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The use of functional neuroimaging to evaluate psychological and other non-pharmacological treatments for clinical pain

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Abstract

A large number of studies have provided evidence for the efficacy of psychological and other non-pharmacological interventions in the treatment of chronic pain. While these methods are increasingly used to treat pain, remarkably few studies focused on the exploration of their neural correlates. The aim of this article was to review the findings from neuroimaging studies that evaluated the neural response to distraction-based techniques, cognitive behavioral therapy (CBT), clinical hypnosis, mental imagery, physical therapy/exercise, biofeedback, and mirror therapy. To date, the results from studies that used neuroimaging to evaluate these methods have not been conclusive and the experimental methods have been suboptimal for assessing clinical pain. Still, several different psychological and non-pharmacological treatment modalities were associated with increased pain-related activations of executive cognitive brain regions, such as the ventral- and dorsolateral prefrontal cortex. There was also evidence for decreased pain-related activations in afferent pain regions and limbic structures. If future studies will address the technical and methodological challenges of today's experiments, neuroimaging might have the potential of segregating the neural mechanisms of different treatment interventions and elucidate predictive and mediating factors for successful treatment outcomes. Evaluations of treatment-related brain changes (functional and structural) might also allow for sub-grouping of patients and help to develop individualized treatments.

Keywords

Pain; neuroimaging; non-pharmacological; psychological modulation; analgesia

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Introduction

With increased evidence for the efficacy of psychological interventions in the treatment of acute and chronic pain [74, 77, 108], these methods are more and more commonly used in pain clinics, either alone or in combination with pharmacological treatment. While these interventions have been investigated by a large number of behavioral studies, remarkably few studies have focused on the exploration of their neural correlates. As we will discuss, an understanding of the neurobiological mechanisms by which these techniques produce alterations in the experience of pain could have a number of significant implications, which might ultimately enhance treatment efficacy. The aim of this review is to highlight the findings from neuroimaging studies that evaluated the neural effects of commonly used psychological and other non-pharmacological treatments for pain. In brief, the present article summarizes the neuroimaging findings from seven different treatment modalities: distraction based techniques, cognitive behavioral therapy (CBT), clinical hypnosis, mental imagery, physical therapy/exercise, biofeedback, and mirror therapy.

The brain is a potent source of pain modulation, and since the advent of neuroimaging techniques, the neural underpinnings of endogenous modulation of pain have been extensively investigated in healthy volunteers. For example, functional Magnetic Resonance Imaging (fMRI) and Positron Emission Tomography (PET) have been used to assess changes in central pain processing in response to distraction techniques [9, 118], hypnotic states [125, 130] and altered anticipation of pain [26, 68, 83, 157]. Overall, findings suggest that psychological modulation of pain is accompanied by objectively measurable changes in neuronal activity (during administration of a noxious stimulus) [162] in regions such as the lateral Prefrontal Cortex (PFC) [119], the rostral Anterior Cingulate Cortex (ACC) [15, 40, 157], the dorsal part of the ACC [9, 94], or the Periaqueductal Gray (PAG) [151] (see Figure 1). Results from neuroimaging studies in healthy volunteers have been important in moving beyond self-report and assessing the neural underpinnings of “psychological” pain modulation in the central nervous system. Direct evidence of neural networks that support endogenous modulation of pain is likely to have improved the general acceptance of psychological treatment strategies and promoted their legitimacy as an effective component of multidisciplinary pain treatment.

Brain imaging studies have contributed to the understanding of cerebral changes associated with chronic pain [5, 140, 141] and evidence includes structural [21, 32, 45, 86, 138], functional [7, 56, 67, 70, 141] and neurochemical brain alterations [59, 75, 165] in patients, compared to carefully matched controls. There are indications of a linear relationship between specific brain changes and the duration of chronic pain [86], suggesting that long-term exposure to pain might cause central alterations such as decreased grey matter of the prefrontal cortex [7], and not vice versa [99, 136]. Furthermore, recent evidence points towards normalization of brain structure and function in response to successful treatment for chronic pain [58, 114, 116, 136, 144], indicating that brain plasticity can be bidirectional. In the presence of persistent pain, patients often suffer from cognitive deficits, and recent neuroimaging studies have linked pain patients’ cognitive dysfunction to specific changes in brain structure [95] and function [54], providing evidence for a pain-cognition interaction. Given the plasticity of the brain in response to analgesia, and the close interaction between pain modulation and executive cognitive function, it is likely that psychological interventions targeting clinical pain are associated with adaptive changes in brain function or structure. To date, few studies have evaluated the neural underpinnings of psychological treatments for pain in clinical populations. It is our hope that this review will inspire neuroscientists and pain clinicians to collaborate in future studies where neuroimaging is used as a tool to evaluate non-pharmacological pain treatments.

