Review article

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

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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 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.

1. Introduction

Pain is a multidimensional experience, often described in terms of sensory-discriminative, cognitive-evaluative, and affective-motivational components [1,2]. These three categories encompass a variety of processes, including nociception [3], attention [4,5], learning [6], memory [7,8], expectation [9,10], personality [11], culture [12–14], socioeconomic conditions [15–17], and more. When peripheral nociceptive information enters the cortex, the signal becomes integrated with complex multidimensional information and is modified via descending projections [18–21]. 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 [22,23].

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 ([24–26]; Mischel, Cantor, & Feldman, 1996).

The exploration of nonpharmacological treatments for chronic pain is important. Opioids, though effective in the short term, may not provide long-term pain relief [27–29]. Furthermore, opioids are prone to abuse [30,31]. Aberrant addiction-like behaviors develop in approximately 24% of cases of chronic back pain patients prescribed opioids [32,33]. There is also a growing epidemic of opioid abuse and opioid-related death in Western countries [34,35], which can sometimes be localized to neighborhoods surrounding opioid-prescribing physicians [36]. Therefore, it is critical for scientists to prioritize investigations of non-opioid, 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 [37] is comparable to both cyclobenzaprine (a 5-HT2A antagonist, pro-adrenargic muscle relaxant [38];) and antidepressants [39]. Furthermore, nonpharmacological treatments of chronic pain, such as mindfulness [40], hypnosis [41,42], yoga [43], and combinations of psychological and physical treatment programs (biopsychosocial multidisciplinary rehabilitation [44];) produce pain-reducing effects comparable to that of opioids (Fig. 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

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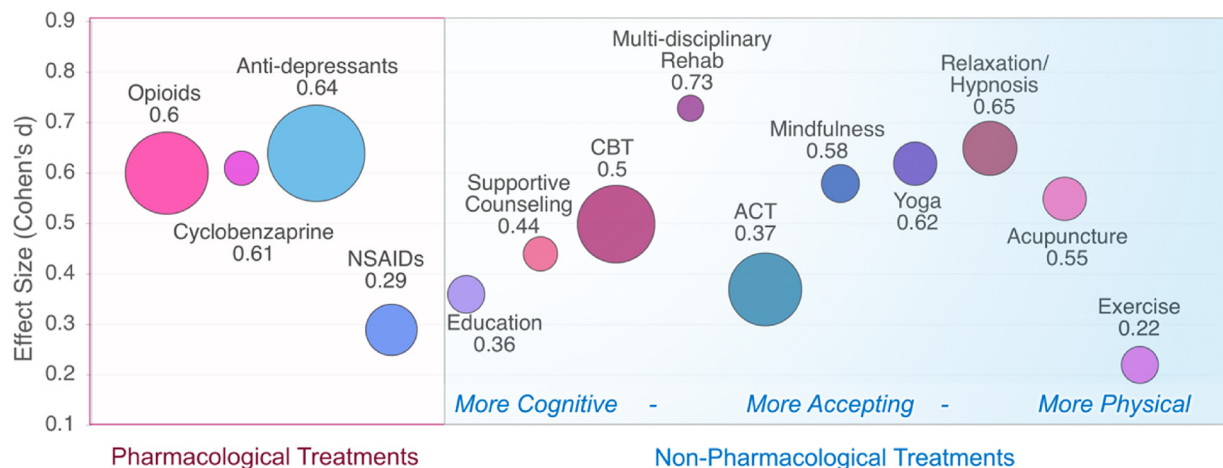
Fig. 1. Effect Sizes of Chronic Pain Treatments on Pain Reports. Several meta-analyses of controlled studies for different treatments of various types of chronic pain were selected. The effect size (Cohen's *d*), of the treatment effect is plotted here. Sizes of the bubbles indicate the number of studies 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 box, are pharmacological treatments (effect sizes relative to placebo), while the right 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 [44]. 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.

targeted by self-regulatory strategies that alter evaluative (i.e., re-appraisal-based strategies) and self-referential processes (i.e., acceptance-based strategies), respectfully.

1.1. 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 [45].

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 [46]. 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 [47–50]. 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 [51], and the pons as related to spontaneous migraine experiencing [52], migraine severity [53], and migraine-related changes in morphology [54]. In phantom pain, pain may be best explained by persistent local cortical representations in S1 [55] or maladaptive cortical reorganization [56]. 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 (Fig. 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 [57]. 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; [58]), 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 ([59–61,1],). 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 [46] nor does activity in these regions predict back pain chronification [62]. The region most heavily implicated in pain chronification is the vmPFC, which changes from being anti-correlated with pain in healthy participants [63] to being positively associated with pain in several patient groups [48–50].

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 [6,64–66]. 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 [67].

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 [68]. 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 [69,70]. One patient's testimony of their experience living with chronic pain elucidates this point:
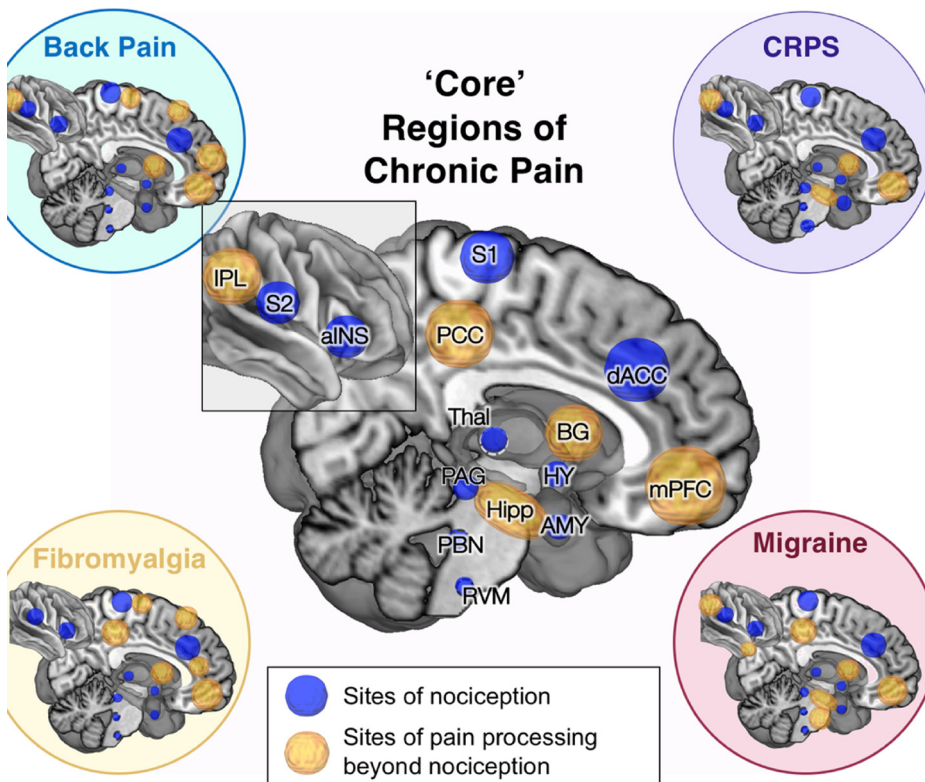
Fig. 2. Chronic pain brain representations are heterogeneous but may share a 'core' network. *Top Left.* The brain regions implicated in the experience of chronic back pain ([46], [205], [134], [206]; [208]; Loggia et al., 2015). *Top Right.* Brain regions implicated in pain experiencing in CRPS patients relative to controls ([204]; [220] [62,211];). *Bottom Left.* Brain regions implicated in fibromyalgia pain experiencing relative to controls ([50]; [48] [219];). *Bottom Right.* Brain regions implicated in the experience of migraine headaches in chronic migraine patients relative to baseline. ([216]; 2012; [53]; Grazzi et al., 2010; Welch et al., 2001; [51]; 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 (dark grey) such as the thalamus (Thal), dACC, SI, SII, and the anterior insula (aINS), as well as sites of pain-related pain processing beyond nociception (light grey) 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.

Table 1
Functional Taxonomy of Pain Self-Regulation Strategies.

Category	Description	Related clinical treatments
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

"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).

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 [71]. 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.

