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THE BRAIN IMPRINT OF ATTENTION AND ITS FIGHT AGAINST THE DISTRACTING EFFECT OF PAIN.

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Summary

The main objective of this article is to share the results of a pilot experience carried out at the recently created Neuroscience Laboratory of UNIMET, in an effort to try to understand the complex relationship between pain and cognitive performance, particularly with regard to the maintenance of attentional capacity despite our suffering.

Abstract

The main goal of this article is to share the results of a pilot study carried out in the recently created Neuroscience Laboratory of UNIMET to understand the complex relationship between pain and cognitive performance, particularly in the maintenance of attentional capacity despite suffering.

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Let us consider, to begin with, a hypothetical situation in which someone challenges us to complete a puzzle of medium difficulty in no more than 20 minutes. Let us now think about what would happen if the person who has challenged us connects a pair of electrodes in some region of the body and randomly stimulates us electrically with an unpleasant level of current, so much so that it generates a certain degree of pain. Under these new conditions, how long would it now take us to complete the puzzle? Most of us would probably answer that it would take us longer, because the pain would distract us from our original goal (completing the puzzle).

But it happens that not all people respond in the same way to pain, even when stimulated in the same way. As logical as the interference generated by the application of a noxious stimulus may be, we may find that people use cognitive distraction, which in our example involves completing the puzzle, to distract themselves from distressing pain. Moreover, it is possible that such people may be able to complete the task in less time and more efficiently while in pain. It all depends on how the body responds to the noxious stimulus; that is, how well we can "cope" with our pain.

What is pain?

According to the most recent definition proposed by the *International Association for the Study of Pain (*IASP) (Raja et al., 2020), pain is an unpleasant sensory and emotional experience associated with, or similar to that associated with, actual or potential tissue damage. Implicit in this definition are several considerations, including:

a. Pain is a personal experience that is influenced to varying degrees by biological, psychological and social factors.

b. Pain is not only the consequence of increased activity of sensory neurons, which are responsible for transmitting the message generated by the application of a noxious stimulus.

c. A person's life experiences determine, in part, how he or she will be able to respond to the same pain again.

d. Although pain often has an adaptive role, warning us of something that may threaten our integrity, it can also have adverse effects on psychological and social function and well-being.

e. Verbal description is only one of several behaviors to express pain. However, the inability to communicate does not negate the possibility that a human being, or a nonhuman animal, may experience pain. This is particularly important when considering pain patients who are cognitively impaired.

Let us now consider how the sensation of pain is produced. When a noxious stimulus is applied to a region of the body, or when some pathological condition causes pain, a series of specific receptors called nociceptors are activated in the area of origin and as a consequence of this activation an electrochemical message is generated (a train of action potentials), which progressively advances through a series of relay stations, which include among other areas the spinal cord, the brain stem and the thalamus, until finally this information reaches different regions of the cerebral cortex. There, as a product of an interaction between these different cortical locations, a conscious decision is made as to what to do with the pain.

In addition to the succession of structures described above, also known collectively as the pain transmission pathway, other nerve structures are activated in parallel in an attempt to endogenously control pain. Some of these structures even guide our ability to pay attention, or not, to pain (Figure 1). The latter is of great importance, since the regions responsible for the achievement of attention and those that modulate the intensity of the pain we can perceive have common elements, which raises the strategic possibility of establishing joint regulatory actions. In other words, pain and cognition share neural substrates and can therefore interact reciprocally. Put differently, pain may negatively affect cognitive processing, but a cognitively demanding task may eventually reduce pain perception (Moriarty & Finn, 2014). The latter is known as the cognitive modulation of pain and is posited as a mechanism that can coadjuvant with pharmacological therapy to improve the quality of life of pain patients, particularly those who are affected by chronic type pain (with more than three months of installation). All these structures work together to create the so-called pain experience, which will have particular nuances according to each person. The sensitivity and efficiency of these neural circuits will determine how much and how a person can react to pain. This is why some individuals may manifest more pain than others, or even develop forms of chronic pain that may be insensitive to more traditional pharmacological therapies.