Neuroimaging of distraction-based techniques in pain patients

Both clinical and experimental studies have demonstrated that noxious stimuli can be perceived as significantly less painful when the attention is directed away from them [140, 153]. For instance, several authors have observed that measures of pain sensitivity are decreased when the attention of healthy volunteers is directed towards simultaneously presented visual [94, 106] auditory [24, 38], olfactory [155] or tactile [94] stimuli, and/or engaging activities [25].

Numerous imaging experiments in healthy volunteers have demonstrated that pain reductions during distraction are associated with decreased pain-evoked activations in structures belonging to the thalamo-cortical ascending pain network [6], such as the thalamus, primary and secondary somatosensory cortices, insula and ACC [10, 17, 24, 51, 66, 94, 143, 152, 154, 163]. Moreover, neurophysiological studies in monkeys have shown that nociceptive neurons in the medullary dorsal horn and the medial thalamus are less responsive to noxious stimuli when the monkey is attending to a distracter, compared to attending to the pain [22, 23]. Distraction from pain is not only accompanied by reduced activity in some pain processing structures, but also by increased activity in brain regions such as the PAG, the rostral parts of the ACC and the orbitofrontal cortex [51, 151, 152]. Taken together, these studies suggest that distraction-related reductions in reported pain are associated with objective neurophysiological changes, some of which occur at early stages of sensory processing, and can therefore not be explained in terms of report bias. It is important to note that some brain structures, such as the ACC, may be divided in sub-regions that serve different aspects of pain processing [156], and therefore a region can sometimes be associated with increases or decreases in response to pain modulation, depending on the exact anatomical location. For example, activation of the rostral ACC has been demonstrated during inhibition of pain [15, 120], whereas activation of the more posterior parts of the ACC has been associated with increased pain affect [46, 47, 139].

In clinical settings, distraction has been employed to reduce pain during uncomfortable procedures, such as venipuncture [4, 166], cataract surgery [146], endoscopy [90] and wound care [65, 110]. Among the most well studied clinical applications of a distraction-based technique is the use of immersive virtual reality (VR) in acute burn patients. When distracted with VR, patients often report significant reductions in pain and discomfort during the painful procedures of wound cleaning and debridement [65, 110]. Although no fMRI study has, to our knowledge, investigated the neural underpinning of VR-analgesia in pain patients, the use of VR in healthy volunteers undergoing heat pain stimulation [66] was shown to be associated with reduced pain-related fMRI signals in the ACC, insula, thalamus, primary and secondary somatosensory cortices, suggesting that an analogous mechanism might mediate the analgesic effect of VR in patient care. While distraction techniques have proved to be successful means of reducing acute pain, their application as strategies to control chronic pain might present some difficulties. In fact, studies have suggested that patients with chronic pain have an attentional bias towards pain, or a failure to disengage from pain [122, 145]. Thus, such patients might benefit from the application of techniques focused at modifying the attentional bias [19, 20].

In summary, results from the literature suggest that distraction could be successfully used as a pain control strategy and neural correlates to distraction based interventions include reduced activation in afferent pain regions, as well as increased activation in structures of the descending pain inhibitory circuitry.

Functional imaging of CBT in pain patients

Cognitive Behavioral Therapy (CBT) is an evidence-based psychotherapeutic method, rooted in behaviorism and cognitive psychological theory. Since the introduction of CBT-based treatments for chronic pain more than 35 years ago [48, 78], there have been many published reports of symptom improvements in patients with various forms of chronic pain [14, 64, 93, 97, 160]. CBT is often conducted through weekly therapy sessions, in combination with home assignments. Central to treatments based on CBT is the identification of maladaptive cognitions and behavior patterns, such as catastrophizing thoughts [39] or avoidance behaviors [100], which can be targeted by exposure-oriented interventions.

