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NO BRAIN NO PAIN: BRAIN CHANGES ASSOCIATED WITH EXPECTATIONS AND LEARNING OF PAIN CONTROL

Noemí Sánchez Nàcher

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Noemí Sánchez Nàcher

Director and tutor: Dr. Carolina Sitges

Doctor by the Universitat de les Illes Balears

Universitat de les Illes Balears

Dra. Carolina Sitges Quirós, Associate Professor of Psychology at the *Universitat de les Illes Balears*

I DECLARE:

The doctoral thesis entitle “NO BRAIN NO PAIN: BRAIN CHANGES ASSOCIATED WITH EXPECTATIONS AND LEARNING OF PAIN CONTROL”, presented by Noemí Sánchez Nàcher to obtain a doctoral degree, has been completed under my supervision.

For all intents and purposes, I hereby sign this document.

Carolina Sitges Quirós

Noemí Sánchez Nàcher

Palma, 2nd December 2020

"La Fe cura a Marta i no la Mare de Dèu de la Barca"

Bàrbara Mota Tàrrega

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Noemí Sánchez Nàcher
Manises
Desembre, 2020

PROLOGUE

This doctoral thesis is presented in a monographic format, following the format criteria for the doctoral thesis at the *Universitat de les Illes Balears* and the updated American Psychological Association Style Journal Article Reporting Standards (APA Style JARS), because it comprises two unpublished studies. Therefore, it includes common sections (introduction, objectives and hypothesis, methods, general discussion and conclusions), a section with the results of both studies, and a final section with future directions.

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ABSTRACT

The main aim of the present thesis is to better understand the top-down inhibition of pain mechanisms, and how they can interfere in treatment outcomes within chronic pain populations by means of learning and expectations. For this purpose, two different experiments were conducted. For the first experiment, it was performed a randomized clinical trial to assess the effectiveness of low frequency repetitive transcranial magnetic stimulation (LF-rTMS) over the right dorsolateral prefrontal cortex (rDLPFC) in major depressive patients (MD) and fibromyalgia patients with major depression (FMD). Alpha asymmetry measures by EEG (electroencephalography) were chosen to asses pre- and post-treatment outcomes. Furthermore, this study was useful to observe the effect of positive verbally induced expectations in clinical trials. The results lead to the conclusion that LF-rTMS over the rDLPFC is not and effective treatment for chronic pain management, and it did not promote any change in FMD patients regarding alpha asymmetry. Besides, it was observed that expectations verbally induced by the practitioner may induce changes in treatment outcomes (in this case, self-reported mesures of depression and pain), which are not reversed by LF-rTMS, revealing different pathways for learning and expecting induced placebo analgesia (PA). The second study was designed to assess differences in PA response between chronic back pain (CBP) patients and healthy controls (HC), in order to evaluate whether neuroplastic changes induced by chronic pain can interfere with the PA response. For this purpose, a response conditioning paradigm was employed, adding experiment settings (in this case, hospital setting and an allegedly analgesic cream formulation) to enrich associative cues. The results indicate that CBP patients benefit from PA, but their response is reduced compared to HC. Furthermore, their brain dynamics during expectancy and pain processing are different, showing alpha desynchronization during anticipation and alpha synchronization in frontal cortex during painful stimulation. Findings from the present thesis suggest the existence of neuroplastic changes associated with chronic pain, which interfere with treatment outcomes. The results of

both studies have relevant clinical implications showing that patients can benefit from PA mechanisms to enhance efficiency of clinical therapy.

RESUM

El principal objectiu de la present tesi és comprendre de forma més extensa els mecanismes descendents d'inhibició del dolor, així com esbrinar com l'aprenentatge i les expectatives poden interferir en els resultats dels tractaments dels pacients amb dolor crònic. Per aquest fi, s'han portat a terme dos experiments. Al primer experiment,es va realitzar un assaig clínic aleatoritzat per avaluar l'efectivitat de l'estimulació magnètica transcranial de baixa freqüència (LF-rTMS) sobre l'escorça dorsolateral prefrontal dret (rDLPFC) en pacients amb depressió major (MD) i pacients amb fibromiàlgia i depressió major (FMD). Mitjançant electroencefalografia (EEG), es realitzaren mesures d'asimetria cerebral de la banda alfa pre- i post-tractament per avaluar els resultats. A més, aquest estudi va ser útil per observar l'efecte de les expectatives positives induïdes de forma verbal en el curs d'un assaig clínic. Els resultats de l'estudi porten a la conclusió de què la LF-rTMS aplicada al rDLPFC no és una teràpia efectiva pel tractament del dolor crònic, i no promou cap canvi en termes d'asimetria cerebral de la banda alfa en pacients amb FMD. Així mateix, es va observar que les expectatives induïdes de forma verbal pel facultatiu poden promoure canvis en els resultats dels tractaments (en aquest cas, autoinformes de depressió i dolor), els quals no es reverteixen mitjançant LF-rTMS, revelant diferents vies per l'analgèsia per placebo (PA) induïda per aprenentatge o expectatives. El segon estudi va ser dissenyat per analitzar les diferències en la resposta de PA entre pacients amb dolor crònic d'esquena (CBP) i subjectes sans (HC), i així avaluar si els canvis neuroplàstics induïts pel dolor crònic poden interferir en la resposta de PA. Amb aquest fi, va ser dissenyat un paradigma de condicionament de resposta on es va afegir un context experimental enriquit amb variables associatives (en aquest cas, ambient hospitalari i formulació d'una crema suposadament analgèsica). Els resultats indiquen que els pacients amb CBP es beneficien de la PA, però les seves respostes estan reduïdes respecte als HC. A més, les seves dinàmiques cerebrals van ser diferents tant durant el processament de les expectatives com del dolor, mostrant desincronització d'alfa durant l'anticipació i sincronització d'alfa al còrtex frontal durant l'estimulació dolorosa. Les troballes de la

present tesi suggereixen l'existència de canvis neuroplàstics associats al dolor crònic que interfereixen amb els resultats dels tractaments. Els resultats d'ambdós estudis tenen implicacions clíniques rellevants, donat que es mostra que els pacients amb dolor crònic es poden beneficiar dels mecanismes de la PA per augmentar l'eficàcia de les teràpies clíniques.

RESUMEN

El principal objetivo de la presente tesis es comprender de forma más extensa los mecanismos descendentes de inhibición del dolor, así como averiguar cómo el aprendizaje y las expectativas pueden interferir en los resultados de los tratamientos de los pacientes con dolor crónico. Para este fin, se han llevado a cabo dos experimentos. En el primer experimento, se realizó un ensayo clínico aleatorizado, para evaluar la efectividad de la estimulación magnética transcraneal de baja frecuencia (LF-rTMS), sobre el córtex dorsolateral prefrontal derecho (rDLPFC), en pacientes con depresión mayor (MD) y pacientes de fibromialgia con depresión mayor (FMD). Mediante electroencefalografía (EEG), se realizaron medidas de asimetría cerebral de la banda alfa pre- y post-tratamiento para evaluar los resultados. Además, este estudio fue útil para observar el efecto de las expectativas positivas inducidas de forma verbal durante un ensayo clínico. Los resultados del estudio conducen a la conclusión de que la LF-rTMS aplicada en rDLPFC no es una terapia efectiva en el manejo del dolor crónico, y no promueve ningún cambio en términos de asimetría cerebral de la banda alfa en pacientes con FMD. Asimismo, se observó que las expectativas inducidas de forma verbal por el facultativo pueden generar cambios en los resultados de los tratamientos (en este caso, autoinformes de depresión y dolor), los cuales no se revierten mediante LF-rTMS, revelando vías distintas para la analgesia por placebo (PA) inducida por aprendizaje o expectativas. El segundo estudio fue diseñado para analizar las diferencias en la respuesta de PA entre pacientes con dolor crónico de espalda (CBP) y sujetos sanos (HC), y de este modo evaluar si los cambios neuroplásticos inducidos por el dolor crónico pueden interferir en la respuesta de PA. Con este fin, fue diseñado un paradigma de condicionamiento de respuesta, donde se añadió un contexto experimental enriquecido con variables asociativas (en este caso, ambiente hospitalario y formulación de una crema supuestamente analgésica). Los resultados indican que los pacientes con CBP se benefician de la PA, pero sus respuestas están reducidas respecto a los HC. Además, sus dinámicas cerebrales fueron diferentes tanto durante el procesamiento de las expectativas como del dolor, mostrando desincronización de alfa

durante la anticipación y sincronización de alfa en el córtex frontal durante la estimulación dolorosa. Los hallazgos de la presente tesis sugieren la existencia de cambios neuroplásticos asociados al dolor crónico que interfieren con los resultados de los tratamientos. Los resultados de ambos estudios tienen implicaciones clínicas relevantes, ya que se muestra que los pacientes con dolor crónico se pueden beneficiar de los mecanismos de la PA para aumentar la eficacia de las terapias clínicas.

ABBREVIATIONS AND ACRONYMS

ACC	Anterior cingulate cortex
AD	Alzheimer disease
AE	Antiepileptic
AMG	Amygdala
ANOVA	Repeated-measures analysis of variance
AP	Antipsychotic
BA	Brodmann area
BDI	Beck depression inventory
Bzd	Benzodiacepine
CBP	Chronic back pain
CBT	Cognitive behavioral therapy
CCK	Cholecystokinin
CNS	Central nervous system
DA	Dopamine
DLPFC	Dorsolateral prefrontal cortex
DNIC	Diffuse noxious inhibitory control
DSM	Diagnostic and statistical manual of mental disorders
EEG	Eletroencephalography
EOG	Electrooculogram
ERD	Event-related desynchronization

ERPs	Event-related potentials
FFT	Fast Fourier transform
FM	Fibromyalgia
FMD	Fibromyalgia and major depression
fMRI	Functional magnetic resonance
HC	Healthy controls
HF-rTMS	High-frequency repetitive transcranial magnetic stimulation
IASP	International association for the study of pain
LEPs	Laser-evoked potentials
LF-rTMS	Low-frequency repetitive transcranial magnetic stimulation
MD	Major depression
MEG	Magnetoencephalography
NAc	Nucleus accumbens
NHWS	National health and wellness survey
NMDA	N-metyl-D-aspartate
OFC	Orbitofrontal cortex
PA	Placebo analgesia
PAG	Periacueductal gray matter
PET	Positron emission tomography
PFC	Prefrontal cortex
rTMS	Repetitive transcranial magnetic stimulation

RVM	Rostral ventromedial medulla
SI	Primary somatosensory cortex
SII	Secondary somatosensory cortex
SMA	Supplementary motor area
SNRI	Dual serotonin and norepinephrine reuptake inhibitor
SSRI	Selective serotonine reuptake inhibitors
STAI	State-trait anxiety inventory
TMS	Transcranial magnetic stimulation

1. INTRODUCTION

Pain is a response comprised of physiological, behavioral-motor, and subjective verbal components. It may have or not a pathological basis, in the way of tissular change. However, pain will always have physiological antecedents and consequences (Flor & Hermann, 2004). Several literature suggests that chronic pain changes brain functionality and morphology (e.g., Apkarian et al., 2004; Baliki et al., 2006, 2011; Flor et al., 1987). These changes are mediated by neuroplasticity, which is a main feature of the central nervous system (CNS).

Repetitive transcranial magnetic stimulation (rTMS) is a method relaying in neuroplastic mechanisms, which may be used as a therapeutic tool in pain management. The rTMS may either excite or inhibit selected areas in the brain modifying intracortical excitability, and activate or inhibit distant brain areas by functional connections (Kobayashi & Pascual-Leone, 2003). The rTMS has been proved as an effective technique for depression and pain relief in chronic pain patients (Khedr et al., 2005; Mhalla et al., 2011; Passard et al., 2007). However, the impact achieved on pain is somewhat low (pain scores decreased by 20-45%), and it is too short compared to the duration of chronic pain (Lefaucheur, 2006). Indeed, long term effects of the therapy remain to be demonstrated (Yang & Chang, 2020). Moreover, optimal rTMS parameters (i.e., frequency of stimulation, number of pulses, and coil type) and locations for some chronic pain patients (e.g., fibromyalgia) are still unclear (Rollnik et al., 2002; Short et al., 2011). Hence, in the first study of this thesis, we will explore how a rTMS intervention affects neuroplasticity (in particular, alpha asymmetry), modulating mood and pain experience (in this case, depressed patients with and without fibromyalgia).

