(6), e38854.
- Kabat-Zinn, J., Lipworth, L., Burncy, R., & Sellers, W. (1986). Four-Year Follow-Up of a Meditation-Based Program for the Self-Regulation of Chronic Pain. *The Clinical Journal of Pain*, 2(3), 159–774.
- Kamper, S. J., Apeldoorn, A. T., Chiarotto, A., Smeets, R. J. E. M., Ostelo, R. W. J. G., Guzman, J., & van Tulder, M. W. (2015). Multidisciplinary biopsychosocial rehabilitation for chronic low back pain: Cochrane systematic review and meta-analysis. *BMJ*, 350, h444.
- Karoly, P. (1993). Mechanisms of Self-Regulation: A Systems View. *Annual Review of Psychology*, 44(1), 23–52.
- Katz, J. N. (2006). Lumbar disc disorders and low-back pain: socioeconomic factors and consequences. *The Journal of Bone and Joint Surgery. American Volume*, 88 Suppl 2, 21–24.
- Kerr, C. E., Sacchet, M. D., Lazar, S. W., Moore, C. I., & Jones, S. R. (2013). Mindfulness starts with the body: somatosensory attention and top-down modulation of cortical alpha rhythms in mindfulness meditation. *Frontiers in Human Neuroscience*, 7, 12.
- Kilpatrick, L. A., Kutch, J. J., Tillisch, K., Naliboff, B. D., Labus, J. S., Jiang, Z., ... Mayer, E. A. (2014). Alterations in resting state oscillations and connectivity in sensory and motor networks in women with interstitial cystitis/painful bladder syndrome. *The Journal of Urology*, 192(3), 947–955.
- Kim, J.-Y., Kim, S.-H., Seo, J., Kim, S.-H., Han, S. W., Nam, E. J., ... Chang, Y. (2013). Increased power spectral density in resting-state pain-related brain networks in fibromyalgia. *Pain*, 154(9), 1792–1797.
- Kolodny, A., Courtwright, D. T., Hwang, C. S., Kreiner, P., Eadie, J. L., Clark, T. W., & Alexander, G. C. (2015). The prescription opioid and heroin crisis: a public health approach to an epidemic of addiction. *Annual Review of Public Health*, 36, 559–574.

- Koyama, T., McHaffie, J. G., Laurienti, P. J., & Coghill, R. C. (2005). The subjective experience of pain: Where expectations become reality. *Proceedings of the National Academy of Sciences*, 102(36), 12950–12955.
- Kuchinad, A., Schweinhardt, P., Seminowicz, D. A., Wood, P. B., Chizh, B. A., & Bushnell, M. C. (2007). Accelerated brain gray matter loss in fibromyalgia patients: premature aging of the brain? *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, 27(15), 4004–4007.
- Kucyi, A., Moayedi, M., Weissman-Fogel, I., Goldberg, M. B., Freeman, B. V., Tenenbaum, H. C., & Davis, K. D. (2014). Enhanced medial prefrontal-default mode network functional connectivity in chronic pain and its association with pain rumination. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, 34(11), 3969–3975.
- Kucyi, A., Salomons, T. V., & Davis, K. D. (2013). Mind wandering away from pain dynamically engages antinociceptive and default mode brain networks. *Proceedings of the National Academy of Sciences of the United States of America*, 110(46), 18692–18697.
- Lachapelle, D. L., Lavoie, S., & Boudreau, A. (2008). The meaning and process of pain acceptance. Perceptions of women living with arthritis and fibromyalgia. *Pain Research & Management: The Journal of the Canadian Pain Society = Journal de La Societe Canadienne Pour Le Traitement de La Douleur*, 13(3), 201–210.
- Lee, M., Manders, T. R., Eberle, S. E., Su, C., D'amour, J., Yang, R., ... Wang, J. (2015). Activation of corticostriatal circuitry relieves chronic neuropathic pain. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, 35(13), 5247–5259.
- Leeuw, M., Goossens, M. E. J. B., Linton, S. J., Crombez, G., Boersma, K., & Vlaeyen, J. W. S. (2007). The fear-avoidance model of musculoskeletal pain: current state of scientific evidence. *Journal of Behavioral Medicine*, 30(1), 77–94.
- Lethem, J., Slade, P. D., Troup, J. D., & Bentley, G. (1983). Outline of a Fear-Avoidance Model of exaggerated pain perception--I. *Behaviour Research and Therapy*, 21(4), 401–408.
- Linton, S. J. (2000). A Review of Psychological Risk Factors in Back and Neck Pain. *Spine*, 25(9), 1148–1156.
- López-Solà, M., Woo, C.-W., Pujol, J., Deus, J., Harrison, B. J., Monfort, J., & Wager, T. D. (2017). Towards a neurophysiological signature for fibromyalgia. *Pain*, 158(1), 34–47.
- Losin, E. A. R., Reynolds Losin, E. A., Woo, C.-W., Krishnan, A., Wager, T. D., Iacoboni, M., & Dapretto, M. (2015). Brain and psychological mediators of imitation: sociocultural versus physical traits. *Culture and Brain*, 3(2), 93–111.
- Lutz, A., McFarlin, D. R., Perlman, D. M., Salomons, T. V., & Davidson, R. J. (2013). Altered anterior insula activation during anticipation and experience of painful stimuli in expert meditators. *NeuroImage*, 64, 538–546.
- Makin, T. R., Filippini, N., Duff, E. P., Henderson Slater, D., Tracey, I., & Johansen-Berg, H. (2015). Network-level reorganisation of functional connectivity following arm amputation. *NeuroImage*, 114, 217–225.
- Makin, T. R., Scholz, J., Filippini, N., Henderson Slater, D., Tracey, I., & Johansen-Berg, H. (2013). Phantom pain is associated with preserved structure and function in the former hand area. *Nature Communications*, 4, 1570.
- Maleki, N., Becerra, L., Nutile, L., Pendse, G., Brawn, J., Bigal, M., ... Borsook, D. (2011). Migraine attacks the Basal Ganglia. *Molecular Pain*, 7, 71.