2. Pain self-regulation

Self-regulation encompasses a wide variety of strategies for deploying conscious thought to shape attention, emotion, decision-making, and behavior [24–26]; Mischel, Cantor, & Feldman, 1996). It has been proven to be effective for the attenuation of both experimental pain [72] and chronic pain [73–77]. Furthermore, it is a feasible option for long-term treatment because it is a free, learnable skill set that can be improved with practice [25,78,79]. When practiced effectively, self-regulatory strategies can reduce reliance on drugs, surgery, and other high-cost and high-risk treatments [80–82]. 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 [83]. Here we identify three categories of self-regulatory strategies with the potential to alter the neural substrate underlying chronic pain: (1) reappraisal-based [84], (2) acceptance-based [85], and (3) attention-based [86] 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 [87,88]. 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; [89–91]; 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 [92–95]. 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 [96,97]. 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 [98–100]; however, it may not be sustainable when pain is chronic [101,102]. Furthermore, there is evidence that distraction from chronic pain during pain-inducing activity has a paradoxical effect of increasing pain immediately after the task [103]. Therefore, we focus here on reappraisal- and acceptance-based strategies.

2.1. Reappraisal-based strategies

2.1.1. 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 [104,105]. CBT is reportedly efficacious for the treatment of pain and stress-related disorders [77,106–109] with treatment effects greater than some drugs and other education-based therapies (see Fig. 1). For example, CBT has been shown to provide pain relief from headaches [110,111], and its protective effects last through six- to nine-week follow up periods [112,113]. 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 [106]. 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 in-patient rehabilitation program had 5.4% fewer work absences six months later than those who received usual care alone [114].

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 [115–117], 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 [77,118,119]. Pain catastrophizing is a key feature of the Fear-Avoidance Model of Pain, which describes two paths for patients after an injury [120–123]. 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 [124–126]. 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 [120].

2.1.2. Brain targets of reappraisal strategies

The basal ganglia (BG) is a crucial structure for both valuation (for a review [127]) and multisensory integration [128,129] implicated in both pain experiencing [130] and emotion reappraisal [131]. There is evidence that thalamo-cortico-BG loops integrate sensorimotor, affective, and cognitive information into the pain experience [130,132,133], 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 [134] and rats (Metz, Yau, Centeno, Apkarian, & Martina, 2009; [135]) 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 [62], and the strength of mPFC-NAc connectivity is correlated with a "shift" in the neural representation of back pain from primarily nociceptive to emotion processing brain regions [57].

In a rat model of neuropathic pain [136], 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 [137]. 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 [136]. 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 [138,139]. 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 [140]. It also decreases activity in limbic regions, particularly the amygdala [141–143,88], which may be associated with individual differences in rumination [144]. Using a mediation analysis, Wager et al. [131] 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. [131] 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 [91]. In animals, stimulation of the PFC can inhibit both sensory and affective pain signals [145] via descending projections to the striatum [146,147], amygdala [148], brainstem, and spinal cord [149]. 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.

2.2. Acceptance-based strategies

2.2.1. 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 [150–152]. 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 [153]. 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 [154–156]. Compared to rest, however, the act of meditation can reduce both pain unpleasantness and intensity ratings to acute noxious stimulations [157].

Mindfulness interventions have been effective for patients with fibromyalgia [158–160], musculoskeletal pain [161,162], rheumatoid arthritis [163,164], and headache (Nash-Mc Feron 2005); however 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 [165]. Still, mindfulness is reported to have a significant impact on distress, depression, and other affective dimensions of the pain experience [166], and in some cases it is more effective for long-term pain management than CBT or usual care [152]. Mindfulness may work by reducing distracting and ruminative thoughts [167]. Other potential psychological mechanisms are meta-awareness, the bringing to consciousness 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. [168] 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.

2.2.2. 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 [169,170]. 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 [157,170–172]. Experienced mindfulness meditators also demonstrate differences in default mode network (DMN) activity [173]. Core regions of the DMN include the mPFC, PCC, angular gyrus, lateral temporal cortex, hippocampus, parahippocampus. and inferior parietal lobule (IPL [174];). 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 [174,175]. It becomes deactivated when an individual's attention is directed toward external tasks [176]. Accumulating evidence suggests that the DMN is critical for self-referential processing [177–180].

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 [181]. 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 [182,183]. Indeed, increased DMN activity in chronic pain is correlated with increased rumination and pain-related depression [181,184,185]. 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

Table 2

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

Pathology	Default Mode Network	Salience Network	Sensorimotor Network
Chronic back pain	altered[1,2,3,4,5,22]	altered[24]	altered[5,24]
Arthritis	altered[4,6,7,8]	altered[6,7]	altered[20]
Fibromyalgia	altered[9,10,11]	altered[9,6]	altered[17]
CRPS	altered[12,4]		altered[12]
Chronic pelvic pain	altered[13]		altered[18]
Migraine	altered[14]	altered[14]	
Diabetic neuropathic pain		altered[19]	
Idiopathic temporomandibular disorder	altered[15]		
Chronic orofacial pain	altered[21]		
Burning Mouth	altered[23]		
Phantom pain	altered[16]		altered[16]

[1] [205], [2] [222], [3]Ceko et al 2015, [4] [206], [5] [217], [6] [221], [7] [191], [8] [194], [9] [50], [10] [212], [11] [221], [12] [207], [13] [218], [14]Hubbar et al, 2014, [15] [184], [16] [215], [17] [214], [18] [213], [19] [209], [20] [210], [21]Alshelh et al., 2018, [22]Loggia et al, 2013, [23]Shariq et al, 2014, [24]Kolesar et al., 2017.
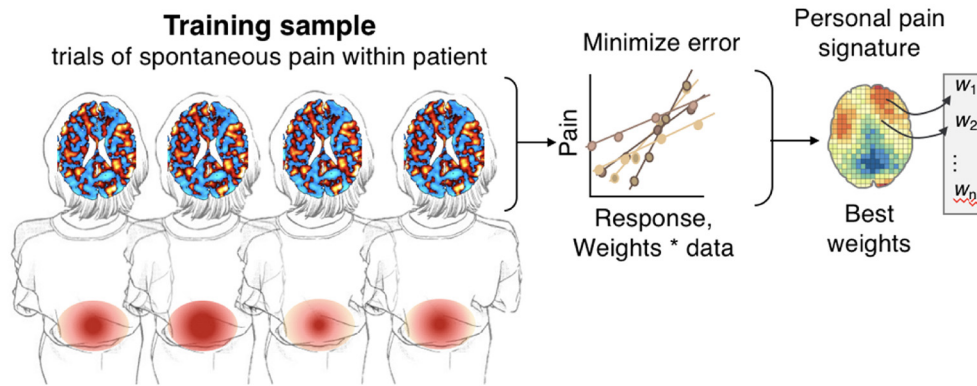A list of all studies to date (to our knowledge) that report alterations to the 'default mode,' 'salience,' or 'sensorimotor' networks in patients with different types of chronic pain. Alterations are not reducible to increases or decreases in relation to pain across studies as there may be increases 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.

network (or 'ventral attention' network) is to identify the most relevant internal and external stimuli [186]. It is comprised of the ventrolateral PFC, anterior insula, ACC [187], as well as subcortical structures including the amygdala and BG [188,189]. The 'salience network' may influence activation in the DMN by aiding in the 'switching' between intrinsic and extrinsic loci of attention [190]. Greater connectivity between the DMN and the salience network may be related to increased disease activity and clinical pain in chronic pain patients [191]. The 'sensorimotor' or 'somatomotor' network primarily integrates information about bodily action and sensation, and involves the primary somatosensory and motor cortices [187,192]. 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 [191].

Normally, the DMN is anti-correlated with the 'salience network,' and has no strong relationship with the 'sensorimotor network' [176,193]. 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 [191,194]. Hemington et al. [194] 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 [195]. 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
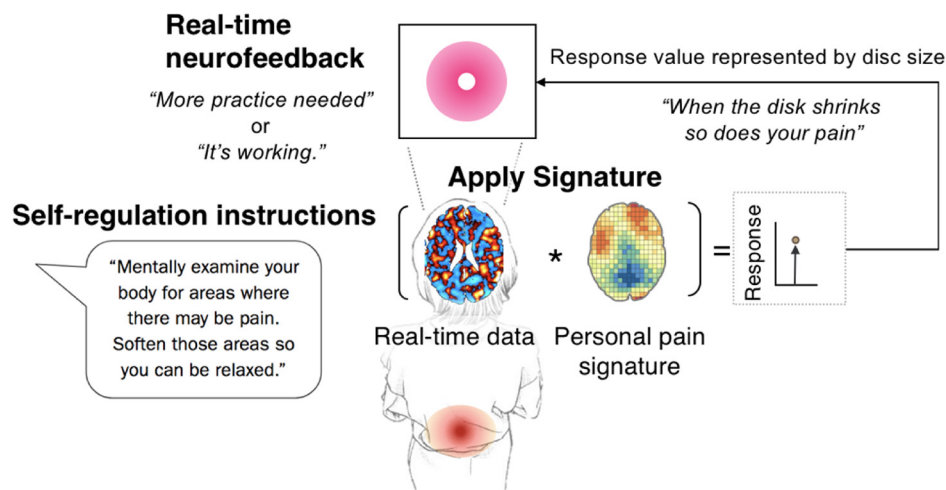
Fig. 3. Towards self-regulation training that targets personal experiences of pain. A proposed framework for studying the effects of self-regulation training on spontaneous chronic pain intensity. *Top Panel:* Whole brain multivariate fMRI patterns of brain activity can be recorded from a patient across may 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.