Neuroplasticity also promotes learning leading to actual physical changes. According to the biopsychosocial model of pain, cognitive factors are important contributors for the maintenance of chronic pain by the modulation of pain pathways. Learning, in particular conditioning, seems to modify pain experience either potentiating or inhibiting pain

perception via neuroplasticity, as well as positive or negative expectations might modulate pain by activating endogenous inhibitory systems in cortical and spinal areas (Goffaux et al., 2007, 2009). Two different pain responses, depending mainly on learning and expectancy mechanisms, are the placebo and nocebo effects. These two effects have been widely studied in the last years. Nevertheless, little is known about how they could be interfering in predisposing and maintaining chronic pain. Consequently, in the second study conducted in the present thesis, we will try to clarify how placebo affects neuroplasticity (in particular, alpha synchronization and desynchronization) generating changes in pain experience in chronic pain patients (in this case, chronic low back pain patients).

1.1. Pain and chronic pain

Pain is an adaptive response to a potential damage, however, this response can become a chronic syndrome with many implications, as we will discuss in the following sections.

1.1.1. Pain definitions

The International Association for the Study of Pain (IASP, 1994, pp. 209-214) defines pain as “An unpleasant sensory and emotional experience associated with, or resembling that associated with actual or potential tissue damage”. Nevertheless, Turk and Monarch (2002, p. 7) offered a broader definition. They defined pain as a “subjective perception resulted from the transduction, transmission, and modulation of sensory information filtered through a person’s genetics and prior learning history, besides is modulated by the person’s current physiological status, mood state, and sociocultural environment”.

Pain is a warning signal, but, what happens when the pain is persistent over the time? According to Linton (2004), pain could be classified taking into account its

temporal course: a) acute pain which last for roughly 3 weeks (during this time the patient believe that the situation is controllable, although is escorted by psychological stress); b) subacute pain, which last for 3 to 12 weeks (pain is variable in intensity and patients may drop off the medication and begin to feel depressive symptoms); c) chronic pain, which is used to denote persistent pain for more than 3 months (in this moment, the patient could lose control over his/her pain, and their life changes into the "*sick role*").

Chronic pain is a disease itself, where the continuous search of relief may lead to negative feelings as helplessness, hopelessness, and demoralization (Turk & Monarch, 2002). In addition, chronic pain is often accompanied by depression, sleep disturbance, anxiety, and psychosocial disability (van Hecke et al., 2013). Actually, chronic pain is considered more than a physical symptom (Turk & Monarch, 2002).

1.1.2. Epidemiology of chronic pain

Chronic pain has become a relevant health problem, showing a prevalence rate of about 20% of the European population, with associated medical costs estimated around €200 billion per year (Breivik et al., 2006; Tracey & Bushnell, 2009). About 17.25% of Spanish inhabitants suffer persistent pain (see Table 1), wherein back pain is leading the ranking with the 60.53% of the pain population, followed by joint pain in the 40.21% (see Figure 1). In Spain, patients suffering from moderate pain take more drugs daily than patients with severe pain (68.62% vs. 15.26%), and only 48.78% of the pain patients have prescriptions for pain medications (National Health and Wellness Survey [NHWS], 2010, extracted from Langley et al., 2011). Despite of the high prevalence of pain within the population, numbers reflect that the adherence to the medical treatment is not fully working.

Table 1. *Prevalence of Pain by Severity and Frequency in Spanish Population*

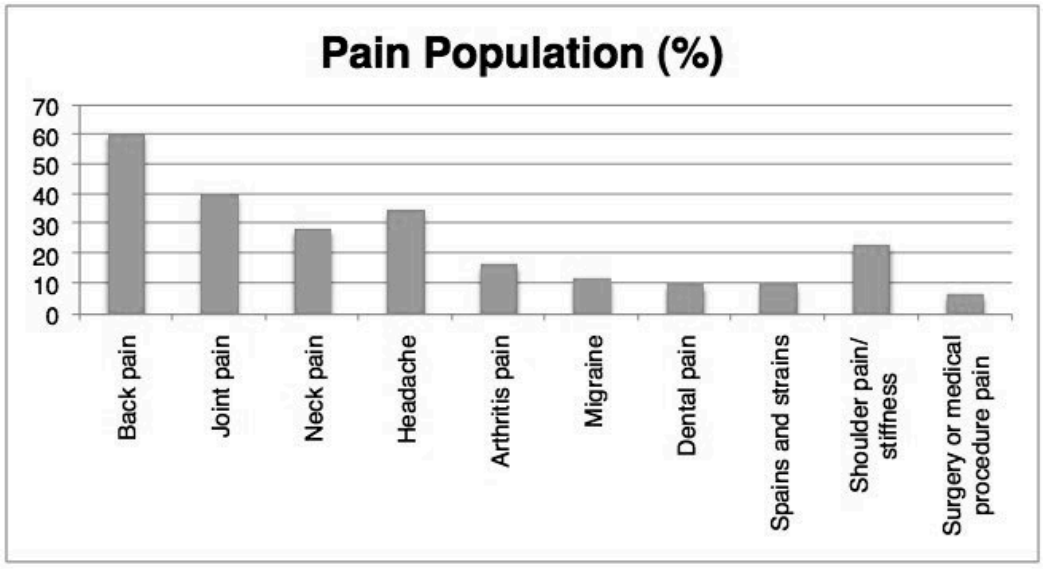
Frequency of pain reported	Severe pain (%)	Moderate pain (%)	Mild pain (%)	Total pain population (%)
Daily	1.63	4.90	---	6.95
4-6 times a week	---	1.57	---	2.20
2-3 times a week	---	2.21	---	3.06
Weekly or less	---	2.39	2.49	5.04
Total pain population (million)	2.02 (0.71)	11.07 (3.92)	4.16 (1.47)	17.25 (6.10)
Distribution within the pain population	11.69	64.17	24.14	100.00

---, Sample size too small to project to total population (n<30)

Note. NHWS, 2010 (from Langley et al., 2011, p.372).

Figure 1.

Conditions Causing Pain in Spanish Population



Note. NHWS, 2010 (adapted from Langley et al., 2011, p.373).

1.1.3. Chronic pain classifications

Classifications of chronic pain syndromes could help to improve diagnose and treatments. For instance, Merskey and Bogduk (1994) created an axial system to provide a more systematic organization of chronic pain syndromes according to five

axes within the IASP: axis I concerned regions, axis II classify by systems involved, axis III pain episode, axis IV severity or chronicity, and axis V mechanisms involved (see Annex I, Table 1). Within these axes it is possible to classify chronic pain states into a general taxonomy of pain syndromes. According to IASP, there exist 32 chronic pain syndromes (Annex I, Table 2) sorted by relatively generalized syndromes, relatively localized syndromes (head and neck), spinal pain (spinal and radicular; cervical and thoracic), local syndromes of the upper limbs and relatively generalized, visceral and other syndromes of the trunk apart from spinal and radicular pain, spinal pain (spinal and radicular pain syndromes; lumbar, sacral and coccygeal), and local syndromes of the lower limbs.

For this thesis, some studies were conducted with patients suffering musculoskeletal pain, specifically chronic back pain (CBP) and fibromyalgia (FM). According to the mentioned axial system created by the IASP, CBP is classified in the spinal pain (spinal and radicular pain syndromes) lumbar, sacral and coccygeal group. CBP concerns to pain referred in the back derived from different etiologies (e.g., disc herniation, mechanical influences, neuropathic pain, central pain), and maintained for more than 3 months, even after the initial cause has been solved. In addition to the physical symptoms, several studies point out to an abnormal brain functioning in this group of patients, in particular in the prefrontal cortex (Apkarian et al., 2004; Baliki et al., 2006) [Further discussed in next sections]. Concerning FM, it would be included within the *relatively generalized syndrome* group. The syndrome of FM constitutes a chronic musculoskeletal pain disorder characterized by widespread lowered pain threshold, fatigue, muscle stiffness, and emotional distress (Wolfe et al., 1990). For the diagnosis of FM, Wolfe et al. (2010) developed three diagnostic criteria: (1) widespread pain index ≥ 7 and symptom severity scale score ≥ 5; (2) persistence of symptoms at similar level for at least three months; (3) the pain cannot be explained by other disorder. Furthermore, pain and depression have a high comorbidity (Romano & Turner, 1985).

1.2. Understanding pain

In order to understand the studies of the present thesis, which are both relying on neuroplastic mechanisms, we consider mandatory to explain, in detail, brain networks and structures involved in pain perception. Pain is a multidimensional experience, interrelating physical, psychological and social features. Pain is differentiated from nociception, which is the physical nerve stimulation that conducts information about the noxious stimulus. For a better understanding of the pain experience and the transition from acute to chronic pain, the present section will describe biological processes involved in nociception. Finally, biological and psychological factors involved in the maintenance of chronic pain will be discussed within the framework of the biopsychosocial model of pain.

1.2.1. Neurophysiology and neuroanatomy of pain

Pain usually begins with a noxious stimulation that may be mechanical, heat, cold, or chemical. The source of the stimulation can be internal referred to as visceral pain, or external, coming from skin and deeper tissues, referred to as somatic pain.

1.2.1.1. Nociceptors. Nociceptor is the name given to a special type of receptors that initiate pain. Nociceptors information's flow is bidirectional, because of the primary afferent fibers morphology, where central and peripheral terminals emerge from a common axonal stalk, called pseudo-unipolar (Basbaum et al., 2009). Even though only peripheral terminal can respond to external stimuli, peripheral and central terminals may host endogenous molecules (e.g., lipids, neurotransmitters, etc.), which regulate nociceptor's sensitivity (Basbaum et al., 2009). When mature, nociceptors express dozens of ion channels and receptors. Indeed, the expression of ion channels is prepared to respond with high threshold stimulus, differentiating nociceptors from sensory neurons for its sensory specificity (Woolf & Ma, 2007).

Nociceptors may be classified by their conduction speed depending on whether they are attached to C unmyelinated or A myelinated axonal fibers. Small diameter C fibers transmit second pain, slower information about burning or aching (for review see Basbaum et al., 2009). C fibers are joined in a net covering a broad area that conducts poorly localized pain, and they show opioid receptors at their terminals that can be activated by inflammation (Basbaum et al., 2009; Swieboda et al., 2013). Most of the C nociceptors are polymodal; it means that they respond to heat or mechanical stimuli. The so-called silent nociceptors respond to heat, but do not respond to mechanical stimuli; however, they can develop mechanical sensitivity in the surroundings of the injury, and are more responsive to chemicals (Basbaum et al., 2009). Aδ are medium diameter myelinated fibers that conduct the fast response to pain. These fibers do not have practically opioid receptors in their terminals, and they produce sharp and first localized pain. Aδ nociceptors are divided into type I (high threshold mechanical nociceptors) and type II nociceptors (lower thermal threshold and very high mechanical threshold) (Basbaum et al., 2009).

