

# Non-Pharmacological Interventions for Chronic Pain and Depression: any Possible Applications of Multisensory Feedback Approaches Based on Body Representation?

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## Abstract

Chronic pain is often associated with sleep disruption, fatigue, cognitive deficits and mood alterations. In particular a bidirectional relationship exists between pain and mood disorders, for example chronic pain and depression. When these morbidities co-occur, the patient's quality of life can significantly decrease. Different pharmacological solutions have been proposed to target both symptom atologies but misuse, addiction and side effects may limit their adoption. Non-pharmacological interventions like psychotherapy and physical activity have been shown to yield promising results in the management of both chronic pain and mood disorders. In the last twenty years multisensory feedback approaches based on body representation have also been shown to be a valid method to treat different forms of chronic pain. However, comorbid mood disorders have not been taken in consideration by this latter approach. The advances in the treatment of chronic pain with comorbid depression may benefit from future studies using multisensory feedback approaches based on body representation.

**Keywords:** Chronic pain; Depression; Cognitive behavioural therapy; Physical activity; Exercise; Body representation; Body ownership; Disability

**Abbreviations:** PFC: Prefrontal Cortex; SNRIs: Serotonin-Norepinephrine Reuptake Inhibitors; CBT: Cognitive Behavioural Therapy; RCT: Randomized Controlled Trials; iCBT: internet-delivered Cognitive Behavioural Therapy; MBSR: Mindfulness-Based Stress Reduction; ACT: Acceptance and Commitment Therapy; BDNF: Brain-Derived Neurotrophic Factor; CRPS: Complex Regional Pain Syndrome; BID: Body Image Dissatisfaction; BPQ: Body Perception Questionnaire

## Introduction

Chronic pain is a clinical condition that can severely affect the patient's quality of life, and it represents a major socio-sanitary concern, especially for an increasing ageing population. Indeed, it is estimated that about 20% of the European population [1] and 30% of the US population is afflicted by it [2] and its prevalence increases with age [3]. Traditional pharmaceutical interventions such as opioids and non-steroidal anti-inflammatory drugs (NSAIDs), may lead to iatrogenic outcomes, substance abuse and side effects [4]. The recent decease of two notorious pop stars like Michael J. Jackson and Prince Rogers Nelson, is just one prominent example of the powerful adverse potential of painkillers.

A gloomier picture is depicted when considering that chronic pain is commonly associated with mood disorders such as anxiety and depression [5]. Indeed, pain and depression share common neurological alterations such as increased limbic area activation, atrophy of the hippocampus and a decreased prefrontal cortex (PFC) activity [6], and it has been deemed that they can co-occur in up to 80% of patients [7]. When this comorbidity is present, the pharmacological aid is usually represented by tricyclic antidepressants, anticonvulsants, or serotonin-norepinephrine reuptake inhibitors (SNRIs), which have been shown to be effective both for chronic pain and mood disorders, especially depression [8]. However, extra pyramidal

symptoms, cardiac and sexual dysfunctions are only few of the possible side effects reported following the use of these drugs [9,10].

### Discussion

Non-pharmacological treatments have been adopted in an attempt to bypass the side effects, abuse and addiction related to drug use. Although mixing results have been reported, the majority of the studies focussing on alternative interventions provide encouraging findings for the treatment of both pain and depression. These studies also hint at the importance of tailor-made interventions whenever necessary and, arguably, at multidisciplinary approaches to maximize the efficacy of the overall treatment.

### Psychotherapy

Psychotherapy, for example, has been successfully used for the management of both conditions. In particular cognitive behavioural therapy (CBT), which targets maladaptive thinking through cognitive restructuring techniques, integrating it with behavioural strategies to modify dysfunctional conduct, has been shown to be efficacious in the treatment of chronic pain [11], depression [12] and both syndromes together [13]. For instance, Tan and co-workers showed that an intensive 6 to 9-day group CBT programme can bring about beneficial outcomes decreasing levels of pain, pain distress, depression, anxiety and stress in a group of chronic pain patients that last at least for 6 months [14]. Similarly, Wong and colleagues found that pain self-efficacy as well as depression levels and quality of life, significantly improved after a 8-week programme of CBT for patients with intractable chronic pain conditions [15]. In recent years, CBT trials took advantage of technological resources for the delivery of the therapeutical sessions. In randomized controlled trials (RCT) using internet-delivered CBT (iCBT) for chronic pain patients with comorbid mood syndromes, treatment-group participants reported significantly greater improvements than control-group participants in levels of depression, anxiety, average pain levels and pain catastrophizing [16,17]. Nevertheless, CBT is not the only psychological intervention that has been used on these type of patients. Valid alternatives have been proposed, such as mindfulness-based stress reduction (MBSR) programs and acceptance and commitment therapy (ACT), however their efficacy do not seem to exceed the efficacy of CBT [13].

