Psychological Pain Interventions and Neurophysiology

Implications for a Mechanism-Based Approach

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This article provides an illustrative overview of neurophysiological changes related to acute and chronic pain involving structural and functional brain changes, which might be the targets of psychological interventions. A number of psychological pain treatments have been examined with respect to their effects on brain activity, ranging from cognitive- and operant behavioral interventions, meditation and hypnosis, to neuro- and biofeedback, discrimination training, imagery and mirror treatment, as well as virtual reality and placebo applications. These treatments affect both ascending and descending aspects of pain processing and act through brain mechanisms that involve sensorimotor areas as well as those involved in affective-motivational and cognitive-evaluative aspects. The analysis of neurophysiological changes related to effective psychological pain treatment can help to identify subgroups of patients with chronic pain who might profit from different interventions, can aid in predicting treatment outcome, and can assist in identifying responders and nonresponders, thus enhancing the efficacy and efficiency of psychological interventions. Moreover, new treatment targets can be developed and tested. Finally, the use of neurophysiological measures can also aid in motivating patients to participate in psychological interventions and can increase their acceptance in clinical practice.

Keywords: neurophysiological, pain, psychological treatment, magnetic resonance imaging

Psychological treatments for chronic pain include a large variety of cognitive-behavioral interventions ranging from biofeedback to pain management training to hypnosis. In general, these interventions have been shown to be successful, with effect sizes in the medium to high range (Williams, Eccleston, & Morley, 2012). In recent years, more information has become available about the structural and functional brain changes that are related to pain (for a review, see Davis & Moayedi, 2013), and successful treatments should reverse these changes. It will be interesting to see whether and how these assessments can help in designing better treatment interventions. Moreover, only a few studies have examined which components of these often very broad treatment approaches are effective and how they affect brain function and peripheral physiological responses. In this overview I first describe typical brain changes associated with the experience of acute and, especially, chronic pain and then discuss how psychological interventions might impact them. Finally, I outline areas of future research and discuss how neurophysiological examinations can help provide a better understanding of chronic pain and aid in the development of new and more refined psychological treatments.

Neurophysiological Characteristics of Acute and Chronic Pain

There are numerous brain changes that have been associated with acute and chronic pain. In acute pain, functional magnetic resonance imaging (fMRI) revealed regions such as the anterior cingulate cortex (ACC), the amygdala, the periaqueductal gray, the anterior insula, and the nucleus accumbens to be associated with affective and motivational processing; the primary (S1) and secondary (S2) somatosensory cortex, the posterior insula, and the thalamus with sensory processing; and frontal areas, including the ACC, with the cognitive modulation of pain (cf. Apkarian, Hashmi, & Baliki, 2011). In addition, social and other context variables such as learnt associations with pain or social reinforcement and empathy can affect how nociceptive stimulation will be processed by the brain and turned into a pain experience. Here, not only is activation in certain brain areas important, but multiple networks may interact at any given point in time and contribute to several aspects of pain. In addition, not only do these regions seem