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 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.

2.3. Towards personalized models of pain experience

The earlier discussion of the heterogeneity of pain experiencing suggests that no two chronic pain conditions are the same, 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 [196–198] 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 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 [199]. 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 Fig. 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 [200]). In this way, a patient could learn through

trial and error what self-regulation strategies work best for them.

3. 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 [201]. 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 is 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 treatFment programs.

References

[1] R. Melzack, Pain and the neuromatrix in the brain, J. Dent. Educ. 65 (12) (2001) 1378–1382.

[2] D. Albe-Fessard, K.J. Berkley, L. Kruger, H.J. Ralston 3rd, W.D. Willis Jr., Diencephalic mechanisms of pai sensation, Brain Res. 356 (3) (1985) 217–296.

[3] J.N. Campbell, R.A. Meyer, Mechanisms of neuropathic pain, Neuron 52 (1) (2006) 77–92.

[4] C. Villemure, M.C. Bushnell, Cognitive modulation of pain: how do attention and emotion influence pain processing? Pain 95 (3) (2002) 195–199.

[5] C. Eccleston, G. Crombez, Pain demands attention: a cognitive-affective model of the interruptive function of pain, Psychol. Bull. 125 (3) (1999) 356–366.

[6] A.R. Mansour, M.A. Farmer, M.N. Baliki, A.V. Apkarian, Chronic pain: the role of learning and brain plasticity, Restor. Neurol. Neurosci. 32 (1) (2014) 129–139.

[7] J. Sandkühler, Learning and memory in pain pathways, Pain 88 (2) (2000) 113–118.

[8] A.A. Mutso, D. Radzicki, M.N. Baliki, L. Huang, G. Banisadr, M.V. Centeno, et al., Abnormalities in hippocampal functioning with persistent pain, J. Neurosci. 32 (17) (2012) 5747–5756.

[9] T. Koyama, J.G. McHaffie, P.J. Laurienti, R.C. Coghill, The subjective experience of pain: where expectations become reality, Proc. Natl. Acad. Sci. 102 (36) (2005) 12950–12955.

[10] L.Y. Atlas, T.D. Wager, How expectations shape pain, Neurosci. Lett. 520 (2) (2012) 140–148.

[11] S.J. Linton, A review of psychological risk factors in back and neck pain, Spine 25 (9) (2000) 1148–1156.

[12] S. Peacock, S. Patel, Cultural influences on pain, Rev. Pain 1 (2) (2008) 6–9.

[13] S.R. Anderson, E.A. Reynolds Losin, A sociocultural neuroscience approach to pain, Cult. Brain 5 (1) (2016) 14–35.

[14] E.A.R. Losin, E.A. Reynolds Losin, C.-W. Woo, A. Krishnan, T.D. Wager, M. Iacoboni, M. Dapretto, Brain and psychological mediators of imitation: sociocultural versus physical traits, Cult. Brain 3 (2) (2015) 93–111.

[15] J.O. Christensen, S. Knardahl, Work and neck pain: a prospective study of psychological, social, and mechanical risk factors, Pain 151 (1) (2010) 162–173.

[16] J.N. Katz, Lumbar disc disorders and low-back pain: socioeconomic factors and consequences, J. Bone Joint Surg. Am. 88 (Suppl 2) (2006) 21–24.

[17] M. Fuentes, T. Hart-Johnson, C.R. Green, The association among neighborhood socioeconomic status, race and chronic pain in black and white older adults, J. Med. Assoc. 99 (10) (2007) 1160–1169.

[18] A.-K. Bräscher, S. Becker, M.-E. Hoeppli, P. Schweinhardt, Different brain circuitries mediating controllable and uncontrollable pain, J. Neurosci. 36 (18) (2016) 5013–5025.

[19] R. Suzuki, L.J. Rygh, A.H. Dickenson, Bad news from the brain: descending 5-HT pathways that control spinal pain processing, Trends Pharmacol. Sci. 25 (12) (2004) 613–617.

[20] T.D. Wager, L.Y. Atlas, The neuroscience of placebo effects: connecting context, learning and health, Nat. Rev. Neurosci. 16 (7) (2015) 403–418.

[21] R.C. Coghill, Individual differences in the subjective experience of pain: new insights into mechanisms and models, Headache 50 (9) (2010) 1531–1535.

[22] B. Darnall, To treat pain, study people in all their complexity, Nature 557 (7703) (2018) 7.

[23] R.J. Gatchel, Y.B. Peng, M.L. Peters, P.N. Fuchs, D.C. Turk, The biopsychosocial approach to chronic pain: scientific advances and future directions, Psychol. Bull. 133 (4) (2007) 581–624.

[24] P. Karoly, Mechanisms of self-regulation: a systems view, Annu. Rev. Psychol. 44 (1) (1993) 23–52.

[25] M. Boekaerts, P.R. Pintrich, M. Zeidner, Handbook of Self-Regulation, Academic Press, 2005.

[26] T.F. Heatherton, Neuroscience of self and self-regulation, Annu. Rev. Psychol. 62 (2011) 363–390.

[27] L.F. Chu, M.S. Angst, D. Clark, Opioid-induced hyperalgesia in humans: molecular mechanisms and clinical considerations, Clin. J. Pain 24 (6) (2008) 479–496.

[28] A.M. Trescot, S.E. Glaser, H. Hansen, R. Benyamin, S. Patel, L. Manchikanti, Effectiveness of opioids in the treatment of chronic non-cancer pain, Pain Phys. 11 (2 Suppl) (2008) S181–S200.

[29] B.J. Collett, Opioid tolerance: the clinical perspective, Br. J. Anaesth. 81 (1) (1998) 58–68.

[30] W.M. Compton, N.D. Volkow, Major increases in opioid analgesic abuse in the United States: concerns and strategies, Drug Alcohol Depend. 81 (2) (2006) 103–107.

[31] J.C. Ballantyne, K.S. LaForge, Opioid dependence and addiction during opioid treatment of chronic pain, Pain 129 (3) (2007) 235–255.

[32] B.A. Martell, P.G. O'Connor, R.D. Kerns, W.C. Becker, K.H. Morales, T.R. Kosten, D.A. Fiellin, Systematic review: opioid treatment for chronic back pain: prevalence, efficacy, and association with addiction, Ann. Intern. Med. 146 (2) (2007) 116–127.

[33] E.A. Salsitz, Chronic pain, chronic opioid addiction: a complex Nexus, J. Med. Toxicol. 12 (1) (2016) 54–57.

[34] A. Kolodny, D.T. Courtwright, C.S. Hwang, P. Kreiner, J.L. Eadie, T.W. Clark, G.C. Alexander, The prescription opioid and heroin crisis: a public health approach to an epidemic of addiction, Annu. Rev. Public Health 36 (2015) 559–574.

[35] N.D. Volkow, F.S. Collins, The role of science in addressing the opioid crisis, N. Engl. J. Med. 377 (4) (2017) 391–394.

[36] I.A. Dhalla, M.M. Mamdani, T. Gomes, D.N. Juurlink, Clustering of opioid prescribing and opioid-related mortality among family physicians in Ontario, Can. Fam. Phys. 57 (3) (2011) e92–e96.

[37] A.D. Furlan, J.A. Sandoval, A. Mailis-Gagnon, E. Tunks, Opioids for chronic non-cancer pain: a meta-analysis of effectiveness and side effects, CMAJ: Canadian Medical Association Journal = Journal de l'Association Medicale Canadienne 174 (11) (2006) 1589–1594.

[38] J.K. Tofferi, J.L. Jackson, P.G. O'malley, Treatment of fibromyalgia with cyclobenzaprine: a meta-analysis, Arthritis Care Res. (Hoboken) 51 (1) (2004) 9–13.