Despite the common use of CBT for chronic pain, only two studies have investigated the neural correlates of CBT in pain patients [71, 89]. The two studies used similar treatment protocols, including weekly CBT sessions in small groups of 3-5 patients, combined with home assignments. Lackner and colleagues [89], used PET to evaluate the effect of a 10-week CBT trial in 8 female patients with Irritable Bowel Syndrome (IBS) and Jensen et al [71] used fMRI to assess the response to a randomized, 12-week, waiting-list controlled trial in 43 female patients with Fibromyalgia syndrome (FM). Results from both studies found that the clinical effect of CBT was paired with significant changes in brain activations post-treatment. More specifically, patients with IBS displayed decreased PET O-15 resting-state activity in the limbic regions post-treatment, including the parahippocampal gyrus and cingulate cortex, bilaterally. It is possible that the decreased limbic activity in response to CBT reflected attenuated vigilance and attention to pain, as both these measures improved post-treatment. fMRI measures in patients with FM revealed that CBT led to increased pain-evoked activation of the lateral PFC after treatment, compared to controls (see Figure 2). Moreover, patients treated with CBT displayed increased connectivity between the PFC and the thalamus. The thalamus is a critical relay site for afferent signals, including pain [150], and decreased thalamic activity has previously been implicated in pain pathology [28, 69, 88, 112]. Therefore, increased coherence between the PFC and the thalamus might be an indication of attenuated central pain pathology.

As an interesting comparison, neuroimaging evaluations of CBT in psychiatric conditions have often reported decreased activation of limbic regions and increased function of the prefrontal cortex (PFC) in response to treatment (for a review see Ribeiro et al.) [133], suggesting that CBT can lead to decrements in maladaptive cognitive and emotional processes (e.g., fear, negative affect, obsessive thoughts, etc.) through increased prefrontal control. Moreover, pre-treatment activity in the ventromedial PFC predicted a positive response to CBT in depression, suggesting that patients with less pre-treatment impairments might be more likely to benefit from cognitive behavioral interventions [134].

In summary, neuroimaging has contributed to the understanding of the neural changes that can be attributed to CBT in chronic pain. However, there are a number of limitations to the present findings. Firstly, the study in IBS assessed the post-treatment effects of CBT without including a control group in the analysis. This means that the natural history or test-retest effects may have confounded the neuroimaging results. Secondly, only six patients were included in the evaluation of post-treatment effects of CBT, suggesting that the study was underpowered and should be interpreted with caution. The FM study included a waiting-list control group but there was no active control for CBT, e.g. weekly social sessions or lectures about pain. Future studies should validate these preliminary findings by randomizing patients to either a CBT arm, pharmacological arm, CBT + pharmacological arm, active control or natural history. Contrasting information about the functional brain changes in response to CBT and other treatments will increase the chances of finding

specific treatment mechanisms for CBT, if they exist. CBT is a relatively expensive treatment and future studies should break down the different components of CBT and see if any specific intervention contributes more to the changes in central processing seen after treatment. In fact, most CBT programs, beyond addressing the maladaptive cognitive and behavioral patterns, also teach elements of physical therapy, mental imagery, or distraction techniques, and therefore studying these modalities separately is of related interest.

Functional imaging of clinical hypnosis in pain patients

Hypnosis is a procedure in which suggestions for imaginative experiences are presented after an hypnotic induction, often including suggestions of relaxation, deep breathing and/or focused attention.[57]. The subject is guided by the hypnotherapist to respond to suggestions for changes in subjective experience, perception, sensation, emotion, thought, or behavior [57]. In the context of pain relief, an initial suggestion of relaxation is often followed by different suggestions which can enhance distraction, positive affect, feelings of self efficacy and control over pain or alter the way pain is experienced [117]. The psychological mechanisms involved in hypnotic analgesia have not yet been fully explained [73, 126], but it is likely that several factors contribute to the desired effect, e.g. altered expectancy, reappraisal, sense of control, mood, and attentional focus.