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to be relevant for the processing of pain, but they may reflect a general salience detection system (Legrain, Iannetti, Plaghki, & Mouraux, 2011). It will be interesting to see how ongoing research efforts to differentiate pain from other attention-capturing and salient events will succeed in defining the core brain processes defining pain perception. For example, recent research using multivariate pattern analysis arrived at the conclusion that there is no single brain region subserving the experience of pain but that the most accurate prediction of pain perception related to acute laser stimuli was enabled by the combined activity in these regions, commonly referred to as the "pain matrix" (Brodersen et al., 2012). In chronic pain states, the medial prefrontal cortex has been identified as a region that best reflects spontaneous fluctuations of pain (Baliki et al., 2006). Many of these areas have been found to have altered gray matter density (cf. May, 2011), and they also show changes in the brain's default mode network and other resting state networks (Baliki, Geha, Apkarian, & Chialvo, 2008; Napadow et al., 2010), suggesting long-lasting brain changes related to the presence of chronic pain. In addition, white matter changes have been examined using diffusion tensor imaging. Here, specifically reduced connectivity in tracts involved in descending pain modulation has been observed in chronic pain patients, and these changes have also been related to deficient cognitive pain control (for a review, see Davis & Moayedi, 2013). It is a matter of debate to what extent the brain changes seen in chronic pain are pain-specific or may reflect comorbid states such as anxiety or depression, may reflect medication effects, or may be induced by the long-lasting states of pain themselves. Electroencephalographic (EEG) and magnetoencephalographic (MEG) recordings have also revealed a number of abnormal brain signatures related to chronic pain, such as a shift or expansion of the representation of painful and nonpainful stimuli in sensorimotor cortex (Moseley & Flor, 2012), general hyperreactivity to pain-related stimulation (e.g., Buchgreitz, Egsgaard, Jensen, Arendt-Nielsen, & Bendtsen, 2008; Flor, Knost, & Birbaumer, 1997; Richter, Eck, Straube, Miltner, & Weiss, 2010), as well as altered oscillatory activity (Hauck, Lorenz, & Engel, 2008). These central changes are accompanied by alterations in peripheral somatosensory processing, including deficient perception of muscle tension and tactile stimulation (e.g., Flor, Schugens, & Birbaumer, 1992; Maihöfner, Handwerker, & Birklein, 2006; Moseley, 2008) as well as a distorted body image (e.g., Lewis et al., 2010; Lotze & Moseley, 2007), that are site-specific and mirrored in specific changes in sensorimotor representations and limbic pain responses. A special role in this brain–body interaction has been assigned to the anterior insula, which is viewed as an integrative relay station for interoceptive input from the body (Craig, 2003). Maihöfner, Seifert, and Decol (2011) described a network involving the anterior insula that responds to sympathetic activation, and Pomares, Faillenot, Barral, and Peyron (2013) suggested that the anterior and posterior insula contribute differentially to the experience of pain.

Changes in peripheral responses have also been observed in chronic pain that range from enduring as well as event-related changes in muscle tension, autonomic functioning, or endocrinological responses (cf. Flor & Turk, 1989; Valença, Medeiros, Martins, Massaud, & Peres, 2009). Effective psychological treatments need to address these changes and reverse them.

Cognitive-Behavioral and Operant-Behavioral Treatments

Although cognitive-behavioral and operant-behavioral treatments, including exposure treatment and acceptance and commitment-based approaches, are the most commonly used psychological treatments for chronic pain and among the most effective (cf. Flor, Fydrich, & Turk, 1992; Glombiewski et al., 2010; Hoffman, Papas, Chatkoff, & Kerns, 2007), relatively few studies have examined their neurophysiological correlates. In a pioneering study, Lackner et al. (2006) used a brief cognitive-behavioral intervention that involved education, cognitive coping strategies, and problem solving training in patients with painful irritable bowel syndrome and achieved significant reductions in pain, anxiety, and gastrointestinal symptoms. These improvements were accompanied by reduced activations in the parahippocampal gyrus, the amygdala, and the subgenual ACC including the medial frontal cortex, all regions involved in affective and cognitive modulation of pain. Bonifazi et al. (2006) studied endocrinological changes in patients with fibromyalgia syndrome as a consequence of cognitive-behavioral treatment and observed improved cortisol function as well as improved glucocorticoid receptor alpha RNA expression in peripheral mononuclear blood cells following effective treatment.