[39] P. Onghena, B. Van Houdenhove, Antidepressant-induced analgesia in chronic non-malignant pain: a meta-analysis of 39 placebo-controlled studies, Pain 49 (2) (1992) 205–219.

[40] F.L.M. Bawa, S.W. Mercer, R.J. Atherton, F. Clague, A. Keen, N.W. Scott, C.M. Bond, Does mindfulness improve outcomes in patients with chronic pain? Systematic review and meta-analysis, Br. J. Gen. Pract. J. R. Coll. Gen. Pract. 65 (635) (2015) e387–e400.

[41] E.C. Devine, Meta-analysis of the effect of psychoeducational interventions on pain in adults with cancer, Oncol. Nurs. Forum 30 (1) (2003) 75–89.

[42] G.H. Montgomery, K.N. DuHamel, W.H. Redd, A meta-analysis of hypnotically induced analgesia: how effective is hypnosis? Int. J. Clin. Exp. Hypn. 48 (2) (2000) 138–153.

[43] S. Holtzman, R.T. Beggs, Yoga for chronic low back pain: a meta-analysis of randomized controlled trials, Pain Res. Manag. J. Can. Pain Soc. Journal de La Societe Canadienne Pour Le Traitement de La Douleur 18 (5) (2013) 267–272.

[44] S.J. Kamper, A.T. Apeldoorn, A. Chiarotto, R.J.E.M. Smeets, R.W.J.G. Ostelo, J. Guzman, M.W. van Tulder, Multidisciplinary biopsychosocial rehabilitation for chronic low back pain: cochrane systematic review and meta-analysis, BMJ 350 (2015) h444.

[45] K.P. Grichnik, F.M. Ferrante, The difference between acute and chronic pain, Mt. Sinai J. Med. 58 (3) (1991) 217–220.

[46] M.N. Baliki, D.R. Chialvo, P.Y. Geha, R.M. Levy, R.N. Harden, T.B. Parrish, A.V. Apkarian, Chronic pain and the emotional brain: specific brain activity associated with spontaneous fluctuations of intensity of chronic back pain, J. Neurosci. 26 (47) (2006) 12165–12173.

[47] A. Kuchinad, P. Schweinhardt, D.A. Seminowicz, P.B. Wood, B.A. Chizh, M.C. Bushnell, Accelerated brain gray matter loss in fibromyalgia patients: premature aging of the brain? J. Neurosci. 27 (15) (2007) 4004–4007.

[48] R.E. Harris, P.C. Sundgren, A.D. Craig, E. Kirshenbaum, A. Sen, V. Napadow, D.J. Clauw, Elevated insular glutamate in fibromyalgia is associated with experimental pain, Arthritis Rheum. 60 (10) (2009) 3146–3152.

[49] M. López-Solà, C.-W. Woo, J. Pujol, J. Deus, B.J. Harrison, J. Monfort, T.D. Wager, Towards a neurophysiological signature for fibromyalgia, Pain 158 (1) (2017)

34–47.

[50] V. Napadow, L. LaCount, K. Park, S. As-Sanie, D.J. Clauw, R.E. Harris, Intrinsic brain connectivity in fibromyalgia is associated with chronic pain intensity, Arthritis Rheum. 62 (8) (2010) 2545–2555.

[51] Y. Cao, S.K. Aurora, V. Nagesh, S.C. Patel, K.M.A. Welch, Functional MRI-BOLD of brainstem structures during visually triggered migraine, Neurology 59 (1) (2002) 72–78.

[52] S.K. Afridi, N.J. Giffin, H. Kaube, K.J. Friston, N.S. Ward, R.S.J. Frackowiak, P.J. Goadsby, A positron emission tomographic study in spontaneous migraine, Arch. Neurol. 62 (8) (2005) 1270–1275.

[53] A. Russo, A. Tessitore, F. Esposito, L. Marcuccio, A. Giordano, R. Conforti, et al., Pain processing in patients with migraine: an event-related fMRI study during trigeminal nociceptive stimulation, J. Neurol. 259 (9) (2012) 1903–1912.

[54] C.D. Chong, J.D. Plasencia, D.H. Frakes, T.J. Schwedt, Structural alterations of the brainstem in migraine, Neuroimage Clin. 13 (2017) 223–227.

[55] T.R. Makin, J. Scholz, N. Filippini, D. Henderson Slater, I. Tracey, H. Johansen-Berg, Phantom pain is associated with preserved structure and function in the former hand area, Nat. Commun. 4 (2013) 1570.

[56] H. Flor, L. Nikolajsen, T.S. Jensen, Phantom limb pain: a case of maladaptive CNS plasticity? Nat. Rev. Neurosci. 7 (11) (2006) 873–881.

[57] J.A. Hashmi, M.N. Baliki, L. Huang, A.T. Baria, S. Torbey, K.M. Hermann, et al., Shape shifting pain: chronification of back pain shifts brain representation from nociceptive to emotional circuits, Brain J. Neurol. 136 (Pt 9) (2013) 2751–2768.

[58] T.D. Wager, L.Y. Atlas, M.A. Lindquist, M. Roy, C.-W. Woo, E. Kross, An fMRI-based neurologic signature of physical pain, N. Engl. J. Med. 368 (15) (2013) 1388–1397.

[59] A.V. Apkarian, M.C. Bushnell, R.-D. Treede, J.-K. Zubieta, Human brain mechanisms of pain perception and regulation in health and disease, Eur. J. Pain 9 (4) (2005) 463–484.

[60] R.C. Coghill, C.N. Sang, J.M. Maisog, M.J. Iadarola, Pain intensity processing within the human brain: a bilateral, distributed mechanism, J. Neurophysiol. 82 (4) (1999) 1934–1943.

[61] R. Melzack, From the gate to the neuromatrix, Pain Suppl. 6 (1999) S121–S126.

[62] M.N. Baliki, B. Petre, S. Torbey, K.M. Herrmann, L. Huang, T.J. Schnitzer, et al., Corticostriatal functional connectivity predicts transition to chronic back pain, Nat. Neurosci. 15 (8) (2012) 1117–1119.

[63] C.-W. Woo, L.J. Chang, M.A. Lindquist, T.D. Wager, Building better biomarkers: brain models in translational neuroimaging, Nat. Neurosci. 20 (3) (2017) 365–377, https://doi.org/10.1038/nn.4478.

[64] M. Ingvar, Learning mechanisms in pain chronification–teachings from placebo research, Pain 156 (Suppl 1) (2015) S18–S23.

[65] J. Zaman, J.W.S. Vlaeyen, L. Van Oudenhove, K. Wiech, I. Van Diest, Associative fear learning and perceptual discrimination: a perceptual pathway in the development of chronic pain, Neurosci. Biobehav. Rev. 51 (2015) 118–125.

[66] M. Roy, D. Shohamy, N. Daw, M. Jepma, G.E. Wimmer, T.D. Wager, Representation of aversive prediction errors in the human periaqueductal gray, Nat. Neurosci. 17 (11) (2014) 1607–1612.

[67] A. Meulders, D. Vansteenwegen, J.W.S. Vlaeyen, The acquisition of fear of movement-related pain and associative learning: a novel pain-relevant human fear conditioning paradigm, Pain 152 (11) (2011) 2460–2469.

[68] H. Flor, N. Birbaumer, Acquisition of chronic pain: psychophysiological mechanisms, APS J. 3 (2) (1994) 119–127.

[69] J.A. Smith, M. Osborn, Pain as an assault on the self: an interpretative phenomenological analysis of the psychological impact of chronic benign low back pain, Psychol. Health 22 (5) (2007) 517–534.

[70] J.A. Hunfeld, C.W. Perquin, H.J. Duivenvoorden, A.A. Hazebroek-Kampschreur, J. Passchier, L.W. van Suijlekom-Smit, J.C. van der Wouden, Chronic pain and its impact on quality of life in adolescents and their families, J. Pediatr. Psychol. 26 (3) (2001) 145–153.

[71] C. Young Casey, M.A. Greenberg, P.M. Nicassio, R.E. Harpin, D. Hubbard, Transition from acute to chronic pain and disability: a model including cognitive, affective, and trauma factors, Pain 134 (1-2) (2008) 69–79.

[72] E. Fernandez, D.C. Turk, The utility of cognitive coping strategies for altering pain perception: a meta-analysis, Pain 38 (2) (1989) 123–135.