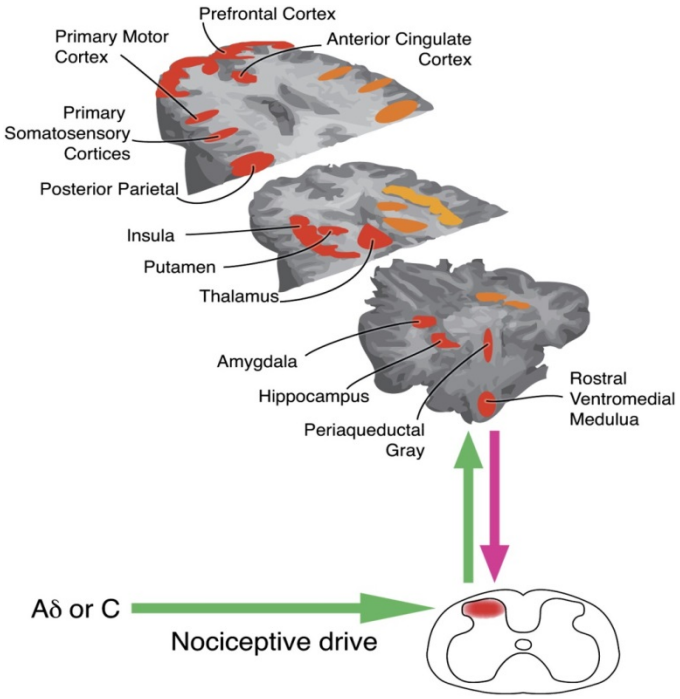
1.2.1.2. Pathways and structures of pain and nociception. When the nociceptors' terminals are stimulated enough, nociceptors activate the fibers, which then transduce the information to the dorsal horn of the spinal cord. There, through the spinothalamic tract of the spinal cord, information arrives to the thalamus, also known as the sensory "*relay station*", right to the ventral posterior lateral and the ventromedial nuclei. From thalamus, stimuli continue over various cortical and subcortical regions, including, periaqueductal grey matter (PAG), primary and secondary somatosensory cortices (SI and SII, respectively), insula, anterior cingulate cortex (ACC), and prefrontal cortex (PFC). These structures taken all together are the so-called "pain matrix" (Apkarian et al., 2005). Other brain regions have been also involved in pain perception, however it seems to be depending on individual differences (cerebellum, amygdala (AMG), basal ganglia, hippocampus and areas from parietal and temporal cortices) (Tracey & Mantyh, 2007). It has been revealed that sensorial aspects of pain perception are located in the lateral nociceptive system (lateral thalamus, and SI and SII), affective components are

associated to the medial nociceptive system (insula, medial thalamic nuclei, and ACC), and the cognitive and behavioral components are located in the PFC (Geuze et al., 2007). Further studies show activations during experimental tonic noxious stimuli in thalamus, basal ganglia, posterior parietal cortex (BA 5/7) and inferior (BA 39/40), striatum, cerebellum, PAG, and supplementary motor area (SMA) (i.e., Peyron et al., 2000). In this line, it has been suggested that central pain emerges from two parallel systems, lateral (sensory discriminatory) and medial (affective-cognitive evaluation) (Apkarian et al., 2005; Tracey & Mantyh, 2007).

While the above-mentioned pathways are involved in the ascending path of nociceptive information, the endogenous inhibiting path forms the descending projections. By the descending pain modulatory system, the brain actively regulates the neural transmission. This system is constituted by ACC, AMG, PFC, insula, hypothalamus, PAG, dorsolateral pons/tegmentum, and rostral ventromedial medulla (Tracey & Mantyh, 2007) (see Figure 2). The activity of these structures modulates pain perception via its projections to interneurons of the dorsal horn that may inhibit or potentiate the incoming stimuli, exerting influence over the noxious input from the spinal cord (Garland, 2012). This descending system can influence pain processing either facilitating or inhibiting the noxious information. In animal experiments, it has been pointed out that electric stimulation of the PAG may exert analgesic effects, whereas stimulation of the rostral ventromedial medulla enhances nociception (see Garland, 2012). Additionally, human studies using functional magnetic resonance imaging (fMRI) have revealed that the descending pathway is the main route to influence pain perception by cognitive and contextual experiences, by the involvement of frontal and limbic regions (Tracey, 2010).

Figure 2.

Neuroanatomy of Pain Processing



Note. Red color indicates bilateral activation during painful experience, however with increased activation in contralateral hemisphere (orange) (Tracey and Mantyh, 2007, p. 379).

1.2.1.3. Pain and neuroplasticity. Plasticity is an intrinsic property of the nervous system, that remains along the whole lifespan, and implies modifications in function and structure environment-dependent (Pascual-Leone et al., 2005). Indeed, plasticity is crucial to the creation and maintenance of brain circuits beneficial to the subject (e.g, learning adaptations after injury), however is also involved in the symptoms of the disease (Pascual-Leone et al., 2011). This property is needed to explain and understand the manifestations or consequences of a disease (Pascual-Leone et al., 2005).

Pain is a result of the involvement of highly plastic molecules and circuits. Indeed, plasticity is also a key property of the nociceptive system, which has the ability to change in experience-dependent manner (Basbaum et al., 2009; Luo et al., 2014). Two conditions that illustrate activity-dependent plasticity of the nociceptor are the peripheral and central sensitization. In *peripheral sensitization*, the stimulus is an aggregate of

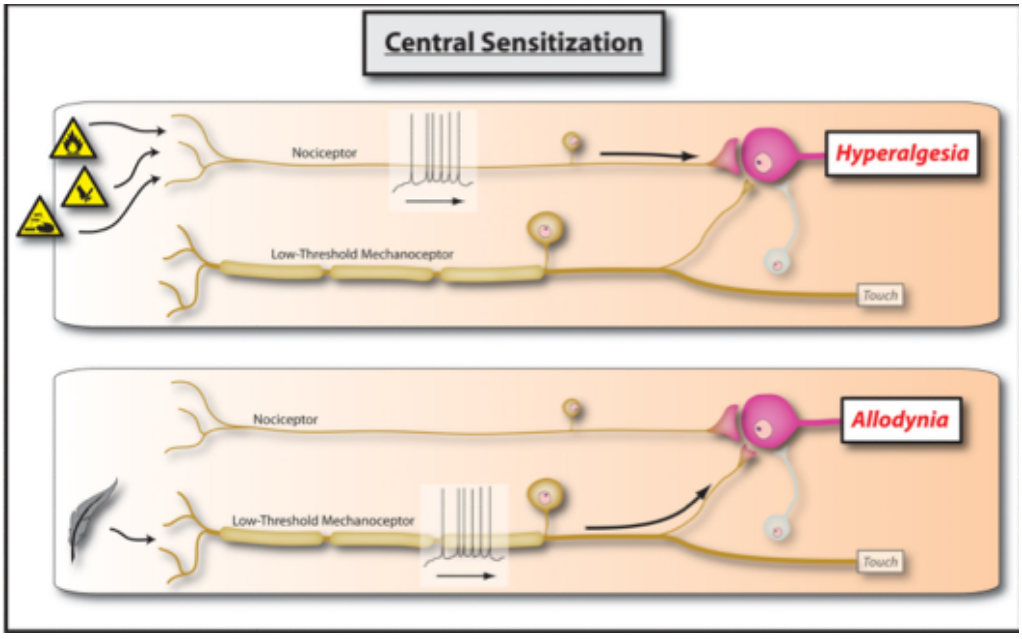
inflammatory mediators (*inflammatory soup*) released from injured and inflammatory cells that sensitize the nociceptor by reducing the threshold only in the injured area, generating primary hyperalgesia (increased pain response in the injured vicinity provoked by a stimulus that causes pain). *Central sensitization* refers to the hyperexcitability state generated in the CNS, where an increased synaptic function of neurons in the spinal dorsal horn leads to increased nociceptive information (Woolf, 1983; Woolf, 2011). Central sensitization was demonstrated in an early study (Woolf, 1983). The author pointed out how peripheral injury generated afferent activity, leading to an increase in the excitability of neurons within the dorsal horn. In the experiment it was observed that brief low frequency (of 10-20 seconds of duration approximately, and 1-10 Hz) bursts of action potentials, produced by electrical activation of the nociceptors, enhanced synaptic efficacy in nociceptive neurons of the dorsal horn. He could show in this experiment, and later on, that this sensitization lasted for several minutes after the conditioned stimulus finish, or just a low level of stimulation of nociceptor to abide stimulated is needed (Woolf, 1983, 2011). Several mechanisms have been involved in central sensitization: alteration in glutamatergic neurotransmission/NMDA receptor-mediated hypersensitivity, loss of tonic inhibitory controls (desinhibition), and glial-neuronal interactions (Basbaum et al., 2009). One theory postulates that most of the synaptic inputs to neurons of the dorsal horn are subthreshold (see Woolf, 2011). However if the gain of neurons is increased, they can now become activated by low threshold innocuous stimulus. In this manner, CNS may change pain qualities in such a way that no longer represents the qualities of the given noxious stimulus, but indeed the “particular functional states of circuits in the CNS” (Woolf, 2011, p. 4).

To explain the phenomena of allodynia (pain induced by innocuous or non-painful stimuli), or secondary hyperalgesia (increased pain sensitivity in the surrounding of the injured area or far from it) (Figure 3) present in the majority of patients with chronic pain (Loh & Nathan, 1978; Woolf & Ma, 2007; Woolf, 2011), numerous studies have signaled the implication of central sensitization (for review see Woolf, 2011). Central sensitization is, nowadays, one of the most studied possible causes for the maintenance of pain

states, and also a therapeutic target (Woolf, 2011). In fact, experiments on animals and humans (healthy or with chronic pain) support the hypothesis that an altered CNS processing could be the basis of hyperalgesia and allodynia, initiated by nociceptor input and maintained by this input and also a non-painful input (Moriwaki & Yuge, 1999).

Figure 3.

Schematic Representation of Hyperalgesia and Allodynia in Central Sensitization



Note. In the upper image, it is observed noxious stimulus stimulating nociceptor terminal, and how the thin unmyelinated C fiber conducts noxious amplified stimulus. The image below represents subliminal inputs or non-painful stimuli that can now activate the pain circuit because of the activity-dependent synaptic plasticity (Woolf, 2011, p. 31).

1.2.2. Pain is more than nociceptors: the biopsychosocial model of pain

Several models have tried to explain the perception and chronification of pain states. However, in contrast to previous models, such as the biomedical model, the biopsychosocial model added more subjective, social, and psychological components to the disease. The focus of the biopsychosocial model is the interaction between subjective experience (illness), and the objective physiological event (disease). Indeed, the biopsychosocial model change around the emphasis from pathophysiology related to the nociception to value patient's cognitive and emotional state (Meints and Edwards,

2018). In this line, illness is derived from the interaction of physiological, psychological and social factors (Gatchel et al., 2007). Indeed, in 1948 the World Health Organization (WHO) defines health as: ”a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity”. The biopsychosocial model will explain the illness, proposing three dimensions: distress, illness behavior, and the *sick role*. Within the pain field, it can be explained in the same terms: *nociception* refers to the nerve stimulation that conducts information about the noxious stimulation, and the potential tissue damage; and *pain*, as defined above, is the subjective perception derived from the sensory information (Gatchel et al., 2007).

Defining pain as a subjective experience implies the featuring of physiological, psychological, and social components that may influence pain perception. Flor & Birbaumer (1994) and Flor (2000) argued that exist ongoing interactions between these components. For instance, psychological factors can influence the evaluation and perception of physiological inputs, besides social factors lead to behavioral responses adapted to the perceptions of the own physical perturbation, just as the biology may be altered by psychological factors and behavior (e.g., hormone production, autonomic system, brain structure and function) (Turk & Monarch, 2002). The model proposes that disease evolution is accompanied by a weigh shift of the different components (Turk & Monarch, 2002). For instance, during acute pain, biological factors may be the most predominant aspects involved in pain perception, whereas in the time course of the disease, psychological and social factors take control over pain and disability (Turk & Monarch, 2002). Moreover, the shift on weights of the components could explain part of the variability in pain responses though subjects hence, the response to similar physical pathology can differ from one individual to other. In that way, the identified physical perturbation not always predicts the pain experience, psychological distress or level of disability.

According to Flor and Hermann (2004), the psychobiological model of chronic pain has some basic components interlinked (see Figure 4):

a) Predisposing factors or diathesis. It is postulated that exist preconditioning factors for the development of chronic pain syndromes. This predisposition is based in reduced thresholds to pain that may be related to genetic variables, trauma history, or prior learning. The result is a stereotypical response pattern to pain within the individual.

