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Neuroscientific Changes of Chronic Neuropathic Pain: A Brief Comment on Evidence-Based Practice

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Introduction

Neuropathic pain is one of the main causes of chronic pain among population, which also leads to social and economic losses. According to the International Association of the Study of Pain (IASP), neuropathic pain has a similar consequence to an injury or disease affecting the somatosensory system [1]. The fact that it is directly related to a neurological disorder sets it apart from other types of chronic pain, such as: musculoskeletal or irritable bowel syndromes and fibromyalgia. Neurophysiological changes can be observed when comparing healthy subjects during the evoked pain and resting state.

Many procedures have been applied as an intervention for analgesia and quality of life. A multidisciplinary professional group is necessary due to the complex pathological process that often seems to be unknown, further hindering the best treatment. One of the experimental sets aiming to verify cortical change due to neuropathic pain is correlated to the comparison between induced and neuropathic pain. In the meta-analysis proposed by Friebel et al. in which functional magnetic resonance imaging were presented by comparing induced and chronic pain experiments, showed important cortical changes according to the stimulus [2].

Neuropathic Pain: Evidence and Treatment

These neurophysiological changes enabled to improve the understanding of pathophysiology and thus allowed developing therapeutic processes that may expand the treatment of neuropathic pain [3]. Animal studies are able to show morphological changes associated with metabolic and behavioral changes. Several studies have shown changes in the anterior cingulate cortex (ACC) at a metabolic level and which are related to the increase of excitatory neurotransmitters leading to increased pain [4-6]. These results can also be observed in humans through neuroimaging techniques, as fMRI [7,8]. Although these studies demonstrate the mechanisms of neuropathic pain by increasing the allodynia and hyperalgesia during evoked pain, it has also been possible to recently observe a considerable growth of researches during the resting state [9].

Based on these researches, studies have shown differences between healthy and neuropathic pain subjects by using Default Mode Network (DMN) at resting state [10,11], making it possible to observe changes in evoked pain process. Previously, DMN was related to resting brain activity. However, it has currently been used as a biomarker for functional changes of cognitive dysfunction [12]. Such changes also appear in neuropathic pain suggesting cognitive disorders that may influence the process of chronic pain associated with mood swings and depression [13,14]. Another analysis using the resting state was the alpha asymmetry in the left frontal region which is related to positive affect [15,16], as well as studies that show functional changes in the sensory motor cortex [11], as dysfunction in areas responsible for spatial and temporal brain activity, such as: anterior cingulate cortex and precuneus [17].

Both induced and neuropathic conditions presented specific activations, as follow: the bilateral secondary somatosensory cortex; right middle cingulate cortex; right inferior parietal lobe; supplementary motor area; right caudal anterior insula and bilateral thalamus. When compared to experimentally induced pain, studies on chronic neuropathic pain showed increased activation in the left secondary somatosensory cortex (SII), anterior cingulate cortex and right caudal anterior insula.

Currently, the golden standard treatment is medication, since painkillers to those acting on the central nervous system as antidepressants (duloxetine, venlafaxine) and anti-epileptics (gabapentin, pregabalin) [18]. According to Finnerup et al. [19] a meta-analysis showed results for recommended drugs (cited above) by the Special Interest Group on Neuropathic Pain (NeuPSIG), resulting on a moderate effect of these drugs for the treatment of neuropathic pain. One of the most important factors in the use of antidepressants for the treatment of neuropathic pain is caused due to these patients' mood swings combined with cognitive impairments that interfere with memory, decision-making and stress [20].

Nevertheless, according to Mulla et al. there is a need for correlation effects among treatments to improve evidences of intervention [21]. Despite weak recommendations made by NeuPSIG, another proposal is the spinal cord stimulation applied to injuries, such as: postherpetic neuralgia; peripheral neuropathies; spinal cord injury and complex regional pain syndrome [3,22]. The spinal cord stimulation has an inhibitory effect on the somatic sensory cortex and works as a mediator between the thalamus and anterior cingulate cortex [23]. A complementary treatment that is not included in NeuPSIG, which also works as a form of stimulation for brain activity areas, is the trans cranial magnetic stimulation. When stimulated in the primary motor cortex, it suppresses the pain induced by the capsaicin in healthy patients, by reducing the medial prefrontal cortex activity and increasing supplementary motor area and anterior cingulate cortex activity [24].