- Mann, E. G., Lefort, S., & Vandenkerkhof, E. G. (2013). Self-management interventions for chronic pain. *Pain Management*, 3(3), 211–222.
- Mano, H., Kotecha, G., Leibnitz, K., Matsubara, T., Nakae, A., Shenker, N., ... Seymour, B. (2018). Classification and characterisation of brain network changes in chronic back pain: A multicenter study. *Wellcome Open Research*, 3, 19.
- Mansour, A., Baria, A. T., Tetreault, P., Vachon-Preseu, E., Chang, P.-C., Huang, L., ... Baliki, M. N. (2016). Global disruption of degree rank order: a hallmark of chronic pain. *Scientific Reports*, 6, 34853.
- Mansour, A. R., Farmer, M. A., Baliki, M. N., & Apkarian, A. V. (2014). Chronic pain: the role of learning and brain plasticity. *Restorative Neurology and Neuroscience*, 32(1), 129–139.
- Martell, B. A., O'Connor, P. G., Kerns, R. D., Becker, W. C., Morales, K. H., Kosten, T. R., & Fiellin, D. A. (2007). Systematic review: opioid treatment for chronic back pain: prevalence, efficacy, and association with addiction. *Annals of Internal Medicine*, 146(2), 116–127.
- Martinez, E., Lin, H. H., Zhou, H., Dale, J., Liu, K., & Wang, J. (2017). Corticostriatal Regulation of Acute Pain. *Frontiers in Cellular Neuroscience*, 11, 146.
- Martucci, K. T., Shirer, W. R., Bagarinao, E., Johnson, K. A., Farmer, M. A., Labus, J. S., ... Mackey, S. C. (2015). The posterior medial cortex in urologic chronic pelvic pain syndrome: detachment from default mode network—a resting-state study from the MAPP Research Network. *Pain*, 156(9), 1755–1764.
- McCracken, L. M., & Eccleston, C. (2005). A prospective study of acceptance of pain and patient functioning with chronic pain. *Pain*, 118(1-2), 164–169.
- McRae, K., Hughes, B., Chopra, S., Gabrieli, J. D. E., Gross, J. J., & Ochsner, K. N. (2010). The neural bases of distraction and reappraisal. *Journal of Cognitive Neuroscience*, 22(2), 248–262.
- Meichenbaum, D. (1977). *Cognitive Behaviour Modification*. *Scandinavian Journal of Behaviour Therapy*, 6(4), 185–192.
- Melzack, R. (1999). From the gate to the neuromatrix. *Pain*, Suppl 6, S121–S126.
- Melzack, R. (2001). Pain and the neuromatrix in the brain. *Journal of Dental Education*, 65(12), 1378–1382.
- Menon, V. (2015). Saliency network. In: Arthur W. Toga, editor. *Brain Mapping: An Encyclopedic Reference*, vol. 2, pp. 597–611. Academic Press: Elsevier.
- Menon, V., & Uddin, L. Q. (2010). Saliency, switching, attention and control: a network model of insula function. *Brain Structure & Function*, 214(5-6), 655–667.
- Meulders, A., Vansteenwegen, D., & Vlaeyen, J. W. S. (2011). The acquisition of fear of movement-related pain and associative learning: a novel pain-relevant human fear conditioning paradigm. *Pain*, 152(11), 2460–2469.
- Miron, D., Duncan, G. H., & Bushnell, M. C. (1989). Effects of attention on the intensity and unpleasantness of thermal pain. *Pain*, 39(3), 345–352.
- Mitchell, K. R., & White, R. G. (1977). Behavioral self-management: An application to the problem of migraine headaches. *Behavior Therapy*, 8(2), 213–221.
- Montgomery, G. H., DuHamel, K. N., & Redd, W. H. (2000). A meta-analysis of hypnotically induced analgesia: how effective is hypnosis? *The International Journal of Clinical and Experimental Hypnosis*, 48(2), 138–153.
- Morley, S., Eccleston, C., & Williams, A. (1999). Systematic review and meta-analysis of randomized controlled trials of cognitive behaviour therapy and behaviour therapy for chronic pain in adults, excluding headache. *Pain*, 80(1-2), 1–13.