[73] E.G. Mann, S. Lefort, E.G. Vandenkerkhof, Self-management interventions for chronic pain, Pain Manag. 3 (3) (2013) 211–222.

[74] P. Escolar-Reina, F. Medina-Mirapeix, J.J. Gascón-Cánovas, J. Montilla-Herrador, J.F. Valera-Garrido, S.M. Collins, Self-management of chronic neck and low back pain and relevance of information provided during clinical encounters: an observational study, Arch. Phys. Med. Rehabil. 90 (10) (2009) 1734–1739.

[75] K.N. Perry, M.K. Nicholas, J.W. Middleton, Comparison of a pain management program with usual care in a pain management center for people with spinal cord injury-related chronic pain, Clin. J. Pain 26 (3) (2010) 206–216.

[76] H. Hadjistavropoulos, J. Shymkiw, Predicting readiness to self-manage pain, Clin. J. Pain 23 (3) (2007) 259–266.

[77] B.D. Darnall, J.A. Sturgeon, M.C. Kao, J.M. Hah, S.C. Mackey, From catastrophixing to Recovery: a pilot study of a single-session treatment for pain catastrophizing, J. Pain Res. 7 (2014) 219–226.

[78] Y.-Y. Tang, Y. Ma, J. Wang, Y. Fan, S. Feng, Q. Lu, et al., Short-term meditation training improves attention and self-regulation, Proc. Natl. Acad. Sci. U. S. A. 104 (43) (2007) 17152–17156.

[79] M. Muraven, R.F. Baumeister, D.M. Tice, Longitudinal improvement of self-regulation through practice: building self-control strength through repeated exercise, J. Soc. Psychol. 139 (4) (1999) 446–457.

[80] A. Bandura, The primacy of self-regulation in health promotion, Appl. Psychol. 54 (2) (2005) 245–254.

[81] J. Kabat-Zinn, L. Lipworth, R. Burncy, W. Sellers, Four-year follow-up of a meditation-based program for the self-regulation of chronic pain, Clin. J. Pain 2 (3) (1986) 159–774.

[82] L.G. Aspinwall, S.E. Taylor, A stitch in time: self-regulation and proactive coping, Psychol. Bull. 121 (3) (1997) 417–436.

[83] H. Flor, Cortical reorganisation and chronic pain: implications for rehabilitation, J. Rehabil. Med. (41 Suppl) (2003) 66–72.

[84] J.J. Gross, Antecedent- and response-focused emotion regulation: divergent consequences for experience, expression, and physiology, J. Pers. Soc. Psychol. 74 (1) (1998) 224–237.

[85] S.C. Hayes, J.B. Luoma, F.W. Bond, A. Masuda, J. Lillis, Acceptance and commitment therapy: model, processes and outcomes, Behav. Res. Ther. 44 (1) (2006) 1–25.

[86] C.S. Carver, M.F. Scheier, 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, Academic Press, 1983, pp. 127–194.

[87] J.J. Gross, Emotion regulation: affective, cognitive, and social consequences, Psychophysiology 39 (3) (2002) 281–291.

[88] J.T. Buhle, J.A. Silvers, T.D. Wager, R. Lopez, C. Onyemekwu, H. Kober, et al., Cognitive reappraisal of emotion: a meta-analysis of human neuroimaging studies, Cereb. Cortex 24 (11) (2014) 2981–2990.

[89] I. Tracey, Getting the pain you expect: mechanisms of placebo, nocebo and re-appraisal effects in humans, Nat. Med. 16 (11) (2010) 1277–1283.

[90] D.C. Turk, M. Genest, 9 - regulation of pain: the application of cognitive and behavioral techniques for prevention and remediation, Cognitive-Behavioral Interventions, Academic Press, 1979, pp. 287–318.

[91] C.-W. Woo, M. Roy, J.T. Buhle, T.D. Wager, Distinct brain systems mediate the effects of nociceptive input and self-regulation on pain, PLoS Biol. 13 (1) (2015) e1002036.

[92] D.L. Lachapelle, S. Lavoie, A. Boudreau, The meaning and process of pain acceptance. Perceptions of women living with arthritis and fibromyalgia, Pain Res. Manag. J. Can. Pain Soc. Journal de La Societe Canadienne Pour Le Traitement de La Douleur 13 (3) (2008) 201–210.

[93] L.M. McCracken, C. Eccleston, A prospective study of acceptance of pain and patient functioning with chronic pain, Pain 118 (1-2) (2005) 164–169.

[94] J.M. Chamberlain, D.A.F. Haaga, Unconditional self-acceptance and responses to negative feedback, J. Rational Emotive Cogn. Behav. Ther. RET 19 (3) (2001) 177–189.

[95] A.A. Ceyhan, E. Ceyhan, Investigation of university students' self-acceptance and learned resourcefulness: a longitudinal study, High. Educ. 61 (6) (2011) 649–661.

[96] D. Miron, G.H. Duncan, M.C. Bushnell, Effects of attention on the intensity and unpleasantness of thermal pain, Pain 39 (3) (1989) 345–352.

[97] C. Eccleston, Chronic pain and distraction: an experimental investigation into the role of sustained and shifting attention in the processing of chronic persistent pain, Behav. Res. Ther. 33 (4) (1995) 391–405.

[98] J. Buhle, T.D. Wager, Performance-dependent inhibition of pain by an executive working memory task, Pain 149 (1) (2010) 19–26.

[99] C. Sprenger, F. Eippert, J. Finsterbusch, U. Bingel, M. Rose, C. Büchel, Attention modulates spinal cord responses to pain, Current Biol. CB 22 (11) (2012) 1019–1022.

[100] N.E. Johnston, L.Y. Atlas, T.D. Wager, Opposing effects of expectancy and somatic focus on pain, PLoS One 7 (6) (2012) e38854.

[101] J. Suls, B. Fletcher, The relative efficacy of avoidant and nonavoidant coping strategies: a meta-analysis, Health Psychol. 4 (3) (1985) 249–288.

[102] J.A. Holmes, C.A. Stevenson, Differential effects of avoidant and attentional coping strategies on adaptation to chronic and recent-onset pain, Health Psycholol. 9 (5) (1990) 577–584.

[103] L. Goubert, G. Crombez, C. Eccleston, J. Devulder, Distraction from chronic pain during a pain-inducing activity is associated with greater post-activity pain, Pain 110 (1-2) (2004) 220–227.

[104] D. Meichenbaum, Cognitive behaviour modification, Scand. J. Behav. Ther. 6 (4) (1977) 185–192.

[105] A.T. Beck, Cognitive Therapy and the Emotional Disorders, Penguin, 1979.

[106] S. Morley, C. Eccleston, A. Williams, 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) (1999) 1–13.

[107] S.Y. Fagerhaugh, Pain expression and control on a burn care unit, Nurs. Outlook 22 (10) (1974) 645–650.

[108] D.C. Turk, D. Meichenbaum, M. Genest, Pain and Behavioral Medicine: A Cognitive-Behavioral Perspective, Guilford Press, 1983.

[109] B.M. Hoffman, R.K. Papas, D.K. Chatkoff, R.D. Kerns, Meta-analysis of psychological interventions for chronic low back pain, Health Psychol. 26 (1) (2007) 1–9.

[110] J.A. Turner, C.R. Chapman, Psychological interventions for chronic pain: a critical review. II. Operant conditioning, hypnosis, and cognitive-behavioral therapy, Pain 12 (1) (1982) 23–46.

[111] K.A. Holroyd, F. Andrasik, T. Westbrook, Cognitive control of tension headache, Cognit. Ther. Res. 1 (2) (1977) 121–133.

[112] K.A. Holroyd, F. Andrasik, Coping and the self-control of chronic tension headache, J. Consult. Clin. Psychol. 46 (5) (1978) 1036–1045.

[113] K.R. Mitchell, R.G. White, Behavioral self-management: an application to the problem of migraine headaches, Behav. Ther. 8 (2) (1977) 213–221.

[114] B. Schweikert, E. Jacobi, R. Seitz, A. Cziske, J. Ehlert, R. Knab, R. Leidl, Effectiveness and cost-effectiveness of adding a cognitive behavioral treatment to the rehabilitation of chronic low back pain, J. Rheumatol. 33 (12) (2006) 2519–2526.

[115] M. Shpaner, C. Kelly, G. Lieberman, H. Perelman, M. Davis, F.J. Keefe,

M.R. Naylor, Unlearning chronic pain: a randomized controlled trial to investigate changes in intrinsic brain connectivity following Cognitive Behavioral Therapy, Neuroimage Clin. 5 (2014) 365–376.