These changes can be observed in other interventions, even though they are not in agreement with the suggestions made by NeuroPSIG, as

in the case of the imagery which has been used jointly with functional electrical stimulation, providing both afferent and efferent response and enhancing the cortico-spinal pathway [25]. Gustin et al. conducted a study with patients with spinal cord injury. Results showed no previous pain activity in the brain area before treatment, but a significant increase of activity in the pain related area. Moreover, there was an increased activity in the left primary motor cortex and in the upper right cerebellar cortex, in addition to a higher magnitude of activation of the anterior cingulate cortex and right dorsolateral prefrontal cortex that are associated with increased pain [26,27].

However, a positive effect can be observed in amputees [28] and complex regional pain syndrome (CRPS) [29]. The imagery process is a cognitive procedure (psycho-education) for motor control training associated with explicitness or intention, sensory modality (visual or kinesthetic) and agency (first or third person perspective). This training is required as a pain management as an emotional self-regulating and functionality improvement [30,31]. Studies have shown neural correlates of motor imagery using neuroimaging (i.e. positron emission computed tomography and functional magnetic resonance imaging) and brain mapping (i.e. electroencephalography and magneto encephalography). Cortical and sub-cortical activated areas involved in the motor imagery are similar to activated area with motor execution, such as: primary motor cortex, premotor and supplementary motor areas, posterior parietal cortex, prefrontal areas, basal ganglia and cerebellum [32].

A similar treatment using cognitive processes (perception, planning and execution), are shown in graded motor imagery which also activates the motor cortex and premotor networks [29]. In the case of CRPS, the discriminative pain processing areas are altered due to decreased pain, but there is no difference for emotional pain processing areas [33], even with decreased pain [34]. This technique consists of three phases: the first phase is responsible for the right and left sides using an image that activates the pre-motor cortex without activating areas of the primary motor cortex; the second phase is consists in the imaging (imagery) which activates motor areas as well as when movement is executed; and the third phase takes place during the mirror therapy, in which the affected limb is behind a mirror bearing the contralateral reflex giving the illusion of motion without pain but also with motor areas activities [35].

Another form of intervention that provides cortical change is mindfulness. Although it is a meditation practice, it has shown results in reducing pain [35], due to emotional self-regulation, self-reference and introspective accuracy [36]. This is evidenced by Garland et al. who analyzed the use of pain medication for addictive purposes. They suggest that patients addicted to painkillers enter a downward spiral that uses the drug before you even feel pain and would be directly related to functional changes in the DMN [37]. The practice of mindfulness activates regions such as the ACC and decreases activity in the DMN network. This increases the reappraisal and stops the downward spiral process [38,39].

Mindfulness would be a psychoeducation therapeutic approach focused on decreasing the perception of pain [40] and the emotional process of pain [41]. The main cortical changes are related to increased activity of the ACC, dorsolateral prefrontal cortex, insula [42], increased hippocampus [43], somatosensory changes [44] and left frontal asymmetry at rest [45]. The regular practice of mindfulness creates a better relationship with pain, generating wellbeing and entering drug treatment [46]. In a recent study, Fox et al. found an average effect size in the magnitude of the following areas changed in

mindfulness practitioners: fronto-polar cortex, sensory cortex and insula, hippocampus, anterior and mild cingulated, orbitofrontal cortex, superior longitudinal fasciculus and corpus callosum [47].

Final Comments

Many interventions based on neuroscience studies should be used for the treatment of neuropathic pain. These researches have shown effective treatment for the pain management as well as promoting quality of life. The neuroscience knowledge is useful and provides a better understanding about the neurophysiology of the neuropathic pain and enables managing techniques based on fundamental concepts.

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