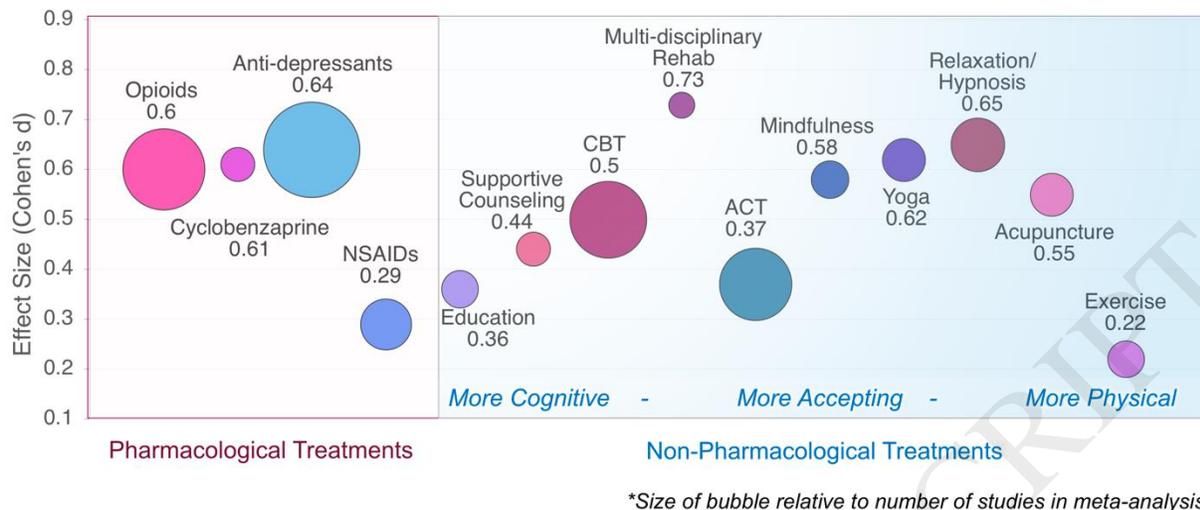
- Morone, N. E., Greco, C. M., & Weiner, D. K. (2008). Mindfulness meditation for the treatment of chronic low back pain in older adults: a randomized controlled pilot study. *Pain*, 134(3), 310–319.
- Muraven, M., Baumeister, R. F., & Tice, D. M. (1999). Longitudinal improvement of self-regulation through practice: building self-control strength through repeated exercise. *The Journal of Social Psychology*, 139(4), 446–457.
- Mutso, A. A., Radzicki, D., Baliki, M. N., Huang, L., Banisadr, G., Centeno, M. V., ... Apkarian, A. V. (2012). Abnormalities in hippocampal functioning with persistent pain. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, 32(17), 5747–5756.
- Nagy, A., Eöördegh, G., Paróczy, Z., Márkus, Z., & Benedek, G. (2006). Multisensory integration in the basal ganglia. *The European Journal of Neuroscience*, 24(3), 917–924.
- Napadow, V., LaCount, L., Park, K., As-Sanie, S., Clauw, D. J., & Harris, R. E. (2010). Intrinsic brain connectivity in fibromyalgia is associated with chronic pain intensity. *Arthritis and Rheumatism*, 62(8), 2545–2555.
- Northoff, G., Heinzl, A., de Greck, M., Bermpohl, F., Dobrowolny, H., & Panksepp, J. (2006). Self-referential processing in our brain--a meta-analysis of imaging studies on the self. *NeuroImage*, 31(1), 440–457.
- Ochsner, K. N., Bunge, S. A., Gross, J. J., & Gabrieli, J. D. E. (2002). Rethinking feelings: an fMRI study of the cognitive regulation of emotion. *Journal of Cognitive Neuroscience*, 14(8), 1215–1229.
- Ochsner, K. N., Ray, R. D., Cooper, J. C., Robertson, E. R., Chopra, S., Gabrieli, J. D. E., & Gross, J. J. (2004). For better or for worse: neural systems supporting the cognitive down- and up-regulation of negative emotion. *NeuroImage*, 23(2), 483–499.
- Ongghena, P., & Van Houdenhove, B. (1992). Antidepressant-induced analgesia in chronic non-malignant pain: a meta-analysis of 39 placebo-controlled studies. *Pain*, 49(2), 205–219.
- Otti, A., Guendel, H., Wohlschläger, A., Zimmer, C., & Noll-Hussong, M. (2013). Frequency shifts in the anterior default mode network and the salience network in chronic pain disorder. *BMC Psychiatry*, 13, 84.
- Peacock, S., & Patel, S. (2008). Cultural Influences on Pain. *Reviews in Pain*, 1(2), 6–9.
- Perlman, D. M., Salomons, T. V., Davidson, R. J., & Lutz, A. (2010). Differential effects on pain intensity and unpleasantness of two meditation practices. *Emotion*, 10(1), 65–71.
- Perry, K. N., Nicholas, M. K., & Middleton, J. W. (2010). Comparison of a pain management program with usual care in a pain management center for people with spinal cord injury-related chronic pain. *The Clinical Journal of Pain*, 26(3), 206–216.
- Peuterl, S., Diestl, I., Vansteenwegen, D., Berghl, O., & Vlaeyen, J. W. S. (2011). Understanding fear of pain in chronic pain: interoceptive fear conditioning as a novel approach. *European Journal of Pain*, 15(9), 889–894.
- Plenz, D., & Wickens, J. R. (2017). Chapter 6 - The Striatal Skeleton: Medium Spiny Projection Neurons and Their Lateral Connections. In H. Steiner & K. Y. Tseng (Eds.), *Handbook of Behavioral Neuroscience* (Vol. 24, pp. 121–136). Elsevier.
- Plews-Ogan, M., Owens, J. E., Goodman, M., Wolfe, P., & Schorling, J. (2005). A pilot study evaluating mindfulness-based stress reduction and massage for the management of chronic pain. *Journal of General Internal Medicine*, 20(12), 1136–1138.
- Pradhan, E. K., Baumgarten, M., Langenberg, P., Handwerker, B., Gilpin, A. K., Magyari, T., ... Berman, B. M. (2007). Effect of Mindfulness-Based Stress Reduction in rheumatoid arthritis patients. *Arthritis and Rheumatism*, 57(7), 1134–1142.