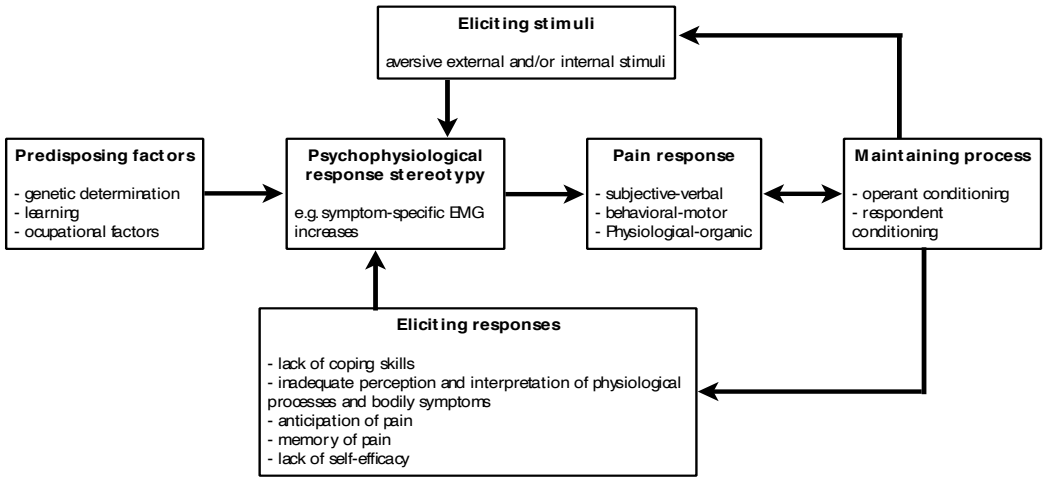
b) Eliciting stimuli. Noxious stimulation or stressors with a negative meaning. Stressors may act as unconditioned or conditioned stimuli, leading to avoidance. In this way, stressors can generate pain and pain behavior.

c) Eliciting responses. Maladaptive responses may enhance the impact of the aversive stimuli, and they are very influenced by cognitive processing of the stimuli (either internal or external). The copy responses to pain may modulate pain perception and hence contribute to chronic pain.

d) Maintaining process. Learning plays an important role in the maintenance of pain states. Learning could generate strong pain memories by interactions with unconditioned stimuli. Furthermore, these memories act as conditioned stimuli maintaining pain perception, even when the disease is solved. Learning processes may appear as respondent conditioning, observational learning, and operant learning.

Figure 4.

Psychobiological model of chronic pain



Note. Flor and Hermann, 2004, p. 49.

In this model, the focus is the interplay between different components, as genetic or acquired predisposition, and eliciting stimuli and response. It is also theorized how learning processes may contribute to the development and chronicity of pain by enhancing pain memories.

Within the proposed components, it is possible to observe that psychological factors have an important weigh for pain maintenance. For instance, a study from Nieto et al. (2012) pointed out that changes in psychosocial factors predicted changes in pain experience and adjustment in patients with muscular dystrophy. Also learning occurs in physiological mechanisms, and these mechanisms may be modified by behavioral and subjective changes (Flor & Birbaumer, 1994; Flor, 2000). A fact that supports the need of psychological factors to explain pain response is the placebo and nocebo effects, that may be caused by expectations and learning (Colloca, 2014), as will be discussed below. Early studies observed that patients without any physiological basis for their symptoms, when treated with any therapy not related to the source of the disease, they reported a significant improvement in their symptoms (Fitzpatrick et al., 1983; Greene & Laskin, 1974). In next paragraphs, will be summarized some of the studies involving psychological features related to pain, cognition and emotion.

1.2.2.1. Cognitive factors. Attitudes, previous experiences about disease, beliefs, coping resources, learning history, and expectancies may affect pain reports and treatment response (Turk & Monarch, 2002). Cognitive factors are theorized to affect functioning by influencing mood, and secondarily by influencing coping efforts, affecting to muscle tension and opioid secretion (Flor et al., 1985; Bandura et al., 1987; in Turk & Monarch, 2002). Indeed, psychological factors modulate activity in brain areas related with descending pain inhibition (Goffaux et al., 2007).

Learning represents a main feature in the predisposing and maintaining processes of pain (Flor & Hermann, 2004). Indeed, pain perception may be influenced by learned responses based in social or cultural transmissions of beliefs and expectations. Thus,

different types of learning that may be modulating pain response exist, and they are contributing for the maintenance of persistent pain, such as social, operant, and respondent learning. In observational social learning, individuals learn to respond to pain by observing others how to behave in pain situations (e.g., children learn about health care by observing how do grown-ups behave when they are injured). However, learning never stops and people can keep learning during their entire lifetime (Bandura, 1969).

Operant learning states that behavior can happen in absence of reinforcement, or be positively or negatively reinforced. When absence of reinforcement, behavior will decrease or disappear, whilst a behavior that is positively or negatively reinforced will persist or increase in the occurrence. Pain behavior can be positively reinforced (e.g.,by getting attention from the caregiver), and negatively reinforced (e.g., by avoiding movement of the painful limb). Avoidance acting as a negative reinforcement may intervene in the acquisition of pain behaviors. Hence, pain patients learn to avoid situations anticipating pain even when the situation does not implies pain anymore, because avoidance is very resistant to extinction (Flor & Hermann, 2004). Verbal expressions of pain and non-verbal behaviors might be also maintaining contingencies of reinforcement (Fordyce, 1976). In this way, learned behaviors might be maintained even when the primary cause of pain is resolved or reduced. This assumption was early proved during several experiments where patients showed different pain levels depending on their knowledge of the presence or absence of patients' wife or care provider (Flor et al., 1987; Knost et al., 1999; Romano et al., 1992). If the wife was present the reported pain level increased, and as more solicitous the wife was, more prominent was the effect. The experiment indicated that solicitous wife was acting as a reinforcer of pain behavior. When brain activity was analyzed, authors observe an increase in EEG power when pain was induced in the presence of the wife (Flor et al., 1987; Knost et al., 1999; Romano et al., 1992).

Respondent learning seems to be also implied in initiating and maintaining pain by conditioning of pain or stress response (Flor & Hermann, 2004; Tracey & Mantyh, 2007).

This type of learning may develop over time and anticipation stress, and usually after operant conditioning (Flor & Hermann, 2004). For example, after injury, avoiding movement may be useful to heal; however, it can derive in fear of movement. In chronic pain states, inactivity may derive in increase of muscle weakness and augmented analgesic medication intake that leads to greater problems (Flor & Hermann, 2004). The fear leads to anticipatory anxiety, and thus to the avoidance of many activities (and to the “sick role”). According to brain imaging studies, pain anticipation activates the ACC, PFC, and the insula (Lorenz et al., 2005; Ploghaus et al., 1999; for review Enck et al., 2008). In a study from Brown and Jones (2008) it was observed during anticipation of pain a widespread activation in the pain matrix during early stages, as pain itself does. Anticipation of pain, besides of generate anxiety and avoidance of activities, may also exacerbate perceived pain. Anxiety can also predict pain severity and behavior in acute and persistent pain; in fact, techniques or drugs to reduce anxiety have been successful in alleviating pain (see Ploghaus et al., 2001).

However, conditioning itself cannot explain all the cognitive aspects of pain. Indeed, other factors have been studied, such as expectations, beliefs, attention and coping strategies. In fact, *beliefs* may also alter perception about pain in different ways. When patients believe that they cannot control the pain or they interpret that pain is going to be transient, they may become passive in the coping strategies. Also the behavioral beliefs can drive to the “sick role” (e.g., if a fibromyalgia patient believe that ill people must rest, and movement worsen the disease, patient will behave following the own belief worsen pain symptoms due to the inactivity). Also, beliefs about pain (e.g., cause, meaning, etc.) and negative expectations are associated with perception of lacking self-efficacy (Bass, 2009) and increase of pain perception via potentiation of emotional reactivity (Vlaeyen & Linton, 2000). In fact, the personal conviction of self-efficacy appears to be a main mediator of therapeutic change (Bass, 2009). It was also found that beliefs about emotional distress provoked by pain may predict the level of pain that can be modulated by anticipatory cues, and this was related to activations in right anterior insula (Brown et al., 2009). Moreover, attitudes and beliefs about present pain are shown as predictors of

people with more chances to develop chronic pain (see van Hecke et al., 2013). *Catastrophizing* is the belief of negative outcomes, misinterpreting situations as exceedingly negative, and it is a potent cognitive error influencing in pain and disability. Pain catastrophizing is a cognitive construct that has been widely related to pain magnification, and seem to be independent of depression. This construct has been related to increase in pain intensity and with mental health (Nieto et al., 2012), enhanced activity of pain anticipation, attention to pain, emotional aspects of pain and motor control related areas (see Tracey & Manyth, 2007). Likewise, positive expectancy seem to be related to enhanced feelings of control, use of active coping strategies and better functional performance, it also appear as a protective factor in the transition form acute to chronic pain (Meints & Edwards, 2018).

Attention is also a cognitive function that has been widely studied within the pain field. Indeed, its automatic processes are suggested to be in the basis for hypervigilance, which is defined as an enhanced attention to pain-related threats (Crombez et al., 2005). In healthy volunteers, it was found distraction of pain results in pain mitigation (Dunckley et al., 2007), whereas increased pain sensation was observed during focused attention to pain (Quevedo & Coghill, 2007). Kòbor et al. (2009) studied the effect of distraction in secondary hyperalgesia induced by capsaicin in healthy subjects showing that attention is modulating pain intensity by reducing perceived pain. However, the effect of distraction on pain minimizes or even may reverse, if the pain lasts longer and has higher intensities (see Snijders et al., 2010). Several studies with chronic pain patients reveal attentional impairments. For instance, a study form Snijders et al. (2010) with unexplained chronic pain patients revealed that patients, unlike healthy subjects, did not feel pain reduction while distraction. According to Apkarian et al. (2005), attentional modulation seem to be localized in the dorsolateral prefrontal cortex (DLPFC), and this region uses to appear more activated in chronic pain patients. One study that was conducted to assess differences in pain processing and attention for visceral and somatic pain, revealed activation in the right DLPFC, positively correlated with somatic but not visceral pain (Dunckley et al., 2007).

Coping strategies are the different ways in which people deal with pain to minimize distress caused by pain. Passive coping strategies have been related to greater pain and depression (Nicassio et al., 1995; Smith et al., 2002), whereas active coping strategies have been associated to the improvement of pain and depression symptoms in patients with myofascial pain (Smith et al., 2002). Some authors state that active coping strategies affects pain perception via positive mood (Esteve et al., 2007). In this line, some authors have studied brain connectivity following cognitive behavioral therapy (CBT) (Shpaner et al., 2014), revealing that the intervention generated alterations in intrinsic functional connectivity among networks related with chronic pain (motor, affective, perceptual, default mode and striatal circuits); in fact, the greater the change, the greater the pain reduction. Moreover, the CBT group showed lower passive coping strategies.

1.2.2.2. Emotional factors. Negative emotions cope the affective components of pain maintenance. Indeed, depression presents high comorbidity in pain conditions (Romano & Turner, 1985). The cortico-limbic pathway (associated to emotions) plays a role in pain processing, because it is proposed that may integrate sensory pain with information from other sensory systems, learning, memory, and attention (Wagner et al., 2009).