[116] M.D. Hollander, J.R. de Jong, S. Volders, M.E. Goossens, R.J. Smeets, J.W.S. Vlaeyen, Fear reduction in patients with chronic pain: a learning theory perspective, Expert Rev. Neurother. 10 (11) (2010) 1733–1745.

[117] S. Peuterl, I. Diestl, D. Vansteenwegenl, O. Berghl, J.W.S. Vlaeyenl, Understanding fear of pain in chronic pain: interoceptive fear conditioning as a novel approach, Eur. J. Pain 15 (9) (2011) 889–894.

[118] M.M. Wertli, J.M. Burgstaller, S. Weiser, J. Steurer, R. Kofmehl, U. Held, Influence of catastrophizing on treatment outcome in patients with nonspecific low back pain: a systematic review, Spine 39 (3) (2014) 263–273.

[119] J.W. Vlaeyen, A.M. Kole-Snijders, R.G. Boeren, H. van Eek, Fear of movement/(re) injury in chronic low back pain and its relation to behavioral performance, Pain 62 (3) (1995) 363–372.

[120] R.J. Gatchel, R. Neblett, N. Kishino, C.T. Ray, Fear-avoidance beliefs and chronic pain, J. Orthop. Sports Phys. Ther. 46 (2) (2016) 38–43.

[121] M. Leeuw, M.E.J.B. Goossens, S.J. Linton, G. Crombez, K. Boersma, J.W.S. Vlaeyen, The fear-avoidance model of musculoskeletal pain: current state of scientific evidence, J. Behav. Med. 30 (1) (2007) 77–94.

[122] J.W.S. Vlaeyen, G. Crombez, S.J. Linton, The fear-avoidance model of pain, Pain 157 (8) (2016) 1588–1589.

[123] J. Lethem, P.D. Slade, J.D. Troup, G. Bentley, Outline of a Fear-Avoidance Model of exaggerated pain perception–I, Behav. Res. Ther. 21 (4) (1983) 401–408.

[124] G. Crombez, C. Eccleston, S. Van Damme, J.W.S. Vlaeyen, P. Karoly, Fear-avoidance model of chronic pain: the next generation, Clin. J. Pain 28 (6) (2012) 475–483.

[125] R.J. Gatchel, D.D. McGeary, C.A. McGeary, B. Lippe, Interdisciplinary chronic pain management: past, present, and future, Am. Psychol. 69 (2) (2014) 119–130.

[126] R.J. Gatchel, A. Okifuji, Evidence-based scientific data documenting the treatment and cost-effectiveness of comprehensive pain programs for chronic nonmalignant pain, J. Pain 7 (11) (2006) 779–793.

[127] O. Hikosaka, H.F. Kim, M. Yasuda, S. Yamamoto, Basal ganglia circuits for reward value–Guided behavior, Annu. Rev. Neurosci. 37 (1) (2014) 289–306.

[128] A. Nagy, G. Eördegh, Z. Paróczy, Z. Márkus, G. Benedek, Multisensory integration in the basal ganglia, Eur. J. Neurosci. 24 (3) (2006) 917–924.

[129] R. Reig, G. Silberberg, Multisensory integration in the mouse striatum, Neuron 83 (5) (2014) 1200–1212.

[130] D. Borsook, J. Upadhyay, E.H. Chudler, L. Becerra, A key role of the basal ganglia in pain and analgesia–insights gained through human functional imaging, Mol. Pain 6 (2010) 27.

[131] T.D. Wager, M.L. Davidson, B.L. Hughes, M.A. Lindquist, K.N. Ochsner, Neural mechanisms of emotion regulation: evidence for two independent prefrontal-subcortical pathways, Neuron 59 (6) (2008) 1037.

[132] E.H. Chudler, W.K. Dong, The role of the basal ganglia in nociception and pain, Pain 60 (1) (1995) 3–38.

[133] C.C.C. Bauer, E.H. Pasaye, J.I. Romero-Romo, F.A. Barrios, The integrative role of the basal ganglia, Basal Ganglia Integr. View (2012) 87.

[134] M.N. Baliki, T.J. Schnitzer, W.R. Bauer, A.V. Apkarian, Brain morphological signatures for chronic pain, PLoS One 6 (10) (2011) e26010.

[135] N. Schwartz, P. Temkin, S. Juardo, B.K. Lim, B.D. Heifets, J.S. Polepalli, R.C. Malenka, Chronic pain. Decreased motivation during chronic pain requires long-term depression in the nucleus accumbens, Science 345 (6196) (2014) 535–542.

[136] W. Ren, M.V. Centeno, S. Berger, Y. Wu, X. Na, X. Liu, et al., The indirect pathway of the nucleus accumbens shell amplifies neuropathic pain, Nat. Neurosci. 19 (2) (2016) 220–222.

[137] D. Plenz, J.R. Wickens, 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, Elsevier, 2017, pp. 121–136.

[138] J.P. Rauschecker, E.S. May, A. Maudoux, M. Ploner, Frontostriatal gating of tinnitus and chronic pain, Trends Cogn. Sci. 19 (10) (2015) 567–578.

[139] F. Brischoux, S. Chakraborty, D.I. Brierley, M.A. Ungless, Phasic excitation of dopamine neurons in ventral VTA by noxious stimuli, Proc. Natl. Acad. Sci. U. S. A. 106 (12) (2009) 4894–4899.

[140] M.R. Staudinger, S. Erk, B. Abler, H. Walter, Cognitive reappraisal modulates expected value and prediction error encoding in the ventral striatum, NeuroImage 47 (2) (2009) 713–721.

[141] K. McRae, B. Hughes, S. Chopra, J.D.E. Gabrieli, J.J. Gross, K.N. Ochsner, The neural bases of distraction and reappraisal, J. Cogn. Neurosci. 22 (2) (2010) 248–262.

[142] K.N. Ochsner, S.A. Bunge, J.J. Gross, J.D.E. Gabrieli, Rethinking feelings: an FMRI study of the cognitive regulation of emotion, J. Cogn. Neurosci. 14 (8) (2002) 1215–1229.

[143] K.N. Ochsner, R.D. Ray, J.C. Cooper, E.R. Robertson, S. Chopra, J.D.E. Gabrieli, J.J. Gross, For better or for worse: neural systems supporting the cognitive down- and up-regulation of negative emotion, NeuroImage 23 (2) (2004) 483–499.

[144] R.D. Ray, K.N. Ochsner, J.C. Cooper, E.R. Robertson, J.D.E. Gabrieli, J.J. Gross, Individual differences in trait rumination and the neural systems supporting cognitive reappraisal, Cogn. Affect. Behav. Neurosci. 5 (2) (2005) 156–168.

[145] J. Dale, H. Zhou, Q. Zhang, E. Martinez, S. Hu, K. Liu, et al., Scaling up cortical control inhibits pain, Cell Rep. 23 (5) (2018) 1301–1313.

[146] M. Lee, T.R. Manders, S.E. Eberle, C. Su, J. D'amour, R. Yang, et al., Activation of corticostriatal circuitry relieves chronic neuropathic pain, J. Neurosci. 35 (13) (2015) 5247–5259.

[147] E. Martinez, H.H. Lin, H. Zhou, J. Dale, K. Liu, J. Wang, Corticostriatal regulation

[148] G. Ji, V. Neugebauer, CB1 augments mGluR5 function in medial prefrontal cortical neurons to inhibit amygdala hyperactivity in an arthritis pain model, Eur. J. Neurosci. 39 (3) (2014) 455–466.

[149] H.L. Fields, J. Bry, I. Hentall, G. Zorman, The activity of neurons in the rostral medulla of the rat during withdrawal from noxious heat, J. Neurosci. 3 (12) (1983) 2545–2552.

[150] R.A. Baer, Mindfulness training as a clinical intervention: a conceptual and empirical review, Clin. Psychol. Sci. Pract. 10 (2) (2003) 125–143.

[151] S. Rosenzweig, J.M. Greeson, D.K. Reibel, J.S. Green, S.A. Jasser, D. Beasley, Mindfulness-based stress reduction for chronic pain conditions: variation in treatment outcomes and role of home meditation practice, J. Psychosom. Res. 68 (1) (2010) 29–36.

[152] D.C. Cherkin, K.J. Sherman, B.H. Balderson, A.J. Cook, M.L. Anderson, R.J. Hawkes, et al., 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 J. Am. Med. Assoc. 315 (12) (2016) 1240–1249.