- Rauschecker, J. P., May, E. S., Maudoux, A., & Ploner, M. (2015). Frontostriatal Gating of Tinnitus and Chronic Pain. *Trends in Cognitive Sciences*, 19(10), 567–578.
- Ray, R. D., Ochsner, K. N., Cooper, J. C., Robertson, E. R., Gabrieli, J. D. E., & Gross, J. J. (2005). Individual differences in trait rumination and the neural systems supporting cognitive reappraisal. *Cognitive, Affective & Behavioral Neuroscience*, 5(2), 156–168.
- Reddan, M. C., & Wager, T. D. (2018). Modeling Pain Using fMRI: From Regions to Biomarkers. *Neuroscience Bulletin*, 34(1), 208–215.
- Reig, R., & Silberberg, G. (2014). Multisensory integration in the mouse striatum. *Neuron*, 83(5), 1200–1212.
- Ren, W., Centeno, M. V., Berger, S., Wu, Y., Na, X., Liu, X., ... Surmeier, D. J. (2016). The indirect pathway of the nucleus accumbens shell amplifies neuropathic pain. *Nature Neuroscience*, 19(2), 220–222.
- Rosenzweig, S., Greeson, J. M., Reibel, D. K., Green, J. S., Jasser, S. A., & Beasley, D. (2010). Mindfulness-based stress reduction for chronic pain conditions: variation in treatment outcomes and role of home meditation practice. *Journal of Psychosomatic Research*, 68(1), 29–36.
- Roy, M., Shohamy, D., Daw, N., Jepma, M., Wimmer, G. E., & Wager, T. D. (2014). Representation of aversive prediction errors in the human periaqueductal gray. *Nature Neuroscience*, 17(11), 1607–1612.
- Russo, A., Tessitore, A., Esposito, F., Marcuccio, L., Giordano, A., Conforti, R., ... Tedeschi, G. (2012). Pain processing in patients with migraine: an event-related fMRI study during trigeminal nociceptive stimulation. *Journal of Neurology*, 259(9), 1903–1912.
- Salsitz, E. A. (2016). Chronic Pain, Chronic Opioid Addiction: a Complex Nexus. *Journal of Medical Toxicology: Official Journal of the American College of Medical Toxicology*, 12(1), 54–57.
- Sandkühler, J. (2000). Learning and memory in pain pathways. *Pain*, 88(2), 113–118.
- Schmidt-Wilcke, T., Leinisch, E., Gänssbauer, S., Draganski, B., Bogdahn, U., Altmeyen, J., & May, A. (2006). Affective components and intensity of pain correlate with structural differences in gray matter in chronic back pain patients. *Pain*, 125(1-2), 89–97.
- Schneider, F., & Karoly, P. (1983). Conceptions of the pain experience: The emergence of multidimensional models and their implications for contemporary clinical practice. *Clinical Psychology Review*, 3(1), 61–86.
- Schütze, R., Rees, C., Preece, M., & Schütze, M. (2010). Low mindfulness predicts pain catastrophizing in a fear-avoidance model of chronic pain. *Pain*, 148(1), 120–127.
- Schwartz, N., Temkin, P., Juado, S., Lim, B.K., Heifets, B.D., Polepalli, J.S., Malenka, R.C. (2014). Chronic pain. Decreased motivation during chronic pain requires long-term depression in the nucleus accumbens. *Science* 345(6196):535-42.
- Schweikert, B., Jacobi, E., Seitz, R., Cziske, R., Ehlert, A., Knab, J., & Leidl, R. (2006). Effectiveness and cost-effectiveness of adding a cognitive behavioral treatment to the rehabilitation of chronic low back pain. *The Journal of Rheumatology*, 33(12), 2519–2526.
- Schweinhardt, P., Kuchinad, A., Pukall, C. F., & Bushnell, M. C. (2008). Increased gray matter density in young women with chronic vulvar pain. *Pain*, 140(3), 411–419.
- Seeley, W. W., Menon, V., Schatzberg, A. F., Keller, J., Glover, G. H., Kenna, H., ... Greicius, M. D. (2007). Dissociable intrinsic connectivity networks for salience processing and executive control. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, 27(9), 2349–2356.