Several studies in healthy humans have specifically examined cognitive processes related to psychological pain modulation and have shed light on core brain regions involved in effective cognitive interventions. For example, Bantick et al. (2002) found that cognitive distraction reduced pain intensity ratings and increased activation in the rostral ACC and decreased activation in the dorsal ACC. Lawrence, Hoeft, Sheau, and Mackey (2011) compared reappraisal and attention diversion and found specific effects of the two strategies on brain activity measures. Whereas attention diversion involved frontal, parietal, and occipital regions, reappraisal involved the ventral lateral prefrontal cortex, the midcingulate cortex, the thalamus, and the amygdala. The postcentral gyrus was active in both conditions. Wiech et al. (2006) also found that self-control over pain was correlated with activation in right anterolateral prefrontal cortex and the dorsal anterior cingulate cortex. Enduring cognitive changes that alter pain processing have also been observed in meditators, in whom the anticipation and experience of pain were accompanied by altered activation of the anterior insula (Lutz, McFarlin, Perlman, Salomons, & Davidson, 2013). Cognitive and learning factors also play a role in placebo analgesia, which can be viewed as a type of psychological modulation of pain. Here a descending network involving the anterior cingulate cortex and the periaqueductal gray has been identified (for a review, see Colloca, Klinger, Flor, & Bingel, 2013) that alters the transmission of nociceptive input already at the level of the spinal cord (Eippert, Finsterbusch, Bingel, & Büchel, 2009). K. B. Jensen et al. (2012) showed that cognitive-behavioral treatment specifically alters activity in the prefrontal cortex in response to pain in fibromyalgia patients. Operant-behavioral treatments have been advocated for persons who have low activity levels, display high pain behaviors, and have significant others who reinforce them for the display of pain behaviors (cf. Thieme, Flor, & Turk, 2006; Thieme, Turk, & Flor, 2007). Diers et al. (2012) showed that patients with fibromyalgia who underwent a pain extinction training based on operant principles displayed a shift from more activation in the anterior insula pretreatment to more activation in the posterior insula posttreatment. Changes in pain-related interference were closely related to changes in blood-oxygen-level-dependent activations in the posterior insula, primary somatosensory cortex, thalamus, and striatum, suggesting more sensory than affective processing and better pain prediction following successful pain control. These changes differ from those shown by K. B. Jensen et al. for cognitive-behavioral treatment and thus suggest that different behavioral treatments may impact different brain circuits.

Meditation

Several studies have examined structural and functional brain changes related to meditation and pain perception. Zeidan et al. (2011) used arterial spin labeling fMRI to analyze the neural mechanisms underlying pain control achieved by mindfulness meditation in healthy humans. They found that four days of meditation training significantly reduced pain intensity and unpleasantness ratings in response to noxious stimulation. In line with these changes, activity in contralateral primary somatosensory cortex was reduced. In addition, activity in the ACC and anterior insula was increased when pain intensity was lower, and thalamic deactivation as well as orbitofrontal activation were associated with unpleasantness reductions. These data suggest that the afferent input to the brain is actively modulated by meditation.

Brown and Jones (2010) examined how experienced meditators anticipated and controlled experimental laser pain using EEG recordings. More experienced meditators perceived the pain as less unpleasant than did controls, with meditation experience correlating inversely with unpleasantness ratings. Event-related potential (ERP) source data for anticipation showed that in meditators, lower activity in midcingulate cortex relative to controls was related to the lower unpleasantness ratings and was predicted by lifetime meditation experience. Meditators also reversed the normal positive correlation between medial prefrontal cortical activity and pain unpleasantness during anticipation. Meditation was also associated with lower activity in S2 and insula during the pain-evoked response, although the experiment could not disambiguate this activity from the preceding anticipation response. Thus, meditation seems to have strong effects specifically on the anticipation of pain.

Grant, Courtemanche, Duerden, Duncan, and Rainville (2010) examined the thickness of gray matter of the brain in long-term Zen meditators and found that they had lower pain sensitivity, which was associated with thicker cortex in the dorsal ACC and secondary somatosensory cortex. Moreover, more years of meditation training were associated with changes in anterior cingulate, and hours of experience were associated with more gray matter in the primary somatosensory cortex. These data suggest that structural brain changes and pain sensitivity are related and that meditation may impact this relationship. In a very interesting study that used functional imaging, Grant, Courtemanche, and Rainville (2011) also looked at brain activation and connectivity changes in Zen meditators and observed that those with the most intense meditation practice reduced activation in areas related to the cognitive-evaluative and emotional components of pain, such as the prefrontal cortex, amygdala, and hippocampus, and increased activation in thalamus, insula, and anterior cingulate cortex. Moreover, they showed reduced connectivity between brain regions involved in executive function and pain processing. This suggests that meditation, in contrast to cognitive strategies, induces a more passive type of pain regulation that results in a decoupling of cognitive and sensory processing, which is in line with notions about the role of passive attention in meditative techniques.