Studies in healthy volunteers have demonstrated a variety of neural underpinnings for hypnotic analgesia. Work by Rainville, Hofbauer, and collaborators has established that suggestions aimed at modifying pain unpleasantness are linearly associated with pain-related activation in the ACC [128], while those altering pain intensity correlate with activity in primary sensory cortex (SI) [63]; suggesting that these discrete aspects of the painful experience could be modulated separately [127]. Collectively, the analgesic effect of hypnotic modulation has repeatedly been associated with altered activity in the ACC [42, 129]. Furthermore, hypnotic analgesia has been proposed to be mediated by an increase in the functional connectivity between the mid-cingulate cortex and a large cortico-subcortical network including the brainstem, thalamus, insulae, ACC, the supplementary premotor cortex and the right PFC, suggesting an alteration in the integration of sensory, affective, cognitive and behavioral aspects of the pain experience [43].

Therapist-delivered hypnosis was shown to benefit patients suffering from chronic pain [73] but self-hypnosis can also lead to analgesia in patients, similarly to other therapies involving relaxation or imagery [72, 73]. To date, four neuroimaging studies evaluated the effects of hypnotic analgesia in chronic pain patients: two studies in FM [35, 164], one in temporomandibular joint disorder [1], and one in patients with chronic low back pain [115]. In contrast to assessments of hypnotic analgesia in healthy volunteers, none of these studies found activity changes in the ACC when comparing hypnotic analgesia to a control condition, and each showed a unique pattern of changed brain activations [1, 35, 115, 164]. Some key methodological differences could explain the absence of a consensual finding from these studies. For example, the study by Derbyshire et al. collapsed hyperalgesic and hypoalgesic suggestions and compared the hypnotic state to the non-hypnotic state, instead of comparing the hypnotic analgesia versus the same non-hypnotic suggestions [35], while Nusbaum et al. did not test the statistical difference between activations in the hypnotic state and the control state [115]. These results could therefore justify further studies asking a more specific question, such as: is hypno-analgesia in patients mediated by different central circuits compared to healthy volunteers? Brain imaging techniques might also help to better understand hypnotic susceptibility, as this personal quality seems to be a determining factor in the response to hypno-analgesia [33, 107]. Finally, these technologies could also participate in identifying other predictors of response to hypnotherapy for pain, since

hypnotic susceptibility appears to explain only a part of the difference in pain ratings in an hypnotic analgesia condition [1].

Neuroimaging of mental imagery in pain patients

Mental images are sensory experiences in the absence of a direct percept, resulting from a cognitive process by which perceptual information is retrieved from memory to create a new experience, allowing to 'see with the mind's eye' or 'smell with the mind's nose' [84]. Mental imagery-based therapy is frequently used in clinical practice for pain relief and consists of suggesting specific (positive) mental images, which the patient tries to experience in his/her mind [121]. Clinical trials of mental imagery have shown benefits for patients with chronic pain [e.g. 3, 8, 18, 49, 50, 87, 91, 92, 96, 102, 124]. Nonetheless, there are methodological issues with many of the studies conducted in this field, as discussed in recent literature reviews [109, 123].

Mental imagery techniques are carried out specifically without the 'induction' phase characteristic of hypnosis. The hypnotic induction might in fact be less important to obtain responsiveness to suggestions than once thought, and most of the effects of hypnosis could be due to the underlying suggestions [82]. In fact, well-controlled hypnotic inductions with no specific suggestions seem to have no analgesic effect [63, 127] thus providing a rationale for studying the neurophysiological underpinnings of suggestions.

However, all brain imaging studies of mental imagery-based pain modulation published to date are control conditions in hypnosis experiments [35, 42, 43, 115]. These control conditions could be more or less valid, as the suggestions in hypnosis and mental-imagery are sometimes different [43] or given in a different way (e.g. tone of voice, prosody) [115]. This, as well as participant's expectations towards hypnosis could significantly impact the effectiveness of the control [82], and therefore the conclusions held about this technique. Furthermore, all of these studies selected participants with high hypnotic suggestibility [35, 42, 43, 115], leaving many questions open about the excluded patients with low hypnotic suggestibility [105].

In summary, while brain activity during mental imagery for pain relief has been assessed using functional neuroimaging [115], no study has compared a mental imagery task to a control condition with similar cognitive load to investigate the specific neural underpinnings of this technique. The studies that compared mental imagery with hypnosis prevented the assessment of specific mental imagery mechanisms by collapsing the mental imagery condition with a rest condition [42, 43]. Future studies could also compare different suggestions, potentially demonstrating the recruitment of different brain networks, and hence the ability of mental imagery to rely on different cognitive mechanisms. This could be useful, as patients with different psychological profiles could benefit more from one or the other cognitive modulation of pain. This viewpoint is supported by studies demonstrating that the meaning of a visual image likely plays an important role in shaping brain responses (e.g., viewing a specific religious image has different effects on pain perception in individuals with differing belief systems) [161], highlighting the potential benefits of tailoring images and suggestions to individual patients.