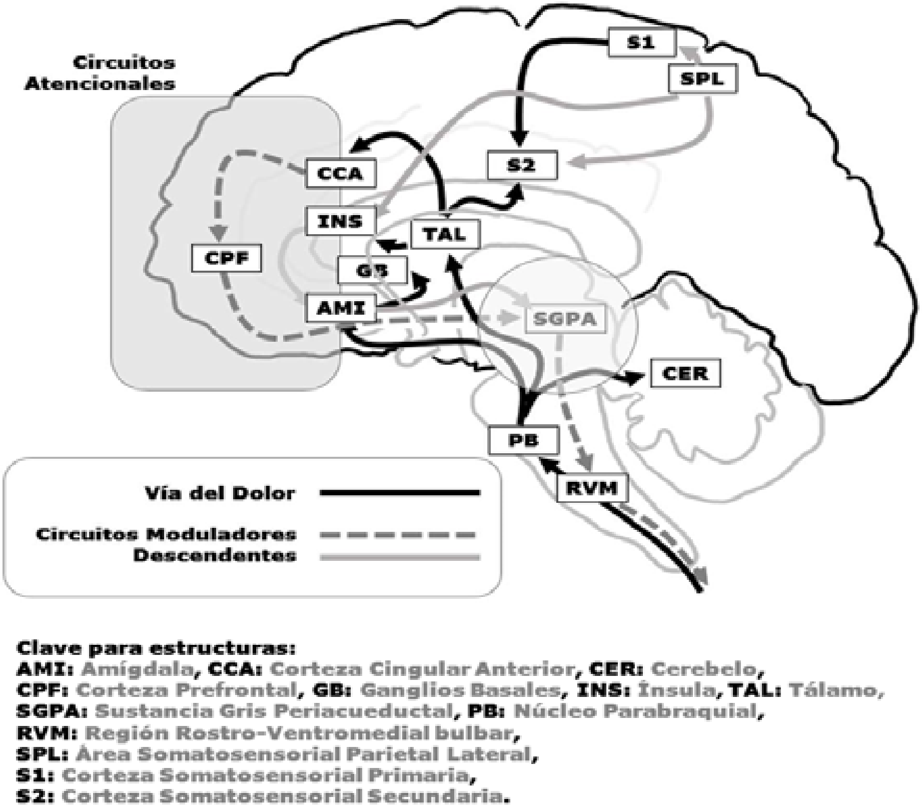


Figure 1.

Neural pathways involved in pain processing and attention. Note the convergence of the different pathways at the mesencephalic level (circle), which justifies the possibility of a cognitive modulation of pain. Modified from: Bushnell et al., 2013.

Treatment

There are different ways to treat pain, some of them using different structures of the nerve pathways described above as therapeutic targets. Among the available options are over-the-counter medications, which are mainly used to treat low to moderate pain. Such drugs are usually indicated to act at the site where the pain signal originates (although they also act at the central nervous system level). Other stronger drugs, and even some anesthetics, act by reducing activity in the pain pathway, or by increasing the capacity of the endogenous modulatory circuit. This group includes, for example, opioid drugs, the sale of which is regulated globally. Some people also use other methods such as distraction, relaxation, meditation, yoga, or therapies that involve the cognitive aspect, modifying, among other things, the attention span we devote to pain.

In the recently created Neuroscience Laboratory at UNIMET, studies are being carried out to contribute to a better definition of the mechanisms involved in the cognitive modulation of pain. In essence, the aim is to try to better understand how our brain functions under pain conditions. The following paragraphs summarize the results of a pilot experience carried out with the first equipment that is part of our inventory, an experience that we plan to expand significantly in the short and medium term.