In line with these findings, Gard et al. (2012) examined persons who practiced mindfulness meditation and showed they had substantial reductions in pain intensity and unpleasantness compared to a control condition, reductions which were associated with reduced lateral prefrontal and increased right posterior insula activation. In addition,

anticipation of pain was associated with increased rostral anterior cingulate activity. Again, decreased cognitive control and increased sensory processing were observed, suggesting an alternate route to effective pain reduction than that of the enhanced cognitive control seen in cognitive-behavioral techniques.

Hypnosis

Seminal studies in healthy humans used hypnosis to induce either affective or sensory components of pain and found them associated with increased activation in either the anterior cingulate or the primary somatosensory cortex (Hofbauer, Rainville, Duncan, & Bushnell, 2001; Rainville, Carrier, Hofbauer, Bushnell, & Duncan, 1999; Rainville, Duncan, Price, Carrier, & Bushnell, 1997). Since then, several studies have focused on the effects of hypnosis on pain processing in healthy humans or in patients with chronic pain. In general, hypnotic techniques are very effective in modulating both acute and chronic pain (cf. M. P. Jensen, 2009, for a review). Derbyshire, Whalley, and Oakley (2009) instructed fibromyalgia patients to experience their clinical pain as differentially intense with and without hypnotic suggestions. These researchers found (a) changes in pain intensity according to instructions that were more pronounced during hypnotic induction and (b) altered activation in a number of brain regions related to the processing of pain such as the thalamus, somatosensory and midcingulate cortex, the insula, and prefrontal regions. Similar results were previously reported by these researchers for pain induced by hypnosis or imagery in healthy persons (Derbyshire, Whalley, Stenger, & Oakley, 2004).

Nusbaum et al. (2011) used positron emission tomography to examine the effects of hypnotic analgesia in chronic low back pain, and they also observed changes in brain networks involved in both emotional and cognitive processing. Abrahamsen et al. (2010) used hypnosis to induce either increased or decreased pain perception (hyperalgesia or hypoalgesia) in patients with temporomandibular disorder pain. They found increased activity in the right posterior insula and BA6 and left BA40 during hyperalgesia and increased activity in the right posterior insula during hypoalgesia. In addition, S1 activity decreased during hyperalgesia. Hypnotic hypoalgesia, compared to a control condition, showed significant decreases in activity in right posterior insula and BA21, as well as left BA40. These data suggest similarities between hypnotic analgesia and cognitive-behavioral interventions.

Sensory Discrimination Training

Phantom limb pain and other neuropathic pain states are characterized by reorganization of the sensorimotor cortex such that neural activity from regions adjacent to the site of the injury expands into the vacated space (in amputees) or changes its size (in complex regional pain syndromes). The magnitude of these changes is correlated with the pain these patients experience in the missing or affected limb. Such patients also show a number of structural changes (cf. Flor, Nikolajsen, & Jensen, 2006; see Henry, Chiodo, & Yang, 2011, for a review). These pain states can be treated by changing the input to the brain region that has been altered. For example, phantom limb pain has been reduced by improving tactile acuity in regions close to the amputation line in order to restore normal input to the brain region affected by the amputation. Two weeks of sensory discrimination training that involved the perception of the frequency and the location of two out of eight possible stimuli to the residual limb were provided. In the course of the training, the discriminability of the stimulus-pairs (in terms of frequency and location) was reduced in a shaping procedure. Verbal and visual feedback was provided. The treatment led to a significant improvement in both frequency and location discrimination, which was also reflected in improved two-point discrimination. It resulted in a more than 60% reduction in phantom limb pain and a significant reversal of cortical reorganization, with a shift of the mouth representation back to its original location (Flor, Denke, Schäfer, & Grüsser, 2001). The alterations in discrimination ability, pain, and cortical reorganization were significantly positively correlated. A control group of patients who received standard medical treatment and general psychological counseling in this time period did not show similar changes in cortical reorganization and phantom limb pain. These findings were confirmed by a study that used a similar protocol (Huse, Preissl, Larbig, & Birbaumer, 2001) with asynchronous tactile stimulation of the mouth and hand region.