Neuroimaging of physiotherapy/exercise in pain patients

Physiotherapy and exercise-based interventions for the management of chronic pain are widely recommended and have proven effective in reducing pain and improving physical function in a variety of pain syndromes, including FM [80], back pain [61], arthritis [79], and many others. These treatments take a variety of forms, from one-on-one sessions with a

licensed physiotherapist, to group aquatherapy sessions, to prescription of stretching and muscle-strengthening exercises at home. In general, the available data suggests that any type of physiotherapy intervention that increases physical activity (e.g., stretching, cardiovascular conditioning, strength training, etc.) may have pain-relieving benefits, with few differences between various schools of physiotherapy or types of exercise [29]. A recent systematic review concluded that clinical improvements in back pain following exercise and physiotherapy treatment were largely uncorrelated with objective improvements in musculoskeletal performance (i.e., range of motion, skeletal muscle strength, muscular endurance), suggesting that other changes, potentially in the central processing of pain or mood, play an important role in these treatments [149].

Recent findings, both from animal studies and clinical trials, provide evidence for central nervous system mechanisms in exercise-induced analgesia [13, 148]. Unfortunately, to date there are few functional neuroimaging studies of the specific pathways by which physiotherapy and exercise may reduce pain perception. One recent report in healthy volunteers used transcranial magnetic stimulation to demonstrate that administration of a noxious mechanical stimulus enhanced the amplitude of motor-evoked potentials [62]. The performance of isometric exercise reduced pain intensity and attenuated the pain-induced increase in motor-evoked potentials, suggesting that exercise may lead to modulation of corticomotor excitability [62]. Somewhat surprisingly, no studies have directly examined brain responses to pain before and after a standardized exercise protocol. Such a study might pose some interpretive difficulties, as recent exercise would likely alter respiration, cardiopulmonary function, and cerebral blood flow, complicating the characterization of the blood oxygenation level dependent fMRI signal following a bout of exercise. However, the PAG and subthalamic nucleus are intimately involved in initiating and integrating cardiovascular responses to exercise [11], and in particular the PAG plays an important role in opioid-dependent pain modulation, highlighting a possible mechanistic link between exercise and pain reduction.

Rather than directly study an exercise intervention, a recent fMRI study of heat pain responses in FM patients and controls separated participants as a function of recent physical activity [101]. Patients and controls who were more physically active over the preceding week demonstrated reduced heat pain ratings and increased brain responses to painful heat in pain-modulatory areas such as the dorsolateral PFC, though PAG responses were unrelated to physical activity measures [101]. The dorsolateral PFC and related areas have been linked to cognitively driven pain inhibition in the context of, for example, placebo analgesia [85]. It is possible that there is substantial mechanistic overlap between physiotherapy/exercise-based interventions and psychological treatments. Outcomes studies suggest that treatments targeted at increasing physical activity among chronic pain patients produce strong reductions in symptoms of distress and catastrophizing thoughts, and that these cognitive and emotional changes mediate the observed reductions in pain intensity and physical disability that the treatment produces [52, 147]. Future trials of exercise and physiotherapy interventions will have to evaluate whether changes in cerebral pain processing are attributable specifically to increases in physical activity, or to ancillary changes in the psychosocial domain.

Neuroimaging of biofeedback in pain patients

Biofeedback is comprised of a set of methodologies whereby individuals are provided with real-time feedback of different physiological parameters, with the goal of developing awareness of and control over these bodily processes, some of which may traditionally be considered “involuntary” [55]. In the context of pain management, the physiological targets of biofeedback are typically processes that are directly associated with pain exacerbations,

or stress responses that are presumed to exacerbate pain. Recent systematic reviews and meta-analyses provide empirical support for a variety of biofeedback methods for managing chronic headache, back pain, orofacial pain, etc [2, 81, 113]. Physiological targets include, among others, heart rate and heart rate variability, surface electromyography of skeletal muscle, skin temperature, galvanic skin response.