The cognitive challenge is carried out through a test of the so-called *NIH Toolbox*, developed by the *National Institutes of Health (*NIH) (Gershon et al., 2013; Hoodes et al., 2013). This toolbox has different tests of the cognitive domain, in Spanish language and works electronically in an iPad environment, which not only facilitates the work of information processing, but also invites our participants to act in a playful way in the evaluation, thus generating greater empathy towards the procedure.

In particular, we are evaluating the effect on pain perception of the working memory test called *Picture sequence memory test*, which is cognitively demanding and involves the presentation, at two different times, of sequences of pictures related to a life condition. Because the cognitive test is presented in two phases, it allows us to use one of them experimentally (during the application of the noxious electrical stimulus), and the other as a control (during the application of a harmless electrical stimulus that is even pleasant). So far all our participants have been healthy, male subjects, aged 18-25 years, students at UNIMET, who have cooperated with the study on a voluntary basis. It is among our immediate plans to incorporate female participants for comparative purposes.

The consequences of the application of the *NIH Toolbox* cognitive test were evaluated by using a headband called *Mind Wave Mobile 2*, from Neurosky, which is a tool used to detect electroencephalography signals in a portable manner. The headband consists of an electrode placed in the left frontopolar position (FP1 position, according to the international 10-20 system), which has been qualified as ideal for the electrophysiological observation of higher cognitive processes, including memory, attention and relaxation, through the use of a series of specific algorithms.

Figure 2.

Experimental setup involved in the study. The upper part shows the headband used for electrophysiological recording, the Numerical Pain Scale and the electrodes placed on the participant's forearm, through which the electrical stimulation was applied. The lower part shows the participant running the cognitive test on the iPad screen with his dominant hand. The brain activity can also be seen on the laptop screen, recorded through the use of the headband.

The signals obtained were processed with the open architecture Lucid Scribe program from LUCIDCODE. Among its capabilities are the ability to detect the establishment of an "attentional focus" during the performance of tasks involving intense concentration, as well as the recording of brain waves of different frequencies. In this way, it was also possible to evaluate the effect of the application of stimuli that act as distractors, altering the focus of attention, or generating anxiety (such as occurs during situations of pain).

A portable *Transcutaneous Electrical Nerve Stimulation* (TENS) device, iStim TENS ev-820, was used to generate the noxious stimulus. Two self-adherent stimulation electrodes (ISTIM, TKF5050 DE 2 “X2”) were placed on the forearm region corresponding to the non-dominant hand of each participant, 10 cm apart. The stimulation pattern used was continuous mode, pulse width 200 μs, pulse frequency between 30-50 Hz. Before starting the cognitive test, the pain threshold for each participant was determined. For this purpose, the stimulation intensity was progressively increased until the first verbal report of pain was heard from the subject. This detected value was increased by 10% more intensity, in order to reach supra-threshold stimulation values. This is a common practice to avoid, among other things, the establishment of pain tolerance while performing cognitive challenges. The characteristics of the noxious stimulation were adjusted so as not to generate unwanted side events and were pretested on the investigator’s forearm in order to verify the qualities of the stimulus. The stimulation time ranged from 5 to 10 min, depending on the response speed of each participant during the execution of the cognitive test.

Pain intensity was determined by using the so-called Numerical Pain Scale (NPS; Downie et al., 1978), which is a scale ranging from 0 to 10, where 0 represents total absence of pain and 10 the maximum pain imaginable.

To perform the cognitive test and to be able to evaluate its effect in terms of perceived pain, each participant was comfortably seated in a chair facing a desk on which an iPad was placed, with the respective cognitive test ready to initiate the corresponding sequence of activities. By this time, the pain threshold had already been determined, but the electrical stimulation electrodes were held in position, in connection with the control of the TENS equipment. Next, the subject was fitted with the headband and a stable brain wave recording was checked on a laptop computer (HP Pavillion Gaming, NVIDIA GTX 950M processor) (Figure 2). In particular, we focused on the recording of the alpha rhythm (8-12 Hz), an indicator of relaxation, as well as the beta rhythm (13-30 Hz), an indicator of a higher level of cognitive processing, and the curve reflecting the participant’s degree of attention (based on the algorithms of the Lucid Scribe program).