Emotions and mood have show up as important features in pain processing. Montoya and Sitges (2006) found that emotions could modulate early somatosensory information, as unpleasant context induced a reduction in the somatosensory P50 component; the results were interpreted as reflection of the filtering of motivationally relevant information allowed by initial sensory gating. Several studies have proved that the induction of negative mood in healthy subjects may lead to a decrease in pain tolerance and increase of catastrophizing scores (see Wagner et al., 2009). These authors suggest that this effect could be mediated by attentional processes, because of the bilateral activation of the thalamus during sad-mood; bilateral activation of thalamus is involved in cognitive tasks via interactions with executive functions (Wagner et al., 2009). Patients

with persistent pain seem to be more prone to the effects of negative mood (Apkarian et al. 2004; Montoya et al., 2005). In this line, one study from our group found that fibromyalgia patients increased their pain ratings after viewing images that induce negative mood; the effect was mirrored in increased the P50 somatosensory component (Montoya et al., 2005). Besides, this effect was also present when tactile stimulation was applied, and localized over the SI. Authors suggested plasticity mechanisms on cortical reorganization, explained via cortical hyperexcitability (Montoya et al., 2005). Sitges et al. (2007) also conducted a self-referent information-processing task, and showed that chronic pain patients assign themselves more negative words related to illness and fewer pleasant words, and also respond slower in the presence of affective and sensory pain descriptors. The authors argued that in chronic pain patients could exist a negative bias, marked by an exaggerated rumination over the word meaning.

Despite of chronic pain has high comorbidity with depressive disorders the relationship between them remain unknown (Tracey & Manyth, 2007). Oftentimes, emotional impairments are explained as consequence of chronic pain syndromes; nevertheless, prospective studies reveal that pre-morbid disfunction is a risk factor for the development o a myriad of pain conditions (see Meints & Edwards, 2018). In addition, Lerman et al. (2015) found that negative affects like anxiety and depression longitudinally predict pain and its related disability, but it did not predict in turn depression or anxiety. Bär et al. (2007) found increased pain tolerance in depressive patients related to hyperactivity in PFC and contra-ventrolateral thalamus interpreted as enhanced top-down suppression of nociception. However, neuroimaging studies show prefrontal impairments and emotion regulation dysfunction during pain (see van Hecke et al., 2013).

Fear and anxiety have been also involved in pain modulation. Fear refers to a reaction to a present threat, and puts the organism on movement (fight or escape); whereas anxiety is a future-oriented, emotion results in an increase of sensory receptivity, negative affect and anticipation of potential threats (Rhudy & Meagher,

2000). Authors suggest that the different emotional consequences derived from fear and anxiety may be modulating the divergences in the pain response. Moreover, these emotions depend upon the same neural circuit, because when the activation is intense humans react with fear and analgesia, but when this activation is moderate the response is anxiety and hyperalgesia (Rhudy & Meagher, 2000). Fear of pain is reflected in the activation of ventral-medial PFC (Tracey, 2010). Nevertheless, the failure in PFC activation leads to anxiety and to an overgeneralization of stimulus, which can worsen pain condition by means of the activation of the hippocampus (for review see Tracey, 2010). According to Ploghaus et al. (2001), pain anxiety may increase pain perception via activations in the hippocampus (specifically, in the entorhinal cortex). Actually, the famous patient H.M. who suffered bilateral hippocampectomy referred also problems in pain perception (see Ploghaus et al., 2001).

1.3. Pain control

In the Greek times, Platon and Charmides believed that “the individual’s beliefs and expectations can significantly influence the therapeutic benefit and adverse effects of a pharmacologic (or other specific) treatment for pain” (Bingel, 2014, p. 127), and it seems that time and science proved they were right.

In the biopsychosocial model of pain it was exposed that learning, expectation, and emotions might be influencing pain perception probably through the modulatory descending pain system. Therefore, it is possible to control pain perception without any pharmacological intervention. In this line, some experiments attempted to stimulate the brain in different ways to achieve pain control by changing brain excitability, for example via magnetic fields, so-called transcranial magnetic stimulation (TMS). In fact, rTMS has been associated with clinical improvements with regard not only to chronic pain, but also to depression (Hou et al., 2016). Other way to reach, in this case, “self-pain control” is the placebo analgesia (PA) effect, which is an example of how cognition may affect pain perception. Supporting this idea, several studies have been conducted (for review see

Tracey, 2010), revealing interesting results. The implications of PA go far beyond clinical trials because also affect clinical practice modulating treatment outcomes (Colloca, 2019). In the following sections, we will introduce about the above mentioned neuroplasticity mechanisms that activate top-down pathways of pain control, starting with the rTMS.

1.3.1. An example of top-down treatment: the rTMS

The rTMS is a method relaying in neuroplasticity mechanisms. By this non-invasive technique, a magnetic field pulse penetrates the brain and induces an electric field in the selected region of the cerebral cortex (Barker et al., 1985). This electric field is propagated over the cortex inducing biological changes by depolarization of cortical neurons, generating action potentials. The rTMS may either excite or inhibit selected areas in the brain modifying intracortical excitability, and activate or inhibit distant brain areas by functional connections (Kobayashi & Pascual-Leone, 2003).

The rTMS has shown a clear effect in the cortico-spinal pathway. The high-frequency rTMS (HF-rTMS, >1 Hz) produce an increase in excitability that results in involuntary motor activity; conversely, low-frequency rTMS (LF-rTMS, <1 Hz) leads to inhibitory changes at the motor cortex (see Atlas et al., 2019; Pascual-Leone et al., 1994; Wassermann et al., 1999). The rTMS has been proved as an effective and safe technique for depression and pain relief in chronic pain patients (Hou et al., 2016, Khedr et al., 2005; Mhalla et al., 2011; Passard et al., 2007; Yang & Chang, 2020) relying in the specific parameters, such as frequency, number of pulses, and stimulation site. In a recent study, which compares two forms of application of rTMS in depressed patients, Fitzgerald et al. (2003) conclude that the application of LF-rTMS at the right DLPFC may be an appropriate initial therapeutic strategy, taking into account the safety, tolerability and efficacy of the technique; nevertheless, the technic requires its application for four weeks to demonstrate a clinical improvement. On the other hand, Graff-Guerrero et al. (2005) have shown that LF-rTMS applied at the right DLPFC increased pain tolerance in

healthy volunteers. In the case of chronic pain, some authors take into account parameters to obtain good therapeutic results, such as frequency of stimulation (10-20 Hz), number of pulses (≥ 1200), and the use of eight-shape coil (focal) (Rollnik et al., 2002).

Optimal rTMS parameters and locations for different chronic pain syndromes are still unclear, in particular with FM (Short et al., 2011; Yang & Chang, 2020). Sampson et al. (2006) applied LF-rTMS over the right DLPFC and showed a reduction in pain ratings in 4 patients with FM, after 20 stimulation sessions. In a replication study by Carretero et al. (2009), with a bigger sample (n=26), the results were not significant, perhaps because subjects were provided with fewer pulses per session compared to the study of Sampson and colleagues (2006). Moreover, LF-rTMS over DLPFC has been also employed for the study of PA and its hemispheric organization (Krummenacher et al., 2010). They found that in the real treatment groups, the rTMS did not affect pain, because it generates a disruption in the PA, blocking the expectation-induced analgesia by breaking the normal PFC function. In addition, pain ratings were reduced for the “analgesia-expectation group”. Moreover, in the real rTMS condition with analgesia-expectation participants they found the treatment less effective than among participants from the “sham group”. Conversely, Passard et al. (2007) applied 10 sessions of HF-rTMS in the motor cortex and found a reduction in FM pain that remained significant for 2 weeks. Short et al. (2011) found, in a group of rTMS-naive outpatients with FM, that 10 sessions of HF-rTMS at left prefrontal cortex resulted in statistically significant reductions in daily pain over time. Similarly, Mhalla et al. (2011) found analgesic effects, directly correlated with changes in intracortical inhibition, after 14 sessions of HF-rTMS over the left primary motor cortex, followed by a "maintenance phase" of: 3 sessions a week, 3 sessions a fortnight, and 3 sessions a month apart. More recently, Atlas et al. (2019) found physical functioning and depression symptoms improvement after rTMS treatment, revealing greater improvement in physical role functioning for those who received HF-rTMS over left DLPFC. Same results collected Philips and coworkers (2018), who also revealed that patients with depression and comorbid pain could benefit

of HF-rTMS over left DLPFC, besides, the higher pain scores the greater the improvement.

1.3.2. Learning and expecting pain: the placebo analgesia effect

One example of a mechanism that influences pain is the capability to regulate pain perception via descending modulatory system that can be observed in PA. However, we still don't know if this effect could be mediating in pain maintenance. One of the most prominent paradigms to study the genesis of placebo response in terms of the principles and mechanisms of learning is the classical conditioning (Colloca, 2014). Nevertheless, PA constitutes a mixture of conditioning effect, cognitive expectancy, and social cues (Colloca, 2014; Kong and Benedetti, 2014). A better understanding of placebo mechanisms may help to elucidate the contribution of learning in pain modulation and maintenance.

1.3.2.1. Definition of placebo. Placebo is a term derived from the latin, meaning "I will please you". Within the pain field, placebo analgesia refers to pain reduction after the administration of a pharmacologically inactive compound instead of an analgesic treatment (Watson et al., 2007). It represents the combination of conditioning (inflexible, instinctual and automatic) and cognitive expectancy (flexible and adjustable by context) (Benedetti et al., 1999, 2003; Kong & Benedetti, 2014; Watson et al., 2007), indicating top down regulation of pain experience.

1.3.2.2. Neuroanatomy and neuropharmacology of placebo analgesia. Antinociception exert a powerful descending control of pain, highly necessary in situations of escape, stress or fear. Besides, descending modulatory system is the principal pathway for cognitive and contextual features to change pain perception (Tracey, 2010). Indeed, the pain matrix reveals a decrease in the activation during analgesia induced by drugs or interventions, and so does in a PA manipulation (Bingel et al., 2011; Tracey, 2010) (see Figure 5a). Wager et al. (2004) were the first group

performing fMRI in a PA study to elucidate the relation between the pain matrix and the PA response. They conducted two experiments using topical creams as placebo and control. In the first experiment, it was applied painful and non-painful electric shock to the wrist, and no conditioning was conducted. Participants underwent five blocks of 15 trials that started with a warning cue, which indicate the intensity level (high or medium). In one-third of the trials, there were no shocks. After the first block, placebo cream was applied in the stimulation area, and half of participants were told that was an analgesic cream. After blocks two and three, the cream was removed and applied back, whereas participants were told that was a control cream (however, it was the same cream). The second experiment was similar to the first, but it was applied thermal stimulation, and the cue was the sentence “get ready”. Conditioning was conducted in this experiment by reducing the temperature to non-painful levels for the placebo condition during the manipulation phase (i.e., participants were told that stimuli was high, but it was low). Nevertheless, during the test phase, temperatures were the same in the control and placebo conditions. Results of the first study indicate an increase of activity of the DLPFC correlated with a reduction in the activity of some pain-related regions (contraletral thalamus, anterior insula, rACC) during placebo analgesia response. Moreover, the magnitude of the decrease in activity of pain-related regions correlates with reductions in pain ratings. In addition, they found activations of PFC during expectation of pain relief, in detail the DLPFC and orbitofrontal cortex (OFC). These activations were correlated with increases around PAG (area with high concentrations of opioid neurons). Results of the second experiment keep in line with the first experiment: placebo induced a reduction in pain-related areas, and PFC seems to mediate anticipation of placebo.