Imagery, Mirrors, and Virtual Reality Treatment

Ramachandran, Rogers-Ramachandran, and Cobb (1995) employed a mirror to train patients with phantom limb pain to move the phantom and reduce phantom limb pain. A mirror was placed in a box, and the patient inserted his or her intact arm and the arm with the phantom. The patient was then asked to look at the mirror image of the intact arm, which was perceived as an intact arm in the location where the amputated arm used to be. The patients were then asked to make symmetric movements with both the intact and the phantom hands, thus suggesting real movement from the lost arm to the brain. This procedure seemed to re-establish control over the phantom and to reduce phantom limb pain in some but not all patients in this anecdotal study.

Extended mirror treatment was highly effective in reducing phantom limb pain in a controlled study (Chan et al., 2007), where it was compared with movement without a mirror and imagined movement. Diers, Christmann, Köppe, Ruf, and Flor (2010) contrasted a session of mirror training in amputees with and without phantom pain and healthy controls with imagery of movement and with actual movement and found that persons with phantom limb pain failed to activate the area in the somatosensory cortex that represented the limb seen in the mirror, whereas patients without pain showed a normal representation related to the mirrored hand and movement. The magnitude of the representation was negatively correlated with phantom limb

pain. This suggests that there is a failure in amputees with pain to adequately integrate the amputated limb in their body image and thus a failure to inhibit maladaptive plastic changes related to pain. Compared with mirror training, imagery had similar but weaker effects in this study. In healthy humans, Egsgaard, Petrini, Christoffersen, and Arendt-Nielsen (2011) examined EEG correlates of the mirror illusion and found that in men more than in women short-term plasticity of the primary somatosensory cortex as evident in early components of the ERP was present.

It can be assumed that imagined movement activates similar but not identical brain regions as actual movement, which can lead to a facilitation of normal movement with an accompanying reduction in pain (Raffin, Mattout, Reilly, & Giraux, 2012). Giraux and Sirigu (2003) showed that phantom limb pain was greatly reduced when patients imagined movements of the hand that had been amputated. The imagined movements led to a site-specific activation in the primary motor cortex. MacIver, Lloyd, Kelly, Roberts, and Nurmikko (2008) also found that therapeutic mental imagery caused a significant reduction in phantom limb pain with a concomitant normalization of brain activation in the sensorimotor cortex. These studies suggest that modification of input into the affected brain region by visual feedback and imagery alone may alter pain sensation and cortical plasticity. However, it needs to be determined whether imagined movements or executed movements of the phantom hand (which amputees can differentiate) are more effective (Raffin, Giraux, & Reilly, 2012). A virtual reality treatment that uses, for example, movement of the intact limb that is then fed back as movement from the phantom limb in virtual reality (e.g., Murray et al., 2007) and the use of full-body virtual feedback (e.g., Schmalzl et al., 2011) might also be useful treatment options and could be even more effective in altering the distorted body image and restoring function.

Neurofeedback and Biofeedback

Neurofeedback refers to all techniques that make use of brain activity to influence the processing of pain-related stimuli or the experience of chronic pain. In the electroencephalogram, three types of ERPs have been identified as correlates of pain perception (they cannot be called measures of pain because they are influenced by a number of factors such as attention and general activation): (a) brainstem potentials (10 to 15 ms after the application of the stimulus); (b) potentials of short latency (15 to 20 ms after the application of the stimulus), which are probably based on thalamocortical sources; and (c) potentials of long latency (50 to 200 ms after the stimulus), which have a cortical basis (Flor & Meyer, 2011). Subjective pain perception correlates with the amplitude of the ERP in the 150–260 ms range, which may provide information in addition to the pain rating.