When all the above was ready, the test was formally initiated, for which the electrical stimulation and the cognitive test were activated simultaneously. In the latter, the participant had to use his dominant hand in order to respond without mechanical interference to the commands indicated on the iPad screen. In the case of the control recordings, all the conditions described above were maintained, except for the intensity of electrical stimulation, which was reduced by 70%, in order to generate a gentle and pleasant massage effect on the forearm of each participant.

Before starting the experiment, each subject was informed of the nature of the test. If, after receiving this explanation, they still wished to participate, they were asked to fill out an informed consent form, which was prepared in accordance with national and international bioethical guidelines. Similarly, it was verified whether the participants exceeded our exclusion conditions, among which were: consumption of analgesics, history of seizures and/or fainting, fatigue, unstable blood pressure and the use of a pacemaker. At all times, the participant had the right to abandon the test if he/she wished to do so, without penalty.

The data obtained were analyzed using the GraphPad Prism 8 statistical package (GraphPad Software). Initially, a descriptive study of the variables was performed to determine the mean and standard error of the sample under each experimental condition. Then, the results were processed with nonparametric statistics, considering the sample size (n=5), since this was a pilot study to evaluate the feasibility of the research paradigm. The Mann-Whitney *U* test was then used to establish possible differences between the two experimental conditions. A level of statistical significance was recognized at a value of $p \leq 0.05$.

The results so far obtained show that in all participants of this pilot experience a significant improvement ($p \leq 0.05$) in cognitive performance occurs while applying noxious electrical stimulation on their forearms.

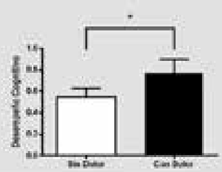
Prueba de secuencia episódica de imágenes de la batería cognitiva del NIH Toolbox	Puntaje Datos Crudos (MEDIA±EEM)	Número de Participantes	ESCALA NUMERICA DEL DOLOR - END (MEDIA±EEM)	Significancia Estadística	Representación Gráfica del Efecto Observado
Primera parte del ensayo con estimulación eléctrica inocua	**17/31 (0,55±0,08)**	**n=5**	**1,15±0,23**	**p≤0,05**	
Segunda parte del ensayo con estimulación eléctrica nociva	**24/31 (0,77±0,13)**	**n=5**	**7,43±0,12**		

Table 1.

Characterization of the pilot experience. The table shows a summary of the results obtained when administering the cognitive test during electrical stimulation on the forearm of the participants. It details the results achieved in the *NIH Toolbox* episodic image sequence test, the number of participants in the trials, the intensity of pain referred by the participants at the conclusion of the electrical stimulation (so as not to interfere with the test), the level of statistical significance obtained by applying the Mann Whitney *U* test and a graph indicating the changes achieved in terms of cognitive performance.

Such improvement in cognitive performance was accompanied by a decrease in the alpha rhythm (indicative of less relaxation), a progressive increase in the beta rhythm (suggestive of a higher level of processing) and a sustained increase in the level of attention, perhaps trying to resist the distracting effect of pain. However, once a certain point in the experiment was reached, a significant decrease in the level of cognitive processing was observed (Figure 3), probably due to the fact that from that point onwards the pain being experienced exceeds the participant's capacity for tolerance and again diverts attention to the pain perceived earlier than in the test being performed, as expressed verbally by some of our participants at the conclusion of the trial.