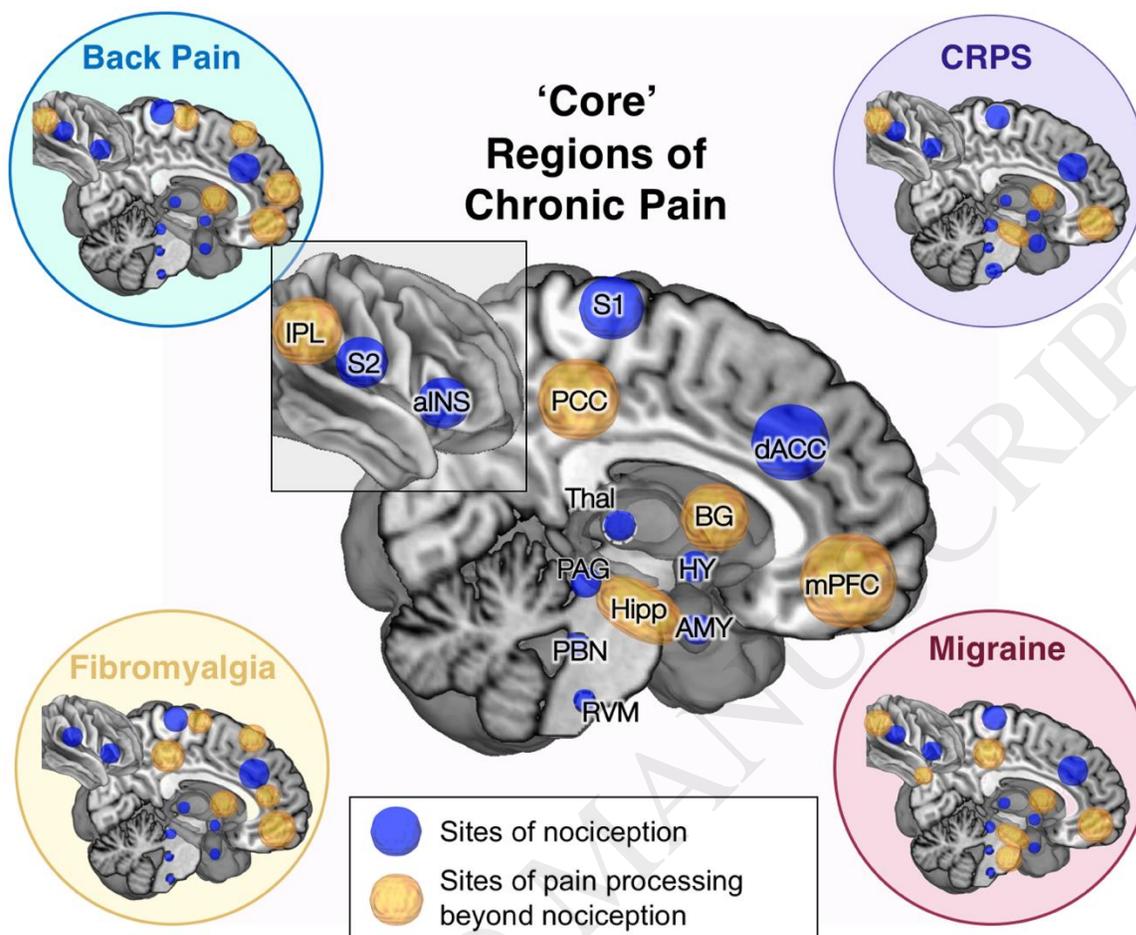
- Sephton, S. E., Salmon, P., Weissbecker, I., Ulmer, C., Floyd, A., Hoover, K., & Studts, J. L. (2007). Mindfulness meditation alleviates depressive symptoms in women with fibromyalgia: results of a randomized clinical trial. *Arthritis and Rheumatism*, 57(1), 77–85.
- Shpaner, M., Kelly, C., Lieberman, G., Perelman, H., Davis, M., Keefe, F. J., & Naylor, M. R. (2014). Unlearning chronic pain: A randomized controlled trial to investigate changes in intrinsic brain connectivity following Cognitive Behavioral Therapy. *NeuroImage. Clinical*, 5, 365–376.
- Smith, J. A., & Osborn, M. (2007). Pain as an assault on the self: An interpretative phenomenological analysis of the psychological impact of chronic benign low back pain. *Psychology & Health*, 22(5), 517–534.
- Sprenger, C., Eippert, F., Finsterbusch, J., Bingel, U., Rose, M., & Büchel, C. (2012). Attention modulates spinal cord responses to pain. *Current Biology: CB*, 22(11), 1019–1022.
- Staudinger, M. R., Erk, S., Abler, B., & Walter, H. (2009). Cognitive reappraisal modulates expected value and prediction error encoding in the ventral striatum. *NeuroImage*, 47(2), 713–721.
- Suls, J., & Fletcher, B. (1985). The relative efficacy of avoidant and nonavoidant coping strategies: a meta-analysis. *Health Psychology: Official Journal of the Division of Health Psychology, American Psychological Association*, 4(3), 249–288.
- Sundermann, B., Burgmer, M., Pogatzki-Zahn, E., Gaubitz, M., Stüber, C., Wessolleck, E., ... Pfliegerer, B. (2014). Diagnostic classification based on functional connectivity in chronic pain: model optimization in fibromyalgia and rheumatoid arthritis. *Academic Radiology*, 21(3), 369–377.
- Suzuki, R., Rygh, L. J., & Dickenson, A. H. (2004). Bad news from the brain: descending 5-HT pathways that control spinal pain processing. *Trends in Pharmacological Sciences*, 25(12), 613–617.
- Tagliazucchi, E., Balenzuela, P., Fraiman, D., & Chialvo, D. R. (2010). Brain resting state is disrupted in chronic back pain patients. *Neuroscience Letters*, 485(1), 26–31.
- Tang, Y.-Y., Ma, Y., Wang, J., Fan, Y., Feng, S., Lu, Q., ... Posner, M. I. (2007). Short-term meditation training improves attention and self-regulation. *Proceedings of the National Academy of Sciences of the United States of America*, 104(43), 17152–17156.
- Taschereau-Dumouchel, V., Cortese, A., Chiba, T., Knotts, J. D., Kawato, M., & Lau, H. (2018). Towards an unconscious neural reinforcement intervention for common fears. *Proceedings of the National Academy of Sciences of the United States of America*, 115(13), 3470–3475.
- Tofferi, J. K., Jackson, J. L., & O'malley, P. G. (2004). Treatment of fibromyalgia with cyclobenzaprine: A meta-analysis. *Arthritis Care & Research*, 51(1), 9–13.
- Tracey, I. (2010). Getting the pain you expect: mechanisms of placebo, nocebo and reappraisal effects in humans. *Nature Medicine*, 16(11), 1277–1283.
- Trescot, A. M., Glaser, S. E., Hansen, H., Benyamin, R., Patel, S., & Manchikanti, L. (2008). Effectiveness of opioids in the treatment of chronic non-cancer pain. *Pain Physician*, 11(2 Suppl), S181–S200.
- Turk, D. C., & Genest, M. (1979). 9 - Regulation of Pain: The Application of Cognitive and Behavioral Techniques for Prevention and Remediation. In *Cognitive-Behavioral Interventions* (pp. 287–318). Academic Press.
- Turk, D. C., Meichenbaum, D., & Genest, M. (1983). *Pain and Behavioral Medicine: A Cognitive-Behavioral Perspective*. Guilford Press.
- Turner, J. A., & Chapman, C. R. (1982). Psychological interventions for chronic pain: a critical review. II. Operant conditioning, hypnosis, and cognitive-behavioral therapy. *Pain*, 12(1), 23–46.