The effects of EEG feedback on pain-related cortical responses were studied by Miltner, Larbig, and Braun (1988), who showed that the pain-related brain potential can be modified by feedback and that the increased or decreased amplitude of the N150/P260 components of the electroencephalogram is also reflected in increased or decreased pain ratings. Dowman (1996) could not replicate these reports that the operantly conditioned P260 component of the somatosensory evoked potential is correlated with altered pain ratings and altered nociceptive reflexes. There is still no evidence that these potentials can be changed by feedback in patients with chronic pain.

EEG measures have also been used to study the characteristics of headache patients, especially those with migraine. Siniatchkin, Gerber, Kropp, and Vein (1998) investigated slow cortical potentials of the electroencephalogram in migraineurs and found them to be elevated, indicative of cortical hyperexcitability. They tested the efficacy of biofeedback training of slow cortical potentials in young migraineurs. Children with migraine are characterized by increased cortical excitability they cannot control. During extended training, the children acquired this skill and could reduce cortical negativity, which was accompanied by a significant reduction of days with migraine and other headache parameters.

The EEG power spectrum provides a measure of the relative "power" of the EEG waves within a certain frequency band. Usually the bands that are discriminated are delta (0.5–3.5 Hz; profound sleep and pathology), theta (3.5–7.5 Hz; deep sleep, but also focused attention if localized in the frontal area), alpha (8–12 Hz; relaxed wakefulness with the eyes closed), and beta (13–30 Hz; eyes open, attentive). Sarnthein, Stern, Aufenberg, Rousson, and Jeanmonod (2006) showed that patients with chronic pain show overactivations predominantly within the high theta (6–9 Hz) and low beta (12–16 Hz) frequency ranges. Theta and beta overactivations were localized to multiple pain-associated areas, primarily to insular, anterior cingulate, prefrontal, and inferior posterior parietal cortices, as well as to primary, secondary, and supplementary somatosensory cortices. Initial attempts to alter EEG frequencies by feedback in patients with chronic pain (e.g., Caro & Winter, 2011; M. P. Jensen, Grierson, Tracy-Smith, Bacigalupi, & Othmer, 2007; Kayiran, Dursun, Dursun, Ermutlu, & Karamursel, 2010) have shown promising effects on pain and physiological indicators (e.g., M. P. Jensen et al., 2007).

DeCharms et al. (2005) found that by using real-time fMRI (rtfMRI) to guide training, subjects were able to learn to control activation in the rostral ACC, a region putatively involved in pain perception and regulation. When subjects deliberately induced increases or decreases in rostral ACC fMRI activation, there was a corresponding change in the perception of pain caused when a noxious thermal stimulus was applied. Control experiments demonstrated that this effect was not observed after similar training conducted without rtfMRI information, with rtfMRI information derived from a different brain region, or with sham rtfMRI information derived previously from a different subject. Patients with chronic pain were also trained to control rostral ACC activation; they reported decreases in the ongoing level of chronic pain after training. Although costly, this method might be an alternative to neurosurgical techniques for patients with otherwise intractable pain.

Several forms of peripheral biofeedback can be employed to effectively reduce the amount of irritating and nociceptive input into the brain region that represents the affected part of the body. Electromyography feedback might be especially effective in musculoskeletal pain syndromes because it can change nociceptive to non-nociceptive input by relaxing tense muscles and relieving the tension-associated pain and reduced blood flow (Andrasik, 2010).

Component Analyses

Several authors have attempted to differentiate the effective components of psychological interventions related to pain. Various types of cognitive interventions were already described above. Villemure and Bushnell (2009) used odors to selectively modulate the affective component of pain and used attentional focus (discrimination of pain or odors) to modulate the attentional component. They found that pleasant odors, independent of attentional focus, induced positive mood changes and led to reduced pain unpleasantness. This reduced pain perception was associated with decreased pain-related activity in the anterior cingulate cortex, medial thalamus, and primary and secondary somatosensory cortices. Attentional modulation was less clear and affected mainly the anterior insula. Affective modulation covaried with activity in the lateral inferior frontal cortex; attentional modulation was correlated with superior posterior parietal and entorhinal activity. These authors also observed covariations between the ACC, left inferior frontal cortex, and periaqueductal gray, indicating a mood-related circuit, and between the insula and the superior posterior parietal cortex, suggesting an attention-related network. They concluded that separate neuromodulatory circuits underlie emotional and attentional modulation of pain. This type of analysis could be extended to other aspects of pain modulation and other brain networks involved in pain regulation.

