INTERVENTIONS ON EMOTIONAL RESPONSES TO PAINFUL STIMULI IN PATIENTS WITH CHRONIC PAIN

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Duration: 3 years
1. Summary of the project

Objectives: To characterize the sensory and emotional components of the response to repeated pain stimuli in patients with chronic neuropathic pain (CNP) and quantify the effects of non-invasive central nervous system interventions.

Methodology:
1. Subjects: Patients with peripheral or central nervous system lesions with or without neuropathic pain. Age-matched healthy volunteers will also participate in some experiments.
2. Psychological and psychophysiological evaluation: Clinical interview, scales of evaluation of mood and cognition, and visual analogue scale scores, will be used to establish baseline conditions. The emotional response to phasic stimuli will be assessed by recording physiological autonomic nervous system responses and their habituation to stimulus repetition.
3. Neurophysiological and neuroradiological evaluation: Pain-related cerebral activity will be recorded by means of contact heat evoked potentials (CHEPs), and functional magnetic resonance imaging (fMRI).
4. Interventions. Repetitive transcranial magnetic stimulation (rTMS) will be used to modify cortical excitability. Virtual reality systems will be used to promote reorganization of central nervous system circuits.

Expected results:
We will define psychological, neurophysiological and neuroimaging features of patients with peripheral or central neuropathic lesions with and without CNP. We will try to identify separate components for emotional and sensory aspects of pain stimuli and define targets for therapeutic interventions.
We hope that our interventions will modulate and modify the emotional reactions to pain stimuli in CNP patients.
The work plan was defined for 3 years, with participation of 3 groups. In the first year we recruited patients with neuropathic pain who were selected according to inclusion criteria. We examined their psychological aspects and psychophysical basic testing of sensation and neurophysiological characteristics.

In the second year we carried out the main bulk of the study. In patients with peripheral neuropathies, we studied magnetic resonance, while in spinal cord injury patients, we applied a specific treatment of pain with virtual reality. In patients with polyneuropathies involving small fibres we did a skin biopsy, the results of which have generated a good number of publications.

In the third year, we continued with the studies that had already started and obtained data that made it possible for us to make a large number of publications. The three groups have cooperated during the research period and, even though there are no joint publications by members of the three groups, all of them have developed interesting branches of the research. In the HCP group we developed more on neurophysiological aspects of healthy volunteers and patients with neuropathies of various causes. In the Guttmann Institute the main interest was to treat pain in patients with spinal cord injury. In the Pompeu Fabra University we devoted the resources to virtual reality and strategies for the evaluation of autonomic nervous system function.

2. Results

The first objective has been fulfilled. We have considerably advanced in our understanding of neuropathic pain and in the characterization of painful polyneuropathies and other forms of peripheral neuropathy that involve pain. In a series of patients with neuropathic pain we have made the following evaluations:

Neurophysiological. Brainstem reflexes and clinical cases.
Histological: Skin biopsy. Clinical correlation and neurophysiological testing.

The second objective has been fulfilled only partially. We treated patients with chronic pain with repetitive magnetic stimuli, but with unconvincing results. This was done with a figure of 8 coil applied over the right dorsolateral prefrontal area. The effect was modest. With continuous cerebral stimulation and virtual reality, however, the effects were consistent and clear in patients with pain in relation with the spinal cord injury.

3. Relevance and possible clinical applicability of the final results

The most important points of our research related to the diagnosis of small fibre neuropathies using skin biopsy and dynamic quantitative sensory testing. Useful findings in these areas have been published or are underway. In fact, there is no other department in Spain where there is a complete study of small fibre neuropathies as we do in our department at the HCP. Also, we have developed a model for treatment of pain in spinal cord injury, based on cerebral stimulation and virtual reality.

Neuromodulation, guided by a dynamic learning for functional recovery from pain and plasticity changes, offers a scientific vision to neurorehabilitation and brings the promise of an improvement in the individual variables of recovery after a spinal cord lesion. Based on the experience gathered in these studies, we decided to implement the combined treatment of virtual reality and cerebral stimulation for the non-invasive treatment of patients with chronic pain.