- Villemure, C., & Bushnell, M. C. (2002). Cognitive modulation of pain: how do attention and emotion influence pain processing? *Pain*, 95(3), 195–199.
- Vlaeyen, J. W., Kole-Snijders, A. M., Boeren, R. G., & van Eek, H. (1995). Fear of movement/(re)injury in chronic low back pain and its relation to behavioral performance. *Pain*, 62(3), 363–372.
- Vlaeyen, J. W. S., Crombez, G., & Linton, S. J. (2016). The fear-avoidance model of pain. *Pain*, 157(8), 1588–1589.
- Volkow, N. D., & Collins, F. S. (2017). The Role of Science in Addressing the Opioid Crisis. *The New England Journal of Medicine*, 377(4), 391–394.
- Wager, T. D. (2005). Expectations and anxiety as mediators of placebo effects in pain. *Pain*, 115(3), 225–226.
- Wager, T. D., & Atlas, L. Y. (2015). The neuroscience of placebo effects: connecting context, learning and health. *Nature Reviews. Neuroscience*, 16(7), 403–418.
- Wager, T. D., Atlas, L. Y., Lindquist, M. A., Roy, M., Woo, C.-W., & Kross, E. (2013). An fMRI-based neurologic signature of physical pain. *The New England Journal of Medicine*, 368(15), 1388–1397.
- Wager, T. D., Davidson, M. L., Hughes, B. L., Lindquist, M. A., & Ochsner, K. N. (2008). Neural mechanisms of emotion regulation: evidence for two independent prefrontal-subcortical pathways. *Neuron*, 59(6), 1037.
- Wertli, M. M., Burgstaller, J. M., Weiser, S., Steurer, J., Kofmehl, R., & Held, U. (2014). Influence of catastrophizing on treatment outcome in patients with nonspecific low back pain: a systematic review. *Spine*, 39(3), 263–273.
- Wertli, M. M., Rasmussen-Barr, E., Weiser, S., Bachmann, L. M., & Brunner, F. (2014). The role of fear avoidance beliefs as a prognostic factor for outcome in patients with nonspecific low back pain: a systematic review. *The Spine Journal: Official Journal of the North American Spine Society*, 14(5), 816–836.e4.
- Woo, C.-W., Roy, M., Buhle, J. T., & Wager, T. D. (2015). Distinct Brain Systems Mediate the Effects of Nociceptive Input and Self-Regulation on Pain. *PLoS Biology*, 13(1), e1002036.
- Woo, C.-W., Chang, L. J., Lindquist, M. A., & Wager, T. D. (2017). Building better biomarkers: brain models in translational neuroimaging. *Nat Neurosci*, 20(3), 365–377. doi:10.1038/nn.4478
- Young Casey, C., Greenberg, M. A., Nicassio, P. M., Harpin, R. E., & Hubbard, D. (2008). Transition from acute to chronic pain and disability: a model including cognitive, affective, and trauma factors. *Pain*, 134(1–2), 69–79.
- Zaman, J., Vlaeyen, J. W. S., Van Oudenhove, L., Wiech, K., & Van Diest, I. (2015). Associative fear learning and perceptual discrimination: a perceptual pathway in the development of chronic pain. *Neuroscience and Biobehavioral Reviews*, 51, 118–125.
- Zautra, A. J., Davis, M. C., Reich, J. W., Nicassario, P., Tennen, H., Finan, P., ... Irwin, M. R. (2008). Comparison of cognitive behavioral and mindfulness meditation interventions on adaptation to rheumatoid arthritis for patients with and without history of recurrent depression. *Journal of Consulting and Clinical Psychology*, 76(3), 408–421.
- Zeidan, F., Martucci, K. T., Kraft, R. A., Gordon, N. S., McHaffie, J. G., & Coghill, R. C. (2011). Brain mechanisms supporting the modulation of pain by mindfulness meditation. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, 31(14), 5540–5548.
- Zeidan, F., & Vago, D. R. (2016). Mindfulness meditation-based pain relief: a mechanistic account. *Annals of the New York Academy of Sciences*, 1373(1), 114–127.