[153] F. Zeidan, D.R. Vago, Mindfulness meditation-based pain relief: a mechanistic account, Ann. N. Y. Acad. Sci. 1373 (1) (2016) 114–127.

[154] A. Lutz, D.R. McFarlin, D.M. Perlman, T.V. Salomons, R.J. Davidson, Altered anterior insula activation during anticipation and experience of painful stimuli in expert meditators, NeuroImage 64 (2013) 538–546.

[155] C.A. Brown, A.K.P. Jones, Meditation experience predicts less negative appraisal of pain: electrophysiological evidence for the involvement of anticipatory neural responses, Pain 150 (3) (2010) 428–438.

[156] D.M. Perlman, T.V. Salomons, R.J. Davidson, A. Lutz, Differential effects on pain intensity and unpleasantness of two meditation practices, Emotion 10 (1) (2010) 65–71.

[157] F. Zeidan, K.T. Martucci, R.A. Kraft, N.S. Gordon, J.G. McHaffie, R.C. Coghill, Brain mechanisms supporting the modulation of pain by mindfulness meditation, J. Neurosci. 31 (14) (2011) 5540–5548.

[158] J.A. Astin, B.M. Berman, B. Bausell, W.-L. Lee, M. Hochberg, K.L. Forys, The efficacy of mindfulness meditation plus Qigong movement therapy in the treatment of fibromyalgia: a randomized controlled trial, J. Rheumatol. 30 (10) (2003) 2257–2262.

[159] S.E. Sephton, P. Salmon, I. Weissbecker, C. Ulmer, A. Floyd, K. Hoover, J.L. Studts, Mindfulness meditation alleviates depressive symptoms in women with fibromyalgia: results of a randomized clinical trial, Arthritis Rheum. 57 (1) (2007) 77–85.

[160] E. Cash, P. Salmon, I. Weissbecker, W.N. Rebholz, R. Bayley-Veloso, L.A. Zimmaro, et al., Mindfulness meditation alleviates fibromyalgia symptoms in women: results of a randomized clinical trial, Ann. Behav. Med. Publ. Soc. Behav. Med. 49 (3) (2015) 319–330.

[161] M. Plews-Ogan, J.E. Owens, M. Goodman, P. Wolfe, J. Schorling, A pilot study evaluating mindfulness-based stress reduction and massage for the management of chronic pain, J. Gen. Intern. Med. 20 (12) (2005) 1136–1138.

[162] N.E. Morone, C.M. Greco, D.K. Weiner, Mindfulness meditation for the treatment of chronic low back pain in older adults: a randomized controlled pilot study, Pain 134 (3) (2008) 310–319.

[163] E.K. Pradhan, M. Baumgarten, P. Langenberg, B. Handwerger, A.K. Gilpin, T. Magyari, et al., Effect of Mindfulness-Based Stress Reduction in rheumatoid arthritis patients, Arthritis Rheum. 57 (7) (2007) 1134–1142.

[164] A.J. Zautra, M.C. Davis, J.W. Reich, P. Nicassario, H. Tennen, P. Finan, et al., Comparison of cognitive behavioral and mindfulness meditation interventions on adaptation to rheumatoid arthritis for patients with and without history of recurrent depression, J. Consult. Clin. Psychol. 76 (3) (2008) 408–421.

[165] A. Chiesa, A. Serretti, Mindfulness-based interventions for chronic pain: a systematic review of the evidence, J. Altern. Complement. Med. 17 (1) (2011) 83–93.

[166] J. Gardner-Nix, Mindfulness-based stress reduction for chronic pain management, in: F. Didonna (Ed.), Clinical Handbook of Mindfulness, Springer New York, New York, NY, 2009, pp. 369–381.

[167] S. Jain, S.L. Shapiro, S. Swanick, S.C. Roesch, P.J. Mills, I. Bell, G.E.R. Schwartz, A randomized controlled trial of mindfulness meditation versus relaxation training: effects on distress, positive states of mind, rumination, and distraction, Ann. Behav. Med. Publ. Soc. Behav. Med. 33 (1) (2007) 11–21.

[168] R. Schütze, C. Rees, M. Preece, M. Schütze, Low mindfulness predicts pain catastrophizing in a fear-avoidance model of chronic pain, Pain 148 (1) (2010) 120–127.

[169] J.A. Grant, P. Rainville, Pain sensitivity and analgesic effects of Mindful States in Zen meditators: a cross-sectional study, Psychosom. Med. 71 (1) (2009) 106–114.

[170] T. Gard, B.K. Hölzel, A.T. Sack, H. Hempel, S.W. Lazar, D. Vaitl, U. Ott, Pain attenuation through mindfulness is associated with decreased cognitive control and increased sensory processing in the brain, Cereb. Cortex 22 (11) (2012) 2692–2702.

[171] C.E. Kerr, M.D. Sacchet, S.W. Lazar, C.I. Moore, S.R. Jones, Mindfulness starts with the body: somatosensory attention and top-down modulation of cortical alpha rhythms in mindfulness meditation, Front. Hum. Neurosci. 7 (2013) 12.

[172] J.A. Grant, J. Courtemanche, E.G. Duerden, G.H. Duncan, P. Rainville, Cortical thickness and pain sensitivity in zen meditators, Emotion 10 (1) (2010) 43–53.

[173] J.A. Brewer, P.D. Worhunsky, J.R. Gray, Y.-Y. Tang, J. Weber, H. Kober, Meditation experience is associated with differences in default mode network activity and connectivity, Proc. Natl. Acad. Sci. U. S. A. 108 (50) (2011) 20254–20259.

[174] R.L. Buckner, J.R. Andrews-Hanna, D.L. Schacter, The brain's default network: anatomy, function, and relevance to disease, Ann. N. Y. Acad. Sci. 1124 (2008)

1–38.

[175] J.R. Andrews-Hanna, The brain's default network and its adaptive role in internal mentation. The Neuroscientist: a Review Journal Bringing Neurobiology, Neurol. Psychiatry 18 (3) (2012) 251–270.

[176] M.D. Fox, A.Z. Snyder, J.L. Vincent, M. Corbetta, D.C. Van Essen, M.E. Raichle, The human brain is intrinsically organized into dynamic, anticorrelated functional networks, Proc. Natl. Acad. Sci. U. S. A. 102 (27) (2005) 9673–9678.

[177] C.G. Davey, J. Pujol, B.J. Harrison, Mapping the self in the brain's default mode network, NeuroImage 132 (2016) 390–397.

[178] J.R. Andrews-Hanna, J. Smallwood, R.N. Spreng, The default network and self-generated thought: component processes, dynamic control, and clinical relevance, Ann. N. Y. Acad. Sci. 1316 (2014) 29–52.

[179] B.T. Denny, H. Kober, T.D. Wager, K.N. Ochsner, A meta-analysis of functional neuroimaging studies of self- and other judgments reveals a spatial gradient for mentalizing in medial prefrontal cortex, J. Cogn. Neurosci. 24 (8) (2012) 1742–1752.

[180] G. Northoff, A. Heinzel, M. de Greck, F. Bermpohl, H. Dobrowolny, J. Panksepp, Self-referential processing in our brain–a meta-analysis of imaging studies on the self, NeuroImage 31 (1) (2006) 440–457.

[181] A. Kucyi, T.V. Salomons, K.D. Davis, Mind wandering away from pain dynamically engages antinociceptive and default mode brain networks, Proc. Natl. Acad. Sci. U. S. A. 110 (46) (2013) 18692–18697.

[182] S. Aldrich, C. Eccleston, G. Crombez, Worrying about chronic pain: vigilance to threat and misdirected problem solving, Behav. Res. Ther. 38 (5) (2000) 457–470.

[183] L.C. Campbell, D.J. Clauw, F.J. Keefe, Persistent pain and depression: a biopsychosocial perspective, Biol. Psychiatry 54 (3) (2003) 399–409.

[184] A. Kucyi, M. Moayedi, I. Weissman-Fogel, M.B. Goldberg, B.V. Freeman, H.C. Tenenbaum, K.D. Davis, Enhanced medial prefrontal-default mode network functional connectivity in chronic pain and its association with pain rumination, J. Neurosci. 34 (11) (2014) 3969–3975.

[185] N. Erpelding, K.D. Davis, Neural underpinnings of behavioural strategies that prioritize either cognitive task performance or pain, Pain 154 (10) (2013) 2060–2071.