### Physical Activity

Physical activity represents another compelling non-pharmacological approach that has been shown to yield promising results. Its beneficial effects on pain and mood have been reported both in animal [18,19] and human models [20-22]. Ekici and co-workers showed how physical exercise (pilates) significantly reduced pain and depression levels in a group of women with fibromyalgia, after a 4-week programme [23]. On a similar sample of patients, Valim and collaborators showed how aerobic exercise was more effective than stretching

in reducing pain and in improving functionality and mood, including depression, after a period of 20 weeks [24]. In another RCT, Tekur and colleagues showed how a 7-day intensive Yoga programme can reduce pain, anxiety and depression in a group of chronic low back pain patients, more successfully than physiotherapy exercises [25]. Lim et al. found improvements in joint mobility, functional capacity, pain and depression following a daily 20-min exercise programme developed over 8 weeks in a group of patients with arthritis as compared to a control group [26].

A down-regulation of the brain-derived neurotrophic factor (BDNF) and of the serotonergic pathway, among other neuroendocrine alterations, has been shown to be common in depression, sleep disturbances and chronic pain [6]. BDNF and serotonin (5-HT) levels have been shown to be mutually influencing [27] and physical exercise, either acute or regular, is known to increase levels of BDNF [28,29] and 5-HT [30]. Thus, interventions based on physical activity could be particularly efficacious in the treatment of chronic pain and depression restoring higher levels of BDNF and 5-HT. Yet, it is likely that the reasons underlying the efficacy of treatments based on physical activity are multi factorial: exercise promotes increasing levels of neurotransmitters and neuropeptides that are essential for mood regulation, it reduces cortisol, distract from negative thoughts and advocate a better functionality and a general sense of well-being [31,32].

### Multisensory Feedback and Body Representation

Over the last 20 years multisensory feedback approaches, especially those based on the vision of the body, have been increasingly adopted in the treatment of both chronic [33] and acute pain states [34]. In healthy participants, the vision of one's own body has been shown to have analgesic properties during acute pain states [35], and such effect has been shown to hold true even during the vision of prosthetic [36] or virtual limbs [37], provided that an illusion of body ownership over the external limb is established [38]. The most meaningful results deriving from approaches based on multisensory feedback however, have been obtained with chronic pain patients. In the seminal study conducted by Ramachandran and Rogers-Ramachandran, the authors showed the scientific community how it was possible to alleviate chronic phantom limb pain, a condition up to then regarded as intractable, by means of a simple mirror [39]. So, in the so-called 'mirror therapy' a mirror is placed vertically on a table and reflects the patients' healthy upper limb, providing the illusory visual feedback that the missing limb is back in place and is able to move [39]. A study using mirror therapy has shown how this type of visual feedback is effective in reducing pain and enhance motor functionality in the affected limb of stroke patients with complex regional pain syndrome (CRPS) type 1 [40]. A recent review has reported how both graded motor imagery and mirror therapy can improve pain in CPRS type 1 patients, although the authors pointed out that results are not conclusive [41].

Not only the vision of the 'normal' healthy own limb has been shown to be useful with chronic pain patients. In fact, also the use of visual distortions of the body has been shown to be particularly promising for certain kind of chronic pain patients. For example, using binoculars Moseley and collaborators made their chronic hand pain patients look at magnified or minified views of their own limb. Pain was found to increase during the vision of the magnified, moving limb, while it was decreased in the minified visual condition [42]. Yet, it is important to note that the same visual distortion might not work for everybody. Preston and Newport made use of a real-time capture system to manipulate the shape of the hands of osteoarthritis patients. The authors found out that stretching or shrinking the painful hand brought about pain relief in the majority of patients, although some individuals benefitted from the vision of the shrunk hand, while others from the vision of the stretched one or even from both visual conditions [43]. In a revised version of the mirror therapy, based on non-immersive virtual reality system, Sato et al. found that 4 out of 5 CPRS patients experienced pain relief following the virtual mirror therapy, and 2 of these ended their visit to the pain clinic after 5 sessions [44]. Using 3D augmented-reality on a group of neuropathic pain patients, Mouraux and colleagues exposed their patients to 5 sessions of a modified version of the mirror therapy. Sessions lasted 20 minutes and were spread over 1 week. What the authors witnessed was an increasing reduction of pain as well as an increase in duration of pain relief in their patients after each session [45].