Most recently, Electroencephalography (EEG) biofeedback has been studied in several trials in patients with FM. In EEG biofeedback, the amplitudes of resting EEG frequency bands (i.e., Theta 4–8 Hz: associated with early-stage sleep; Alpha 8–12 Hz: associated with a relaxed and defocused attentional state; Beta 13 Hz or greater: associated with higher-order cognition) are represented visually and participants attempt to learn to increase or decrease the power or amplitude of particular frequency bands. Prior work in healthy adults had demonstrated that subjects were able to alter the relative power of particular EEG frequency bands; for example, increasing the Theta/Alpha ratio [12], or reducing relative Alpha power [137]. In studies of patients with FM, participants were able to learn to modulate EEG signals over the course of ten to forty sessions [27, 76]. In general, patients treated with EEG biofeedback showed improvements in a variety of symptoms, including pain, fatigue, anxiety etc. Putative mechanisms that might underlie such effects include the promotion of functional neuroplasticity and enhancement of motor cortex excitability [137], as well as the facilitation of thalamocortical inhibitory pathways [76].

To date, no functional neuroimaging studies have scanned participants before and after the application of a pain-reducing biofeedback technique, so data on the neural mechanisms underlying the analgesic benefits of biofeedback are not available. Some researchers have used real-time fMRI to perform “neurofeedback” during a scan, providing immediate visual feedback to subjects about brain activation in areas involved in pain processing and regulation such as the ACC. This emerging technique has been discussed in detail by deCharms et al [34] and Weiskopf et al [159].

One significant challenge in this field will be the selection of the physiological parameter to provide feedback on. While EEG is an attractive target, other processes have been effectively targeted as well. For example, a recent study of heart rate variability and biofeedback (intended to dampen autonomic reactivity) in patients with FM reported increased heart rate variability over the course of 10 weeks of training, which was associated with significant decreases in pain and depression, and improvement in physical function at 3-month follow-up [60]. In this field, additional research is needed to clarify which physiological parameters subjects are most able to modulate, and which parameters are most closely related to pain. In addition, further studies will be required to evaluate the specificity of any brain responses to pain, since biofeedback treatments may produce a host of non-specific effects [81].

Neuroimaging of mirror therapy in pain patients

Mirror therapy is an exposure-based therapy for painful limbs, using a 24 × 24 inches mirror box, propped in between the patient’s unaffected and affected limb [131]. When looking at the box, the patient sees the mirror image of the unaffected limb taking the place of the affected limb in their visual field. By moving the normal limb, the affected side is perceived to move as well. Mirror boxes are available for as little as 40 U.S. dollars and treatment can be effectively self-delivered at home [31].

The discovery of mirror neurons in the brain [36], and reports of perceptual correlates of cortical reorganization following limb amputation [132], has provided a rationale for mirror therapy in patients with hemiparesis or chronic pain. As mirror neurons are activated both

during the performance of a motor action and during observation of another individual performing a similar action [44, 98] [135], it has been suggested that the treatment mechanisms in mirror therapy are related to brain neuroplasticity induced by the vicarious (“mirror”) activation of the somatotopic representation of the affected limb [53].

A few randomized controlled trials have assessed the effect of mirror therapy for pain. One study was a 4-week crossover trial in 18 patients with phantom limb pain (PLP) [30], and one was a 6-week crossover trial performed in 13 patients with complex regional pain syndrome Type I [111]. In both studies the majority of subjects who received mirror therapy had more than 50% improvement of pain when assessed at 8 and 24 weeks, respectively.

The neural correlates to the treatment effect of mirror therapy have been investigated by means of fMRI. In patients with stroke, the mirror illusion was associated with increased activations in the precuneus and the posterior cingulate cortex; areas associated with awareness of the self and spatial attention [104]. Interestingly, the authors did not observe mirror-therapy related brain activations in areas of the motor cortex or other regions of mirror neuron system. The findings from this stroke trial question whether mirror neurons underlie the efficacy of mirror therapy. In a follow up randomized clinical trial by the same group, 16 subjects with stroke underwent 6 weeks of mirror therapy, or a control condition, and repeated fMRI scans. While mirror therapy was only weakly effective in improving function, it was associated with a shift in activation balance of the primary motor cortex toward the affected brain hemisphere, suggesting cortical reorganization [103]. In 14 patients with upper extremity amputation (7 with and 7 without PLP), Diers and colleagues demonstrated that patients without PLP had greater mirror-related activation in primary somatosensory and primary motor cortices during fMRI scanning [37]. However, in a recent fMRI treatment study by Seidel and colleagues [142], 12 sessions of mirror therapy in amputees with PLP were not associated with changes in mirror-related activation in the primary somatosensory and motor cortices, even though patients reported more than 50% mean improvement of pain. These results question whether sensorimotor reorganization underlies mirror therapy success or if it is a relevant precondition for pain relief.