In collaboration studies, we have also obtained interesting results. We have developed software that is usable in external fields. We have also
developed a study of **autonomic nervous system function** in the context of changes in **affective processes** in patients with migraine.

A large part of our results have been published in journals of widespread distribution and high impact factor such as those with an interest in clinical neurophysiology (Clinical Neurophysiology, Journal of Neurophysiology), the study of pain (Pain; Journal of Pain) and general interest within the field of neurology (Brain, Experimental Brain Research, Muscle Nerve and others).

### 4. Publications

**Neurophysiological evaluation in healthy subjects**


IF: 3.652


**Comments:**

In the first article we put on show the various patterns of response that occur in facial muscles due to nociceptive stimulation of upper and lower limbs. In that study we also pointed out the important differences that
can be used to distinguish between the startle reaction to somatosensory inputs and the withdrawal reaction.

In the second article we studied the implication of inhibitory circuits in the control of action during preparation. This is the case during preparation for execution of a movement in the context of a reaction time task experiment. In that condition preparation is extreme and, therefore, we have to engage an inhibitory circuit for control. We examined if such inhibitory circuit was the corticocortical inhibition. However, even if the reasoning for that possibility is logical, there was no evidence that corticocortical inhibition participated in the control of movement.

In the third work we characterized the functional state of the brainstem in patients with well defined focal lesions. We found that the blink reflex induced by trigeminal stimuli was affected in lower (medullary) brainstem lesions such as Wallenberg’s syndrome, whereas the blink reflex induced by stimuli to the upper limbs (somatosensory blink reflex) was affected in rostral brainstem lesions (midbrain). This indicates a different site for the integration of trigeminal and upper limb afferent inputs at the brainstem.

In the fourth work we analyzed the perception of nociceptive stimuli in healthy subjects. Any stimulus can generate cerebral evoked potentials, which are measured according to their latency and amplitude. However, we do not know what is the relationship between the occurrence of these evoked potentials and the conscious perception of the stimulus. We have observed that conscious perception is a different phenomenon from the generation of evoked potentials because it is advanced or delayed depending on the amplitude of the evoked potentials and the intensity of the sensation attributed to the stimulus.

Neurophysiological evaluation in patients with neuropathic pain and spinal cord injury
Kumru H, Kofler M, Valls-Solé J, Portell E, Vidal J. Brainstem reflexes are enhanced following severe spinal cord injury and reduced by continuous intrathecal baclofen. Neurehabil Neural Repair. 2009;23:921-927. IF: 2.403


Comments
The first two studies put on show the increase in excitability that takes place in the brainstem after a spinal cord injury. That is to say that there is a certain degree of plasticity above the lesion. One of the responses that are exaggerated is the startle. Studies in this regard speculate on the possibility of taking advantage of such enhancement for the benefit of the patient. Studies 3 and 4 demonstrate that stimuli to the motor pathway whether magnetic or vibration, cause a significant decrease of spasticity measures such as the modified Ashworth scale, the Tardieu scale, etc).
In study number 5, we showed for the first time the beneficial effect of cerebral stimulation with direct current while the patient is watching a video with an avatar legs walking at different rhythms. This combination of cerebral stimulation and virtual reality improved more the condition of the patient than the sum of both types of therapy separated.

In article number 6, we draw the attention to one of the syndromes that can occur in spinal cord injury and are difficult to explain: the referred sensation. This results from synaptic reorganization and can involve different sensory modalities.

**Histological evaluation of small fibre polyneuropathies**


**Comments**
In the first work we examined the relationship between intraepidermal fibre density and the evoked potentials to nociceptive stimuli (radiant and contact heat). We observed that the laser evoked potentials were more
sensible to lesions while CHEPs are better related to the density of fibres reaching the skin.

In the second study we presented the results of developing a new method for quantification of intraepidermal and dermal nerve fibres.

In the third article, we present the finding that the Langerhans cells, pro-inflammatory cells, may contribute to the generation of pain in patients with small fibre neuropathy.

In the fourth article we show the results of colocalization of axons and mitochondria, based on the method described in the point number 2. Loss of mitochondria could signal the start of the lesion.