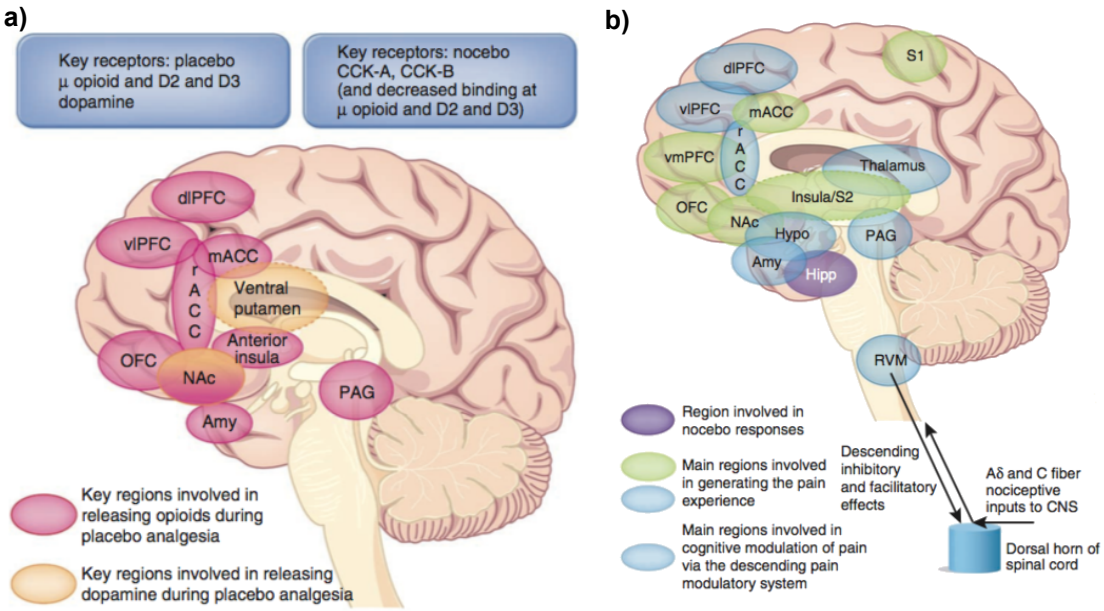
Thereby, PFC has been showed as a key area in PA response (Schultz, 1998; Wager et al., 2004; Schweinhardt et al., 2009; Tracey, 2010). Indeed, exist a relation between the magnitude of the placebo-induced analgesia and PFC gray matter density (Schweinhardt et al., 2009). The activation of PFC during placebo-induced analgesia appears to be associated to expectations of relief (Petrovic et al., 2010; Schultz, 1998;

Tracey, 2010) (see Figure 5). However, mechanisms involved in placebo analgesia response remain unclear (Enck et al., 2008).

Among many authors exist a general agreement on the implication of endogenous opioids in some types of PA response (Wager et al., 2004, 2007; Zubieta et al., 2005). This assumption comes from an early study from Levine et al. (1978) in which was demonstrated that PA can be blocked by naloxone (an opioid antagonist), evidencing the opioid implication in the PA. Nevertheless, it has been observed that this blocking effect was body-region specific, implying that the opioid release is directed (Amanzio & Benedetti, 1999). However, PA does not seem to be framed in one single neurotransmitter system; research on the field support more complex interactions between systems. According to Fields and Levine (1984), mechanisms involved in the placebo response can be divided between opioid and non-opiod components.

Figure 5.

Schematic Illustrations of Endogenous Pain Modulation in Placebo and Nocebo Responses



Note. a) Blue areas indicate the descending endogenous pain and cognitive modulatory networks that placebo and nocebo use to elicit their influence on nociceptive processing. The hippocampal region (purple) is important for amplifying pain experiences during nocebo or increased anxiety. b) Schematic illustration indicating where endogenous opioid and dopamine neurotransmission occurs in the human brain during placebo analgesia. Note the overlap with many of the brain regions involved in cognitive

modulation of pain, and for some brain regions (nucleus accumbens -NAc-) there is a bidirectional response of both opioid and dopamine release that produces either placebo (increased release) or nocebo (decreased release) effects (modified from Tracey, 2010, p. 1279).

To investigate the implication of the opioid system and related structures in PA, several neuroimaging studies have been carried out. In an attempt to clarify the mechanisms and neural systems involved in the PA, Bingel et al. (2006) designed an fMRI study to assess if right ACC interacts with subcortical areas (PAG and AMG) during PA response. The implication of these structures it was studied because of their engagement in the endogenous opioid system. Painful stimulation was applied via laser pulses. Participants were told that they participate in a study to test an analgesic cream. Besides the induced expectation, subjects were conditioned by reducing laser intensity in the placebo condition. Researchers found that rACC plays an important role in PA, and its activity covariate with subcortical structures linked to the antinociceptive network. These data gives support to the implication of descending pain modulation and the opioid system in the PA response. Wager et al. (2007) also conducted a positron emission tomography (PET) study to elucidate the opioid mechanisms underlying PA and how placebo interacts with opioid at central level. For these purposes, it was used heat stimulation as painful stimuli. A conditioning procedure was conducted to enhance the pain relief expectations in the placebo condition. It was observed increases of activity in opioid rich regions in response to placebo expectancy (PAG, nucleus cuneiformis, dorsal raphe nucleus, OFC, AMG, two regions of the anterior cingulate cortex (rACC and pgACC), ventral anterior insula, and thalamus). Authors suggest several mechanisms how placebo might affect opioid response: (1) by potentiating the regular opioid release generated by noxious stimulus (in OFC, rACC, nucleus accumbens, nucleus cuneiformis, dorsal raphe nucleus, ventral tegmental area, right AMG, and thalamus); (2) reducing anticipatory opioid activity (in lateral PFC, anterior insula, pregenual ACC, and left AMG). Moreover, in the study it was also possible to discriminate between placebo responders and non-responders depending on the magnitude of the opioid response. However, authors suggest that PA could be also mediated by other non-opioid mechanisms.

An early study from Amanzio and Benedetti (1999) was aimed to show the existence of different systems than opioid involved in PA. They made a complex experimental design of pharmacological conditioning to assess several possible explanations. In this experiment, ischemic pain was induced by the tourniquet technique, and morphine, naloxone, saline, or ketorolac (non-opioid painkiller) were administered to healthy individuals in open-hidden conditions. The results indicate that the only expectation of relief may induce a placebo response, which can be blocked by naloxone. They could also observe that morphine conditioning plus expectation generate more robust placebo responses and is also opioid-dependent. Intriguingly, the condition of ketorolac conditioning plus expectation generates placebo responses that are partial or completely insensitive to naloxone, demonstrating a different system involvement than opioid. These authors argument that the responses induced by PA conditioning rather that be opioid-dependent, so they are mediated by specific subsystems depending on the drug employed for the conditioning procedure. The implication of non-opioid mechanisms was also highlighted by a study from Petrovic et al. (2010). Researchers conducted a PET study to elucidate differences in opioid analgesia and PA. It was observed that the rACC was more active during the opioid analgesia than during the PA; however, the OFC was more activated during the placebo condition. Hence, this study suggests that besides the implication of the opioid system in PA, other mechanisms may be mediating the response.

Non-opioid components that have been hypothesized to be involved in PA are cholecystokinin (CCK), the endogenous cannabinoid system, dopamine (DA) and reward system (Benedetti et al., 2011; Benedetti & Frisaldi, 2013; Tracey, 2010). CCK inhibits (antagonizes) the opioid system. In fact, CCK receptors antagonists increase PA response by enhancing the opioid release, whereas CCK agonists may abolish PA response under morphine preconditioning (Benedetti & Frisaldi, 2013; Tracey, 2010). On the other hand, a study from Benedetti et al. (2011) tested the implication of the cannabinoid receptor CB1 in PA**.** In the experiment it was performed an opioid and non-

opioid conditioning with morphine or ketorolac, respectively. The CB1 receptor antagonist, rimonabant, was administered and blocked the PA response induced by ketorolac conditioning. However, no effect was observed in the PA response induced by morphine conditioning. Results point out the implication of the endocannabinoid system in some kinds of PA. Indeed, CB1 receptors have been found in the striatum, structure traditionally involved in the DA system (Benedetti & Frisaldi, 2013), so, it may occur a complex interaction between several neurotransmitter systems (see Enck et al., 2008). Furthermore, the implication of DA and the reward system has been also studied in PA. It has been hypothesized that reward expectation (i.e., pain relief) is an important mechanism in placebo, and it is linked to activation of tegmental or prefrontal DA neurons. After reward, it also appears DA activation, which is larger when the reward is uncertain (Enck et al., 2008). One study linking DA with PA was a PET study conducted on Parkinson's disease patients (De la Fuente-Fernández et al., 2002). The study revealed that PA was associated with a release of DA in the striatum. The study concludes that PA is mediated by the expectation of reward. Furthermore, an imaging study with PET and fMRI was done to evaluate the correlation between monetary reward and PA (Scott el al., 2007). Authors found that both conditions activated dopaminergic neurons in the nucleus accumbens. In addition, they revealed a correlation between placebo and monetary responses, when NAc show a great response to monetary reward so does in the placebo condition. To further investigate DA implication in PA, a study was run to assess ventral striatum role, and personality dopamine-related traits in PA response (Schweinhardt et al., 2009). Saline hypertonic infusion was used to induce muscle pain in healthy volunteers. PA conditioning was conducted by reducing the saline concentration when placebo cream was applied. The results indicate that individual differences in the PA response may be predicted by dopamine-related traits, and the magnitude of the placebo-induced analgesia is related to gray matter density over PFC and ventral striatum. The authors suggest several explanations of how DA can contribute to PA (i.e., they expose the DA implication in the reward system), and its crucial role for the motivational drive to get rewarding stimuli.

However, DA and opioid systems are not necessarily in conflict. Indeed, a study from Scott et al. (2008) shows the implication of both systems. A PA neuroimaging study with PET plus fMRI was conducted with healthy participants. The experiment was designed to maintain muscle pain, performed via 15 ml bolus of 5% sodium chloride, subjects rated their pain intensity every 15 seconds. Placebo effect was induced by verbal suggestions of pain relief, and the placebo was 1 ml of 0,9% isotonic saline solution. With this experiment was highlighted the involvement of two neurotransmitter system during placebo administration: mesolimbic dopamine system, involving the activation of DA receptors in ventral basal ganglia; opioid system involving the rostral and subgenual ACC, OFC, anterior and posterior insulae, medial thalamus, NAc, AMG, and PAG. Activation of DA neurotranmission in ventral caudate, ventral putamen, and nucleus accumbens was positively correlated with expectations of analgesia and the magnitude of analgesia.

1.3.2.3. Cognitive factors of placebo analgesia. It is assumed that expectations and learning, are fundamental to placebo response. Indeed, learned prior expectation and expectations of contextual cues may modify the response to the treatment (Morton et al., 2010). In fact, studies support the idea that cognitive expectations, in addition to conditioning and the emotional state, generate neurobiological changes that modify the pain response, as theorized the biopsychosocial model of pain.

Several studies have also related expectations in PA with the activation of prefrontal areas. For instance, Petrovic et al. (2010) suggest that prefrontal implications in PA, rather than opioid implication, might be more related to the expectation or a relative reward (i.e., pain relief). Moreover they added that the discrepancy between the expected stimuli and received stimulation (i.e., error signal) is also related to PFC activation. Expectations of relief has been also related to ACC (Bingel et al., 2006; Lorenz et al., 2005). It seems that ACC activity covariates with subcortical structures linked to antinociceptive network, associating expectations with endogenous pain control

(Bingel et al., 2006). Moreover, activity of ACC was enhanced after painful stimulation indicated by certain cues (Lorenz et al., 2005).

In this line, Goffaux et al. (2007, 2009) conducted two studies in order to clarify the neural mechanisms involved in PA response related to expectation. The first of them was performed with healthy subjects, and the second one with FM patients. Subjects in both studies undergo through an experiment in which expectations regarding the analgesic effect of immersing their right arm in water were altered, by saying them either that it would generate hyperalgesia or analgesia to the electrical stimulation that they will receive (to the sural nerve). EEG measures were acquired for the analyses of brain responses. Authors observe that expectations modify the activation of endogenous pain inhibitory systems which affect spinal and cortical pain responses. Indeed, negative expectations blocked the normal endogenous analgesic processes produced by the diffuse noxious inhibitory control (DNIC). However, they conclude that part of the expectation effect is mediated not only by spinal mechanisms, but also by cortical locations; in particular P260 reveal that ACC, which is functionally connected with DLPFC, may be by facilitating the integration and interpretations of sensory information based on expectations.