ACCEPTED MANUSCRIPT

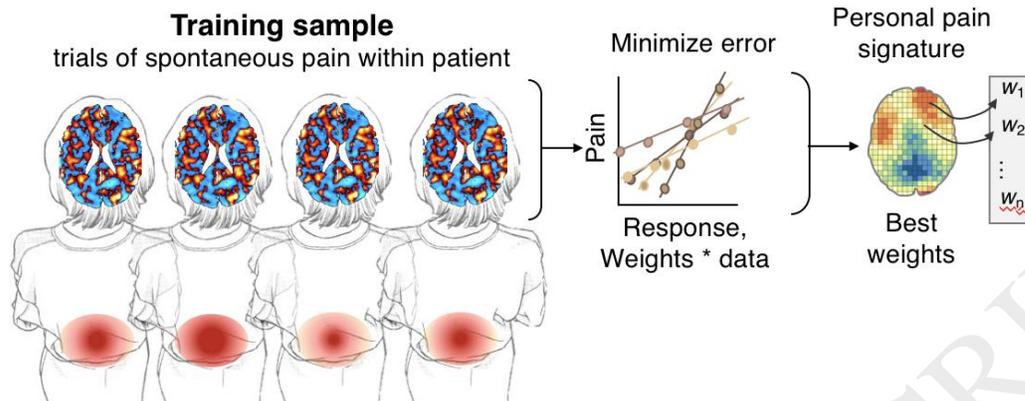


**Figure 1. Effect Sizes of Chronic Pain Treatments on Pain Reports.** Several meta-analyses of controlled studies for different treatments of various types of chronic pain were selected. The effect size (Cohen's  $d$ ), of the treatment effect is plotted here. Sizes of the bubbles indicate the number of studies included in the meta-analysis, therefore, larger bubbles are likely to be more reliable than smaller bubbles. Treatments are arranged from left to right where the left, in the pink box, are pharmacological treatments (effect sizes relative to placebo), while the right, in the blue box, are non-pharmacological treatments. Non-pharmacological treatments refer to self-regulation techniques that include cognitive-based, acceptance-based, and physical activity-based strategies in varying degrees. The largest effect size ( $d = 0.73$ ) in this comparison was for a multi-disciplinary rehabilitation program for chronic lower back pain patients compared to a usual care control. The multidisciplinary rehabilitation in this meta-analysis was defined according to the biopsychosocial model of pain; a study was eligible for inclusion if the multidisciplinary intervention involved a physical component and a psychological (i.e., CBT or ACT) or a social/work component (Kamper et al, 2015). Please see Supplementary Table 1 for more details on the meta-analyses included. Further investigation is needed to better compare the durability of these effects in relation to disease progression.