While mirror therapy is a promising intervention for painful conditions such as PLP and complex regional pain syndrome, there is a need for larger clinical trials with better chances of detecting possible responders and non-responders. Neuroimaging techniques are well suited to study potential reorganization of cortical function and future studies might provide better characterization of the neural changes attributable to mirror therapy. A large randomized clinical trial that combines continuous measures of treatment outcomes and neuroimaging assessments, would be a most favorable approach to addressing these issues.

Discussion

To date, only few studies used functional neuroimaging to evaluate psychological and other non-pharmacological treatments for pain, however, the advances of modern neuroimaging techniques holds the promise for more such studies in the future. Hitherto, most neuroimaging methods were optimized for experimental pain paradigms, and the ability to assess clinical improvements of naturally occurring pain have been limited. Nevertheless, new neuroimaging techniques are being developed and Arterial Spin Labeling, for example, could be a useful tool for measuring slow fluctuations of chronic pain [158]. Also, the development of spinal fMRI tools [16, 41] might lead to better characterization of differences in pain processing after treatment with psychological and other non-pharmacological interventions. If future studies will address the technical and methodological challenges of today’s experiments, neuroimaging might have the potential of segregating the neural mechanisms of different treatment interventions and elucidate

predictive and mediating factors for successful treatment outcomes. Evaluations of treatment-related brain changes (functional and structural) might also allow for sub-grouping of patients and help to develop individualized treatments. Compared to pharmacological treatment, psychological and non-pharmacological treatments for pain often require more personal and economic resources. Therefore, it would be valuable to develop standardized neuroimaging assessments for predicting responders to certain treatment modalities. Moreover, it is possible that neuroimaging will become a standardized method for acquiring biomarkers/objective correlates to pain ratings in clinical trials. Finally, while the translation from the neuroimaging-lab to the clinic could lead to some clear benefits, it is also likely that the understanding of how psychological treatments change the brain will increase our general understanding of the role of the brain in chronic pain.

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Highlights

- Summary of neuroimaging studies of psychological treatments for clinical pain
- Advantages/limitations of using neuroimaging to evaluate these interventions
- Future implications for using neuroimaging to develop effective treatments for pain

Figure 1. Possible neural pathways of cognitive pain modulation (adapted from Wiech, Ploner and Tracey, 2008)

Cognitive modulations of pain are related to activation of prefrontal brain areas such as the dorsolateral prefrontal cortex (DLPFC), ventrolateral prefrontal cortex (VLPFC), and to the anterior cingulate cortex (ACC); shown in orange. These regions may modulate activation in afferent pain regions in the cortex (ACC, primary- and secondary somatosensory cortex, insula and thalamus), as well as the periaqueductal gray (PAG) and dorsal horns of the spinal cord; shown in blue. The DLPFC and VLPFC are connected to the ACC, which, in turn, projects to thalamus and the PAG, a core component of the descending pain modulatory system. This system eventually facilitates and/or inhibits pain processing at the level of the spinal cord dorsal horn. Direct cortico-cortical modulations from VLPFC and DLPFC to pain-associated cortical areas are probable but have not been directly shown yet (broken lines). Areas most closely associated with afferent pain processing are densely interconnected, as indicated by the connecting circle.

Figure 2. Results from an fMRI evaluation of CBT in FM patients (Jensen et al. 2011)
 Statistical maps of the fMRI activations during subjectively calibrated pressure pain (n=43). All maps represent brain activations after treatment minus before treatment, for the contrast [CBT > control group]. The top panel: significantly increased pain-evoked brain activity in the left lateral prefrontal cortex in the CBT group after treatment, compared to controls. The lower panel: significantly increased connectivity between the left lateral prefrontal cortex and the thalamus in the CBT group, compared to controls, measured by Psychophysiological Interaction effects. All anatomical locations are given in Montreal Neurological Institute coordinates (MNI).