Conditioning has been recognized as crucial to generate a strong PA response. Nevertheless, there are not a dichotomy between conditioning and expectations, because conditioning implies processing of information in which the individual expects a future event and may be conscious or unconscious (Colloca, 2014). Indeed, according to this author, learning can be understood as a process that generates expectations and conditioned responses. Mechanisms involved in PA have been explained from learning theories as classic conditioning, where repeated associations generate this response (Amanzio & Benedetti, 1999). In this sense, all the stimuli associated to the efficacy of the treatment may become conditioned stimuli because of the repeated association (Colloca, 2014). Several ways of conditioning procedures have been used to investigate placebo responses. Studies that performed pharmacological conditioning (conditioning

with drugs, as previously described) expose that the derived learned responses show specific effects depending on the drug (e.g., Amanzio & Benedetti, 1999). Non-pharmacological conditioning procedures are based in the previous experience of pain relief. So, in these studies noxious stimulation is reduced in presence of placebo (e.g., Wager et al., 2004). This kind of procedure generates more robust placebo responses than expectation induction alone (Colloca and Benedetti, 2006; Vase et al., 2002). As above mentioned, pain responses may be learned from others (Bandura, 1969), and so it happens with placebo responses (Colloca & Benedetti, 2009). In this case, studies indicate that empathy could be facilitating observational learning of placebo responses (Colloca & Benedetti, 2009; Hunter et al., 2013). By any of the proposed ways of conditioning, learning mechanisms have been proved as a main mediator in placebo responses (Colloca, 2014).

Prior experiences and likelihood of positive outcomes influence expectations , which may be induced by explicit suggestions of positive outcomes or by implicit subject's previous experience (Colloca, 2014). In this line, Lorenz et al. (2005) conducted a study to investigate how false expectations may modulate pain response. Researchers used measures of EEG and magnetoencephalography (MEG) to analyze event-related potentials (ERPs) and source localization. Authors examined the role of SII and ACC on expectancy of certain and uncertain cues of stimulus intensity. For this aim, it was applied two different intensities laser stimuli to healthy volunteers and signals were recorded by 31-channel MEG and 32-channel for the EEG. In the experimental paradigm, before the stimulation an informative cue about the pain intensity appeared, but 20% of the cues were false. The results indicate that false expectations of low intensity generate lower pain scores, and false expectation of higher temperature generates more elevated pain scores. They further found that MEG potentials generated in SII were increased in high-expectation condition, whereas they were reduced in the low expectation condition. The analysis of laser-evoked potentials (LEPs) was focus on latencies from 200 to 500 ms when the N2-P2 occurs. This complex is generated in the anterior and posterior cingulate cortices, and appears from the activation of Aδ fibers

(Wager et al., 2006). In this study, it was pointed out that the manipulation of expectations of pain modulates the pain response.

1.3.2.4. Emotional factors of placebo analgesia. Emotions are also hypothesized to be involved in the PA by modulating the pain response. According to Vase et al. (2005), analgesic properties of placebo could be mediated by reduction in anxiety levels. As was theorized in the biopsychosocial model of pain, the negative emotions reduction involves an increase of the pain thresholds (see section 2.2.2. of this thesis). This notion matches the results of neuroimaging (Wager et al., 2004) and EEG studies (Wager et al., 2006), pointing out the implication of affective structures in the PA response. Indeed, the study from Scott et al (2007) found a reduction of negative emotions independent of the pain reduction, and an increase of positive ones after placebo manipulation, indicating that placebo manipulation was also affecting mood in a positive way.

1.3.2.5. Explaining placebo analgesia: the dual-process model. The biopsychosocial model explains pain and its chronification as a subjective experience implying the involvement of psychological, physiological and social features. Therefore, PA can also be explained from this wide perspective, and not only by either conditioning or expectation, as some authors trend to argue. Nevertheless, only few models have ventured to explain how PA is formed. For instance, the *expectation model* (Kirsch, 1985), point to a common pathway in PA relaying completely on expectation (Stewart-Williams & Podd, 2004). However, scientific evidence reveal that solo expectation inductions have failed to induce PA (Colloca et al., 2008, 2009), and that is possible to induce PA without conscious expectations (see Schafer et al., 2018). Conversely, Colloca & Miller (2011) developed a theory critically based on learning, as an essential mediator of expectation. Arguing that learning, either conscious or unconscious, generate changes in expectation that affect PA response. In this line, Schafer et al. (2018) recently developed the *dual-process model*, in opposition with the “expectation model”, backing up in the biopsychosocial model, but adapted to explain in detail the PA

mechanisms. For the authors, PA would imply “mechanisms of endogenous self-regulation and healing” (p. 2), as we learnt from the previous sections.

The model arise from separate but connected learning processes, and with that, the neurobiological systems more related with PA, opioid and cannabinoid systems. The model is framed within the reasoning theory from Kanheman and Frederick (2002), which assumes that reasoning can be achieved by two different systems, the so-called “System 1” which represents more automatic and unconscious reasoning, and oftentimes implying the use of “shortcuts”, and “System 2”, which refers to conscious and harder reasoning. Moving to the pPA field, Schafer et al. (2018) assume two processes: “accumulative” (comparable to “System 1”) and “dynamic” (resembling to “System 2”). The accumulative process implies a slow collection of information to generate pre-cognitive associations, not requiring conscious thoughts to get activated. The associations made, for instance by conditioning, lead to adaptive responses, which in turn, strength the associations. Authors asume that this kind of analgesia requieres the basic associative learning system, PAG-rostral ventromedial medulla (RVM)-spinal cord (AMG included), and it would be dependent mainly on the cannabinoid system. On the other hand, the “dynamic” process works in the way of the expectation model of PA, by generating a *mental schema* in order to understand the context and guide the behavior. As we know, mental schemas are flexible organized thinking patterns, a mental structure that represent the surrounding world that organize the behavior. However, they are flexible because they have to adapt to new situations adding new learnings. In the PA field, mental schemas are also updated with contextual incoming information (in that sense, expectations of relief strength the schema correlating with the magnitude of the PA). Regarding neuroanatomy, the schema activation would depend on the activity of frontal (rACC and DLPFC) and medullar areas (PAG and RVM) and the resulted analgesia would depend mainly on the opioid system.

To contend their model, Schafer et al. (2018) expose a myriad of studies supporting their hypothesis, with neuroanatomical, neurochemical, genetical, psychological, and

contextual explanations. Nevertheless, some warnings set by the authors must be taken in consideration. For instance, the model only describes two neurochemical systems despite of the knowledge of other systems, such as dopaminergic and serotonergic, that can also interfere in the PA response, and with it also different pathways of pain modulation.

1.3.2.6. Placebo analgesia in clinical samples. Data is limited regarding placebo studies with patients, however it shows that they achieve analgesia by placebo interventions. Several experiments have investigated the immune response under conditioning placebo manipulation in patients with immune disorders (e.g., lupus erythematosus and multiple sclerosis), obtaining positive outcomes after the placebo, since the placebo acted as the immunosuppressive drug cyclophosphamide (Giang et al., 1996; Goebel et al., 2002; Olnes & Ader, 1992). Within the pain field, literature is scarce regarding PA experiments conducted in chronic pain patients. Studies with visceral pain patients show equivalent placebo response than healthy participants. Thus, a reduction in activation of brain pain related areas, and PFC enhancement during the PA response (Price et al., 2007). Moreover, it has been find also an implication of anxiety in this group of patients in the placebo response; as less anxiety, more strong placebo response (Vase et al., 2005).

Regarding musculoskeletal pain, Goffaux et al. (2009) conducted a study with FM patients showing that despite of they achieve analgesia induced by expectations, they have and impairment of their descending inhibitory circuits, reflected in an enhancement of the reflex responses during experimental pain, even when they reported analgesia, demonstrating spinal hyperexcitability. They also found that P260 (a waveform which source is located within the ACC), and P45 (a waveform located in the SI) are sensitive to the modulation of pain depending on expectancy. Authors conclude that when FM patients anticipate pain, they engage early attention monitoring. Charron et al. (2006) carried out an experiment to assess differences in PA regarding clinical and experimental pain. For this purpose, they analyze behavioral responses of chronic low

back pain patients when a placebo is given to reduce their back pain and experimental pain induced by the cold pressure procedure. They found that placebo effect was more enhanced for clinical than experimental pain.

2. OBJECTIVES AND HYPOTHESIS

The previously presented literature shows that exist several flaws in the PA knowledge; for instance, how does it interact with clinical treatments and if chronic pain patients can achieve PA in the same way than healthy volunteers. According to the above mentioned biopsychosocial model of pain, psychological factors, such as negative emotions, have an enormous weigh for pain maintenance. Indeed, depression shows high comorbidity with chronic pain syndromes, shared at least in the 80% of cases (Poole et al., 2009), and they oftentimes do not respond to available pharmacologic treatments (Gameroff & Olfson, 2006). In a recent review, Lefacheur et al. (2020) indicate that LF-rTMS over DLPFC shows level B efficacy (probable efficacy) in depression treatment. Previous research also indicates that placebo responses are mainly mediated by learning mechanisms and cognitive expectations (Coleshill et al., 2018; Colloca, 2014). Indeed, conditioning, observational, and instructional learning are supposed to combine generating positive or negative expectations, and conditioned responses (Colloca, 2014). Moreover, placebo suggestions (positive expectation generation) accompanied with conditioning, produce a greater placebo response than each one separated (Amanzio & Benedetti, 1999; Vase et al., 2002).

Therefore, the general aim of this thesis is to better understand the role of top-down inhibition of pain mechanisms in chronic pain populations, and assess whether neuroplastic changes associated with chronic pain may interfere in PA, and thus in treatment outcomes. To fulfill our main objective, it was used rTMS plus expectation induction in a first study, and a conditioning procedure, in addition to verbal instructions and experimental setting to increase positive expectations in order to study PA in a second study. The specific objectives and hypothesis for the different studies composing this thesis were:

1. The first objective of the thesis was to explore the effectivity of LF-rTMS over rDLPFC in reducing depressive symptoms and pain ratings in patients with a clinical

history of major depression (MD) and in patients with fibromyalgia and major depression (FMD).

2. The second objective was to examine neuroplasticity, in terms of brain dynamics, in particular EEG alpha asymmetry, after LF-rTMS.
3. Moreover, the first study was also useful to better understand placebo response induced by positive expectations, and it therefore constituted our third objective.
4. The fourth objective was to analyze if CBP have equal PA response than healthy volunteers.
5. The fifth objective aimed to know whether PA could be reflected in differences observed with EEG, specifically in alpha synchronization and desynchronization.

The main hypothesis of the first study was that patients with MD and FMD could benefit of LF-rTMS therapy, alleviating pain and depressive symptoms, and it will be reflected in EEG asymmetry indices. Regarding conductual measurements, we expect to find an improvement in the depression indices and the pain subjective ratings pre- to post-treatment held to LF-rTMS. Regarding EEG measurements, we hypothesized that EEG asymmetry will be reflected in an increased left hemisphere alpha activity after the treatment. Finally, we also want to observe how positive expectations could modulate treatment response.

In the second study, we hypothesize that despite of CBP patients will achieve PA, as previous studies predicted (see section 2.3.2.5 of the present thesis), they would show lower PA response than healthy subjects, reflected in subjective ratings and in brain dynamics during expectancy and painful stimulation. Regarding brain dynamics, we expect that CBP patients would show a decrease in alpha power in frontal locations, indicating cognitive processing of the painful stimulation during anticipation phase, and an enhancement of alpha power in frontal cortex, during painful stimulation, indicating an impairment in inhibiting pain response.

3. METHODS

In this section will be provided an overview of the methods used for conducting the two studies of this thesis. However, the specific methods for each study will be explained in detail in following sections. Below, we will briefly describe general characteristics of the experimental subjects, questionnaires, and brain activity measurement technic employed.

3.1. Experimental subjects

Participants included in the two studies were mainly chronic pain patients. For the first study, a group of female fibromyalgia patients that were also suffering from major depression (FMD) and a group of patients diagnosed with major depression (MD) were enrolled. Pathologies should have been previously diagnosed by an specialist (i.e., by a psychiatrist, according to Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV, and by a rheumatologist, according to the criteria of the American College of Rheumatology (Wolfe et. al., 1990)). Moreover, both should be resistant at least to one therapeutic treatment with antidepressants up to the maximum tolerated dose, for no less than 6 weeks.