Placebo Treatment and Motivation of the Patient

The neurophysiological effects of effective placebos have been studied quite extensively and may permit us to draw conclusions about the effects of psychological interventions, since the underlying mechanisms in placebos are modifications in expectancy and classical conditioning (Carlino, Pollo, & Benedetti, 2011), mechanisms similar to those underlying psychological treatments. A network ranging from dorsolateral prefrontal and orbitofrontal cortex to the rostral ACC, the periaqueductal gray, the rostroventral medulla, and the spinal cord seems to mediate the effects of placebos on pain perception (Krummenacher, Candia, Folkers, Schedlowski, & Schonbachler, 2010; Tracey, 2010). In addition, opioidergic and dopaminergic pathways are involved (Eippert et al., 2009; Scott et al., 2008). Interestingly, in patients, conditioning (i.e., the actual experience of pain reduction related to a placebo intervention), compared with expectancy alone, seems to have better and more stable effects (Klinger, Soost, Flor, & Worm, 2007). In placebo studies, conditioning is usually realized by associating the placebo with the experience of pain relief, which leads to pain reduction when the placebo is later given without a concurrent change in pain intensity (Colloca et al., 2013). This suggests that the assessment of prior experiences with pain treatments including psychological interventions may be useful, because they may have become conditioned stimuli for the experience of pain. Placebo effects should also be actively used to improve both psychological and pharmacological pain interventions.

In addition, neurophysiological changes related to pain but also to pain-related interventions can be employed to motivate patients to participate in psychological pain treatments, which is often difficult, because many patients insist on a somatic intervention and regard psychological interventions as inferior. Informing patients about neurophysiological alterations related to pain and the effects psychological treatments can have on the brain and peripheral measures can greatly enhance treatment motivation and facilitate treatment. This can also help to increase the acceptance of psychological interventions in clinical practice (Newman, 2004).

Discussion

In this article, pain-related alterations in the structure and function of the brain have been described. Numerous studies have employed neurophysiological measures to demonstrate changes related to a range of effective psychological interventions and individual components such as cognitive or emotional modulation. These studies have also shown that seemingly similar interventions such as attention diversion, enhanced cognitive control, or meditation act through different neurophysiological mechanisms that involve frontal, parietal or limbic brain regions.

The analysis of psychological and neurophysiological mechanisms related to chronic pain can thus aid in the determination of subgroups of patients who might differentially profit from certain psychological interventions. To achieve this, we need more component analyses of psychological interventions that should also involve neurophysiological measures. For example, cognitive-behavioral interventions include a range of cognitive and behavioral components, and we presently do not know if they are all necessary or if some are superior to others. Likewise, many treatment approaches that are viewed as different—for example, acceptance and commitment-based approaches and cognitive-behavioral interventions—share many similarities, thus making it difficult to disentangle their specific components and determine if certain ones are actually superior. Here, component analyses with concomitant neurophysiological studies would also be helpful. It would also be interesting to contrast the neurophysiological mechanisms by which psychological versus pharmacological interventions exert their effects. Showing that psychological interventions act on both functional and structural aspects of brain function may also increase their acceptance in both the scientific realm and among patients, who are often still

skeptical of psychological interventions, especially with respect to seemingly "somatic" disorders such as chronic pain. The use of neurophysiological indicators of both changes related to the experience of chronic pain and changes related to the use of psychological pain modulation strategies may counteract this skepticism and convey that psychological interventions also have effects on somatic processes. Finally, the analysis of neurophysiological mechanisms may also lead to the development of new psychological interventions that can target these changes in a much more specific manner than pharmacological interventions (see Moseley & Flor, 2012). A further important issue that was only addressed in a cursory fashion in this article is the close interaction of central and peripheral physiological processes in chronic pain that involves site-specific disruptions in body perception and physiological regulation. These issues need to be examined in more detail in the future.

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