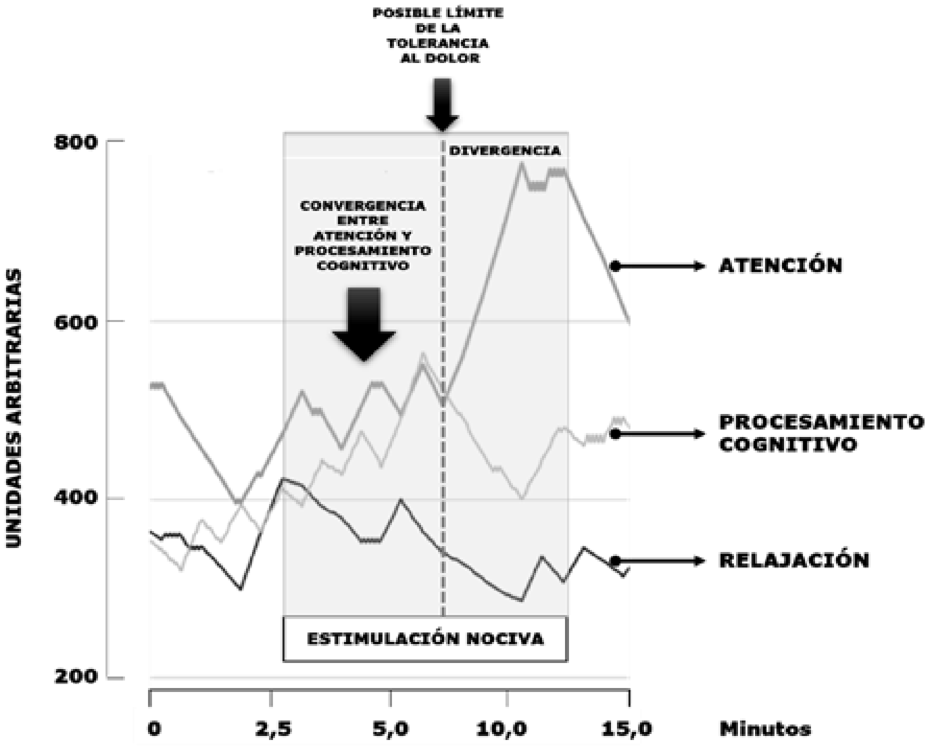


Figure 3.

Linkage of the variables under study. The image represents the recording obtained from one of the participants. It shows that at the beginning of the noxious electrical stimulation, the level of alpha activity (indicative of less relaxation) begins to decrease, while the level of beta activity (indicative of greater cognitive processing) and the degree of attention progressively increase. After a certain time, the convergence between attention and cognitive processing is lost, which could be due to the participant's pain tolerance level being exceeded.

Conclusions

In conclusion, these preliminary results suggest that a level of cognitive challenge of some complexity may be able to promote pain tolerance, which in this case resulted from the application of an acute noxious stimulus. Additionally, the change in the recording pattern of brain rhythms seems to correlate, to some extent, congruently with the changes in attention and processing level observed during the execution of the cognitive tests, pointing to improved performance. However, it is required to enlarge the experimental sample size and to consider the effect of repeating the exposure to the memory test scenario, in order to establish more definitive conclusions, which would allow affirming the possible therapeutic potential of this type of cognitive intervention and even verify the consequences of a learning process as a consequence of duplicating the experience.

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Related websites:

Current definition of pain:
https://www.iasp-pain.org/terminology?navItemNumber=576#Pain
How your brain responds to pain:
https://www.youtube.com/watch?v=I7wfDenj6CQ
The NIH Toolbox:
http://www.healthmeasures.net/images/nihtoolbox/NIH_Toolbox_Brochure_2012.pdf
Mind Wave Mobile 2:
https://store.neurosky.com/pages/mindwave
System 10-20:
https://en.wikipedia.org/wiki/10%E2%80%9320_system_(EEG)
Lucid Scribe:
https://lucidcode.com/lucidscribe/
TENS device iStim TENS ev-820:
http://www.istim.com/products/istim-820