In general, approaches based on sensory feedback, like those focussing on the vision of the body, seem to be particularly effective in those chronic pain conditions where a distorted representation of the body is present, such as in CRPS [46,47], back pain [48], osteoarthritis [49] and fibromyalgia [50]. After all, there seem to be a strong link between the magnitude of persistent pain states, the degree in body image alteration and extent of changes in the cortical representation of the body [51,52]. While some authors believe it is unlikely that the distortion in body image or the cortical reorganization can cause pain, but rather pain may influence them [51], others support the view that, at least in some patients, pain can be a consequence and not the cause of an altered body representation [53]. As body representations are mainly resulting from the integration of sensory information, and chronic pain conditions are characterized by disturbances in the proprioceptive, exteroceptive and interoceptive systems [54], a distorted body image in chronic pain patients is likely the result of an alteration of the sensory systems, which relates to a cortical (maladaptive) reorganization of the sensory-motor maps [52]. On the same line, recently it has been suggested that the vision of the body generates analgesia by increasing intracortical inhibition in the primary somatosensory cortex (SI), which in turn could lead to an increased organization of the somatosensory maps within this area, shrinking the size of their receptive fields (called "somatosensory sharpening") [55].

Can there be an application of multisensory feedback approaches based on the vision of the body in patients with comorbid depression? It is known that depression is associated to high levels of body image dissatisfaction (BID) [56-58]. Furthermore, it has been shown how pain, BID and depression can be interconnected: higher levels of pain lead to higher BID states which in turn lead to greater depressive symptoms in a group of patients with lymphedema [59]. However, BID refers to the emotional, and not to the perceptual (for ex. shape, size) component of the body image, targeted by multisensory feedback approaches. Still, depression can also be associated with the physical representation of one's body. So, similarly to chronic pain patients, patients with major depression can be affected by an altered body image in its sensorial/physical aspects. For instance, Wiebking and collaborators investigated the behavioural and the neural correlates of interoception in depressed subjects and healthy controls using the Body Perception Questionnaire (BPQ) and a heartbeat perception task in fMRI [60]. Patients showed significantly higher scores in the BPQ and reduced anterior insular activity during the resting periods of the heartbeat perception task. Importantly, BPQ scores correlated with depression severity. Thus, patients with major depression reported behavioural, neural and somato-vegetative abnormalities related to their interoceptive awareness [60], which is one of the key factors for shaping one's own body representation [54].

Anyway, more studies are needed to assess whether the perceptual aspect of body image are altered in patients with depression. Given the strong bidirectional relationship between chronic pain and depressive symptoms, and taking into account the beneficial effects on pain of multisensory feedback approaches based on the vision of the body, it could be important to measure the impact of this type of intervention on depression levels, besides pain. However, to the author's knowledge, there are no studies, so far, taking into account the effects of such approach on pain and mood disorders. Future studies filling up this hole in the scientific literature are welcome.

### Conclusion

The relationship between chronic pain and depression is bidirectional, so that chronic pain can trigger depression and vice versa. These two conditions are strictly intertwined, sharing common predictors [61], and partly relying on the same neural mechanism [8]. They are so interrelated that whichever of the two kicks in first, there is a high probability that the other one will follow in two years' time [61]. Furthermore, these two conditions implies wide-spread and profound neurobiological complex alterations [5]. Given the emotional and economic burden that chronic pain and depression can represent for the patient, a diverse range of treatments is currently available. However, despite the great attention given to explain why depression and anxiety often co-occur during chronic pain, there is a paucity of investigations that target these morbidities

collectively. Multisensory feedback interventions, especially those relying on illusory body perception, have been shown to be an effective non-pharmacological solution to treat different forms of chronic pain. Unfortunately, depression seems to have been completely neglected by this approach so far. It is therefore advisable that future studies making use of multisensory feedback take in consideration the assessment of both chronic pain levels and mental health variables. This will allow a more extensive comparison between treatments, therefore fostering the creation of better multidisciplinary interventions.

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