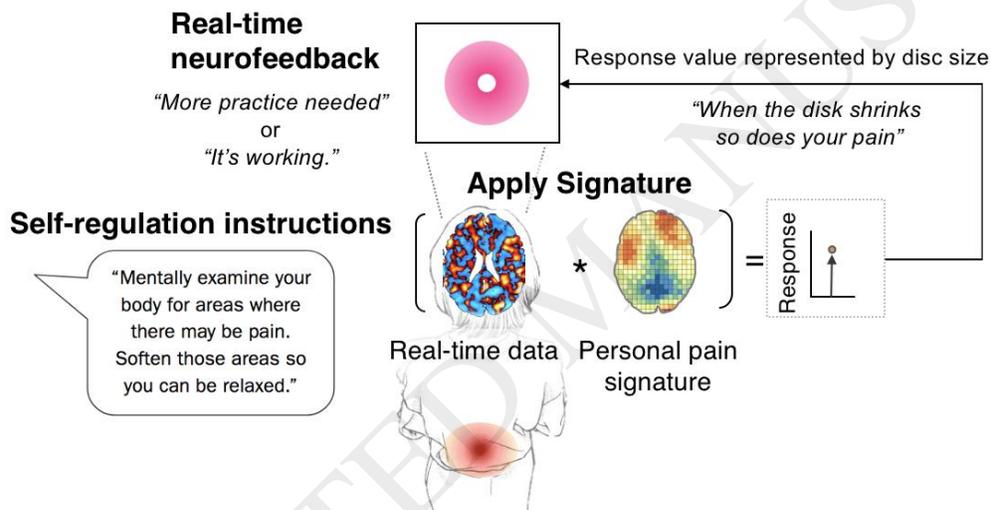


**Figure 2. Chronic pain brain representations are heterogeneous but may share a 'core' network.** *Top Left.* The brain regions implicated in the experience of chronic back pain (Baliki et al., 2006, 2008, 2011, 2014; Callan et al., 2014; Loggia et al., 2015). *Top Right.* Brain regions implicated in pain experiencing in CRPS patients relative to controls (Azqueta-Gavaldon et al., 2016; Schwartzman et al., 2006; Baliki et al., 2012; Geha et al., 2007). *Bottom Left.* Brain regions implicated in fibromyalgia pain experiencing relative to controls (Napadow et al., 20120; Harris et al., 2009; Schmidt-Wilcke et al., 2007). *Bottom Right.* Brain regions implicated in the experience of migraine headaches in chronic migraine patients relative to baseline. (Maleki et al., 2011; 2012; Russo et al., 2012; Grazi et al., 2010; Welch et al., 2001; Caso et al., 2002; Schwedt & Dodick, 2009). *Center.* 'Core' Regions of Chronic Pain. Despite the heterogeneity in the brain representations of different chronic pain pathologies, some regions are consistently implicated across diseases. These include, sites of nociception (in blue) such as the thalamus (Thal), dACC, S1, SII, and the anterior insula (aINS), as well as sites of pain-related pain processing beyond nociception (yellow) such as the hippocampus (Hipp), medial prefrontal cortex (mPFC), basal ganglia (BG), posterior cingulate cortex (PCC), and inferior parietal lobule (IPL). Both functional and morphological studies were surveyed to make this diagram.

### Session 1: Develop personalized pain signature



### Session 2: Self-regulation training with real-time personalized neurofeedback



**Figure 3. Towards self-regulation training that targets personal experiences of pain.** A proposed framework for studying the effects of self-regulation training on spontaneous chronic pain intensity. *Top Panel:* Whole brain multivariate fMRI patterns of brain activity can be recorded from a patient across many trials of spontaneous pain. Participant self-reports of the intensity of their pain can be used to train a personalized brain-based biomarker of chronic pain within that individual. *Bottom Panel:* A participant can practice various self-regulation strategies, such as mindfulness, while their brain activity is recorded. As they practice, real-time feedback on the expression of their personalized pain signature can be displayed in various formats, such as a disc that shrinks as 'pain,' determined by their brain activity, decreases.

**Table 1. Functional Taxonomy of Pain Self-Regulation Strategies**

<b>Category</b>	<b>Description</b>	<b>Related clinical treatments</b>
Reappraisal-based strategies	Focused attention to sensations, conscious modification of the meaning of sensation	Cognitive Behavioral Therapy (CBT)
Acceptance-based strategies	Focused attention to sensations without appraisal	Mindfulness meditation Yoga Acceptance and Commitment Therapy (ACT)
Attention-based strategies	Removal of attention from bodily sensations	Distraction, working memory tasks, engagement with external task/stimuli

**Table 2. Reported evidence of changes to resting-state networks across chronic pain pathologies relative to healthy controls.**

Pathology	Default Mode Network	Saliency Network	Sensorimotor Network
Chronic back pain	altered <sup>1,2,3,4,5,22</sup>	altered <sup>24</sup>	altered <sup>5,24</sup>
Arthritis	altered <sup>4,6,7,8</sup>	altered <sup>6,7</sup>	altered <sup>20</sup>
Fibromyalgia	altered <sup>9,10,11</sup>	altered <sup>9,6</sup>	altered <sup>17</sup>
CRPS	altered <sup>12,4</sup>		altered <sup>12</sup>
Chronic pelvic pain	altered <sup>13</sup>		altered <sup>18</sup>
Migraine	altered <sup>14</sup>	altered <sup>14</sup>	
Diabetic neuropathic pain		altered <sup>19</sup>	
Idiopathic temporomandibular disorder	altered <sup>15</sup>		
Chronic orofacial pain	altered <sup>21</sup>		
Burning Mouth	altered <sup>23</sup>		
Phantom pain	altered <sup>16</sup>		altered <sup>16</sup>
<sup>1</sup> Baliki et al 2008, <sup>2</sup> Tagliazucchi et al 2010, <sup>3</sup> Ceko et al 2015, <sup>4</sup> Baliki et al 2014, <sup>5</sup> Mano et al 2018, <sup>6</sup> Sundermann et al 2014, <sup>7</sup> Hemington et al, 2016, <sup>8</sup> Hemington et al, 2018, <sup>9</sup> Napadow et al, 2010, <sup>10</sup> Ichesco et al, 2014, <sup>11</sup> Sundermann et al, 2017, <sup>12</sup> Bolwerk et al, 2013, <sup>13</sup> Martucci et al, 2016, <sup>14</sup> Hubbar et al, 2014, <sup>15</sup> Kucyi et al., 2014, <sup>16</sup> Makin et al, 2015, <sup>17</sup> Kim et al., 2013, <sup>18</sup> Kilpatrick et al, 2014, <sup>19</sup> Cauda et al., 2010, <sup>20</sup> Flodin et al., 2016, <sup>21</sup> Alshelh et al., 2018, <sup>22</sup> Loggia et al, 2013, <sup>23</sup> Shariq et al, 2014, <sup>24</sup> Kolesar et al., 2017			

**Table 2. Reported evidence of changes to resting-state networks across chronic pain pathologies relative to healthy controls.** A report of all studies to date (to our knowledge) that report alterations to the ‘default mode,’ ‘saliency,’ or ‘sensorimotor’ networks in patients with different types of chronic pain. Alterations are not reducible to increases or decreases in relation to pain across studies as there may be increases between two regions and decreases between two others within one network, so for brevity, this chart only indicates if any changes relative to neurotypicals were found. This chart includes functional as well as structural findings.