[186] V. Menon, L.Q. Uddin, Saliency, switching, attention and control: a network model of insula function, Brain Struct. Funct. 214 (5-6) (2010) 655–667.

[187] S.L. Bressler, V. Menon, Large-scale brain networks in cognition: emerging methods and principles, Trends Cogn. Sci. (Regul. Ed.) 14 (6) (2010) 277–290.

[188] V. Menon, Salience network. Arthur, in: W. Toga (Ed.), Brain Mapping: An Encyclopedic Reference, 2 Academic Press: Elsevier, 2015, pp. 597–611.

[189] W.W. Seeley, V. Menon, A.F. Schatzberg, J. Keller, G.H. Glover, H. Kenna, et al., Dissociable intrinsic connectivity networks for salience processing and executive control, J. Neurosci. 27 (9) (2007) 2349–2356.

[190] N. Goulden, A. Khusnulina, N.J. Davis, R.M. Bracewell, A.L. Bokde, J.P. McNulty, P.G. Mullins, The salience network is responsible for switching between the default mode network and the central executive network: replication from DCM, NeuroImage 99 (2014) 180–190.

[191] K.S. Hemington, Q. Wu, A. Kucyi, R.D. Inman, K.D. Davis, Abnormal cross-network functional connectivity in chronic pain and its association with clinical symptoms, Brain Struct. Funct. 221 (8) (2016) 4203–4219.

[192] J.S. Damoiseaux, S.A.R.B. Rombouts, F. Barkhof, P. Scheltens, C.J. Stam, S.M. Smith, C.F. Beckmann, Consistent resting-state networks across healthy subjects, Proc. Natl. Acad. Sci. U. S. A. 103 (37) (2006) 13848–13853.

[193] M.D. Fox, D. Zhang, A.Z. Snyder, M.E. Raichle, The global signal and observed anticorrelated resting brain networks, J. Neurophysiol. 101 (6) (2009) 3270–3283.

[194] K.S. Hemington, A. Rogachov, J.C. Cheng, R.L. Bosma, J.A. Kim, N.R. Osborne, et al., 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 (2018), https://doi.org/10.1097/j.pain.0000000000001252.

[195] A. Otti, H. Guendel, A. Wohlschläger, C. Zimmer, M. Noll-Hussong, Frequency shifts in the anterior default mode network and the salience network in chronic pain disorder, BMC Psychiatry 13 (2013) 84.

[196] F. Schneider, P. Karoly, Conceptions of the pain experience: the emergence of multidimensional models and their implications for contemporary clinical practice, Clin. Psychol. Rev. 3 (1) (1983) 61–86.

[197] R. Auksztulewicz, B. Spitzer, F. Blankenburg, Recurrent neural processing and somatosensory awareness, J. Neurosci. 32 (3) (2012) 799–805.

[198] A. Mansour, A.T. Baria, P. Tetreault, E. Vachon-Presseau, P.-C. Chang, L. Huang, et al., Global disruption of degree rank order: a hallmark of chronic pain, Sci. Rep. 6 (2016) 34853.

[199] M.C. Reddan, T.D. Wager, Modeling pain using fMRI: from regions to biomarkers, Neurosci. Bull. 34 (1) (2018) 208–215.

[200] V. Taschereau-Dumouchel, A. Cortese, T. Chiba, J.D. Knotts, M. Kawato, H. Lau, Towards an unconscious neural reinforcement intervention for common fears, Proc. Natl. Acad. Sci. U. S. A. 115 (13) (2018) 3470–3475.

[201] D. Bakker, N. Kazantzis, D. Rickwood, N. Rickard, Mental health smartphone apps: review and evidence-based recommendations for future developments, JMIR Ment. Health 3 (1) (2016) e7.

[204] M. Azqueta-Gavaldon, H. Schulte-Göcking, C. Storz, S. Azad, A. Reiners, D. Borsook, et al., Basal ganglia dysfunction in complex regional pain syndrome - A valid hypothesis? Eur. J. Pain 21 (3) (2017) 415–424.

[205] M.N. Baliki, P.Y. Geha, A.V. Apkarian, D.R. Chialvo, Beyond feeling: chronic pain hurts the brain, disrupting the default-mode network dynamics, J. Neurosci. 28 (6) (2008) 1398–1403.

[206] M.N. Baliki, A.R. Mansour, A.T. Baria, A.V. Apkarian, Functional reorganization of the default mode network across chronic pain conditions, PLoS One 9 (9) (2014) e106133.

[207] A. Bolwerk, F. Seifert, C. Maihöfner, Altered resting-state functional connectivity in complex regional pain syndrome, J. Pain 14 (10) (2013) 1107–1115 e8.

[208] D. Callan, L. Mills, C. Nott, R. England, S. England, A tool for classifying individuals with chronic back pain: using multivariate pattern analysis with functional magnetic resonance imaging data, PLoS One 9 (6) (2014) e98007.

[209] F. Cauda, F. D'Agata, K. Sacco, S. Duca, D. Cocito, I. Paolasso, et al., Altered resting state attentional networks in diabetic neuropathic pain, J. Neurol. Neurosurg. Psychiatr. 81 (7) (2010) 806–811.

[210] P. Flodin, S. Martinsen, R. Altawil, E. Waldheim, J. Lampa, E. Kosek, P. Fransson, Intrinsic brain connectivity in chronic pain: a resting-state fMRI study in patients with rheumatoid arthritis, Front. Hum. Neurosci. 10 (2016) 107.

[211] P.Y. Geha, M.N. Baliki, D.R. Chialvo, R.N. Harden, J.A. Paice, A.V. Apkarian, Brain activity for spontaneous pain of postherpetic neuralgia and its modulation by lidocaine patch therapy, Pain 128 (1-2) (2007) 88–100.

[212] E. Ichesco, T. Schmidt-Wilcke, R. Bhavsar, D.J. Clauw, S.J. Peltier, J. Kim, et al., Altered resting state connectivity of the insular cortex in individuals with fibromyalgia, J. Pain 15 (8) (2014) 815–826 e1.

[213] L.A. Kilpatrick, J.J. Kutch, K. Tillisch, B.D. Naliboff, J.S. Labus, Z. Jiang, et al., Alterations in resting state oscillations and connectivity in sensory and motor networks in women with interstitial cystitis/painful bladder syndrome, J. Urol. 192 (3) (2014) 947–955.

[214] J.-Y. Kim, S.-H. Kim, J. Seo, S.-H. Kim, S.W. Han, E.J. Nam, et al., Increased power spectral density in resting-state pain-related brain networks in fibromyalgia, Pain 154 (9) (2013) 1792–1797.

[215] T.R. Makin, N. Filippini, E.P. Duff, D. Henderson Slater, I. Tracey, H. Johansen-Berg, Network-level reorganisation of functional connectivity following arm amputation, NeuroImage 114 (2015) 217–225.

[216] N. Maleki, L. Becerra, L. Nutile, G. Pendse, J. Brawn, M. Bigal, et al., Migraine attacks the basal ganglia, Mol. Pain 7 (2011) 71.

[217] H. Mano, G. Kotecha, K. Leibnitz, T. Matsubara, A. Nakae, N. Shenker, et al., Classification and characterisation of brain network changes in chronic back pain: a multicenter study, Wellcome Open Res. 3 (2018) 19.

[218] K.T. Martucci, W.R. Shirer, E. Bagarinao, K.A. Johnson, M.A. Farmer, J.S. Labus, et al., 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) (2015) 1755–1764.

[219] T. Schmidt-Wilcke, E. Leinisch, S. Gänssbauer, B. Draganski, U. Bogdahn, J. Altmeppen, A. May, Affective components and intensity of pain correlate with structural differences in gray matter in chronic back pain patients, Pain 125 (1-2) (2006) 89–97.

[220] P. Schweinhardt, A. Kuchinad, C.F. Pukall, M.C. Bushnell, Increased gray matter density in young women with chronic vulvar pain, Pain 140 (3) (2008) 411–419.

[221] B. Sundermann, M. Burgmer, E. Pogatzki-Zahn, M. Gaubitz, C. Stüber, E. Wessolleck, et al., Diagnostic classification based on functional connectivity in chronic pain: model optimization in fibromyalgia and rheumatoid arthritis, Acad. Radiol. 21 (3) (2014) 369–377.

[222] E. Tagliazucchi, P. Balenzuela, D. Fraiman, D.R. Chialvo, Brain resting state is disrupted in chronic back pain patients, Neurosci. Lett. 485 (1) (2010) 26–31.