On the other hand, for the purposes of the second study, it was selected a sample of patients diagnosed with CBP, lasting more than 6 months, and recruited from Kovacs' Clinic (Palma, Spain) where all them were previously diagnosed. In order to compare CBP results, a set of healthy controls (HC), matched in age and gender, were recruited by public advertisements in the *Universitat de les Illes Balears*. Exclusion criteria included the presence of neurological disease, high blood pressure, and opioid consumption in the last 2 weeks.

3.2. Clinical assessment

Previous to the experimental task, participants were interviewed in order to assess sociodemographic criteria, and medication intake. In addition, several questionnaires assessing either pain or emotional state were conducted. Participants from both studies completed the Spanish version of the Beck Depression Inventory (BDI) (Beck et al., 1961; Conde et al., 1976). Conversely, in the first study, FMD patients completed also a numerical pain rating scale, and in the second, the Spanish version of the State and Trait Anxiety Inventory (STAI) (Seisdedos, 1982; Spielberger et al., 1970).

3.2.1. Emotional assessment

The Beck Depression Inventory (BDI) is a self-administered questionnaire, consisting in 21 items of multiple choice in which is assessed the presence and seriousness of depressive symptoms and attitudes. The items derived from clinical observations are the following: (1) mood, (2) pessimism, (3) sense of failure, (4) lack of satisfaction, (5) guilt feelings, (6) sense of punishment, (7) self-dislike, (8) self-accusation, (9) suicidal wishes, (10) crying, (11) irritability, (12) social withdrawal, (13) indecisiveness, (14) distortion of body image, (15) work inhibition, (16) sleep disturbance, (17) fatigability, (18) loss of appetite, (19) weight loss, (20) somatic preoccupation, and (21) loss of libido. Regarding cutoff scores, they are distinguish as mild (direct score <4), moderate (direct score between 14 and 20) and severe (direct score >20) (Steer, 1986). The questionnaire shows a high internal consistency (Cronbach alpha = 0.83) (Sanz & Vázquez, 1998).

The State-Trait Anxiety Inventory (STAI) was developed in order to evaluate the anxiety level in the assessment moment (“how do you feel right now, at this moment”), and also the personal predisposition to the stress response (“how do you generally feel”). It consists of 40 items either direct or reversed, 20 for each part, state and trait. The questionnaire is responded by using a 4-point Likert scale, distinguishing responses

from state to trait (state: “not at all” to “very much so”; trait “almost never” to “almost always”). Scoring might vary form 0 to 60, and the more score the more anxiety. The internal consistency for Spanish sample in anxiety state is above 0.90; and for anxiety trait oscillates between 0.84 and 0.87.

3.2.2. Pain assessment

Only in the first study, participants were asked for their pain level because we were aimed to asses possible variations in the subjective pain ratings after the intervention. For this purpose, patients had to respond to a simple question: “How bad has your pain been?”, and they had to respond in a 0 to 10 point-Likert rating scale that was graded from “no pain” to “very severe pain”.

3.2.3. Electrophysiologic recording and data analysis

EEG was used for both studies of the present thesis because its temporal resolution allows to know the precise timing of the studied events Furthermore, from affective research studies, it is known that alpha power seems to be involved in emotional modulation of perception and attention via cortical inhibition (Uusberg et al., 2013), which in turn can modulate pain perception. Moreover, pain and cognitive studies point out the positive correlation between the subjective pain intensity and alpha power (Nir et al., 2010), and the presence of aberrant activity in the brain frequency domains of chronic pain patients, in particular regarding alpha, because slowness of peak alpha frequency, and increased alpha oscillations have been observed (see Kisler et al., 2020).

For both experiments, EEG recordings were conducted in accordance with the International 10-20 System using an Electro-Cap (Inc. Ohio, USA). In the first study, EEG was recorded from a 32-channel BrainAmp amplifier (Brain Products, Munich, Germany), whereas for the second study, EEG was recorded from a 64-channel

QuickAmp amplifier (Brain Products, Munich, Germany). An electrooculogram (EOG) channel was also recorded using two electrodes placed above and below the left eye in order to correct possible ocular artifacts. Mastoid electrodes were used as reference channels for the first study, and a common reference in the second study, and ground was placed anteriorly to location of FCz electrode. A 50 Hz notch filter was applied. Electrode impedances were kept below 10kΩ (in the second study, it was possible to keep them below 5 kΩ). The sampling rate was set to 1kHz.

Finally, Fast Fourier Transform (FFT) was computed for different bands depending on the study. The bands used in the present thesis were: theta (3-8 Hz), alpha (8-12 Hz), and beta (12-30 Hz) bands. FFT power density (μV2/Hz) was corrected with a Hanning window (10%), and exported with a resolution of 0.1 Hz.

4. RESULTS

The results of the different studies will be exposed in manuscript format (introduction, methods, results, and discussion) in the following sections, because they are in preparation to be submitted to scientific journals.

4.1. Study 1: Brain dynamics associated with LF-rTMS treatment in fibromyalgia and major depression patients

4.1.1.Introduction

Repetitive transcranial magnetic stimulation (rTMS) is a therapeutic non-invasive method that modulates cortical excitability by trains of magnetic pulses given at the same frequency to a single brain area (Kobayashi & Pascual-Leone, 2003). However, the rTMS has shown a clear dissociate effect in cortico-spinal pathways depending on the stimulation frequency, producing temporary increases in cortical excitability (high-frequency rTMS; HF-rTMS, > 1 Hz) or by inhibiting cortical activity (low-frequency rTMS; LF-rTMS. < 1 Hz) (Pascual-Leone et al., 1994; Wassermann et al., 1999). For that reason, rTMS has been investigated as treatment in several neurological and psychiatric disorders, including chronic pain and resistant depression.

The syndrome of fibromyalgia (FM) constitutes a chronic musculoskeletal pain disorder characterized by widespread lowered pain threshold, fatigue, muscle stiffness, and emotional distress (Wolfe et al., 2010). Furthermore, depression disorders are a common comorbidity in this syndrome (Romano & Turner, 1985), including major depression (MD) disorder. According to DSM V, MD reflects a persistent emotional state characterized by feelings of sadness, worthless, and guilt, together with cognitive (e.g., lack of concentration) and physical (e.g., fatigue) symptoms that generate impairments in daily life.

Some studies proved rTMS to be effective to relief pain in chronic pain patients and also as antidepressant therapy (Khedr et al., 2005; Passard et al., 2007). Despite rTMS for pain treatment has been mainly applied to the motor cortex, in some of the studies it has been also applied to the dorsolateral prefrontal cortex (DLPFC) (Moisset et al., 2015). In fact, DLPFC has been proved to be a key area for the regulation of emotional processing and in top-down modulation of pain (Lorenz et al., 2003; Ochsner et al., 2004). The DLPFC is theorized to exert its influence by inhibiting the orbitofrontal cortex (OFC) activity, being a crucial area in the perception of negative affect, hence also pain (Goel & Dolan, 2003; Price, 2000;). However, a recent meta-analysis put forward that low-frequency rTMS applied over the PFC does not seem to effective (O'Connell et al., 2018).

The predominant model of hemispheric specialization, theorizes that activation of left frontal cortex reflects the activation of the behavioral approach system, whereas right frontal cortex activation would reflect activity of the behavioral withdrawal system (Henriques & Davidson, 1997; Sutton & Davidson, 1997). Lesion studies also support this hypothesis, because left frontal lobe lesions lead to decreased spontaneous verbal behavior, social withdrawal, and some instances to "catastrophic reaction" resembling depression (Kolb & Whishaw, 1996; Kolb & Taylor, 2000). An asymmetrical functional distribution is called frontal lobe asymmetry, and represents the difference between activity in right and left hemispheres (Henriques & Davidson, 1997; Sutton & Davidson, 1997).

Frontal asymmetry (less left frontal activation and more right frontal activation) noted in depressed patients pointed towards a neurobiological basis for depression (Davidson, 1995; Henriques & Davidson, 1990, 1991; Roemer et al., 1992). This asymmetry pattern seems to be stable trough time in patients with current depression and those in remission (Allen et al., 2004; Blackhart et al., 2006; Hagemann et al., 2002; Tomarken et al., 1992; Vuga et al., 2006). In accordance to these findings, brain asymmetry could be a trait marker for the disposition toward negative affect.

Furthermore, the asymmetrical emotional processing might be related with different distribution of monoamines (García-Toro et al., 2001). This could explain the change in frontal EEG asymmetry induced by tryptophan depletion that predicts the likelihood of future depression (Allen et al., 2009). However, some research failed to replicate these previous studies, finding hypoactivation in right frontal activity in depressed individuals relative to those non depressed (Knott 2001; Reid et al., 1998), and the same occurred with posterior alpha asymmetry (Reid et al., 1998; Schaffer et al., 1983). For instance, Henriques and Davidson (1991) did not found differences in frontal asymmetry in groups which were on tricyclic and serotonin reuptake inhibitors (i.e., imipramine and fluvoxamine).

Alpha asymmetry studies linked this band with depression, emotional states, and individual differences in the emotional processing (Davidson, 1995). Moreover, it is considered that alpha activity has an inverse relation to cortical activation (Lindsley, 1952; Shagass, 1972). Hence, alpha asymmetry in depression is reflected in less alpha power in right frontal and larger alpha power in left frontal (Jesulola et al., 2015). Regarding pain, alpha band was differentiated in low alpha (8-10 Hz) and high alpha (10-12 Hz), for a better understanding, resting on the basis that they reflect different mechanisms. Low alpha power is considered to reflect perceived muscle pain intensity (Chang et al., 2003), and power increase can also indicate an increase of attention (Klimesch, 1999; Ray & Cole, 1985). On the other hand, high alpha power is related to the selective encoding of stimuli and the extraction process of perceived information of long-term memory (Klimesch, 1996).

The main objective of our study is to explore alpha asymmetry before and after a LF-rTMS treatment at rDLPFC in MD patients and in FM with major depression (FMD) patients. Our hypothesis is that FMD patients could benefit of LF-rTMS treatment, due to both antinoniceptive and antidepressive effects. Specifically, we expect to find an improvement in a depression index and in a 11-point numerical pain rating scale pre- compared to post-treatment held to LF-rTMS. Moreover, according

to Davidson (1990, 1992), the left hemisphere asymmetry (e.g., larger activity in left than right hemisphere) is more likely to display behaviors associated with approach motivation and positive affect. In this line, we expect differences in brain asymmetry after the LF-rTMS treatment, increasing left frontal hemisphere asymmetry.

4.1.2. Methodology

4.1.2.1. Participants. This study was carried at the Hospital Son Dureta and the Universitat de les Illes Balears (UIB) from Mallorca (Spain). To be included in the study, subjects had to fulfill either the diagnosis criteria of major depression (MD group), diagnosed by a psychiatrist according to Diagnostic and Statistical Manual of Mental Disorders-IV, or diagnosis of fibromyalgia, confirmed by a rheumatologist according to the criteria of the American College of Rheumatology, and major depression (FMD group). Moreover, all patients had to be resistant at least to one therapeutic treatment with antidepressants up to the maximum tolerated dose, for no less than 6 weeks. This pharmacological treatment was maintained and unchanged during the month before and during the study.

Forty-seven patients agreed to participate in the study until the end; twenty-seven patients who fulfill the criteria for MD and twenty FMD patients. Within each group, they were pseudo-randomly assigned to placebo and treatment group. In the MD group, 16 received real rTMS, and 11 received placebo treatment, whereas in the FMD group, 12 received real rTMS, and 8 received placebo treatment (see Table 2).

At the time of recruitment, subjects were verbally informed about the objectives of the study as antidepressant and analgesic therapy, and of the possible side effects of the technique. Afterwards, they were invited to ask questions about the study before signing the written informed consent. The study was in accordance with the Declaration of Helsinki (1991) and the ethics committee of the UIB approved the study.

Table 2.

Group Distribution and Sociodemographic Data and Medication

	Treatment group		Placebo group	
Patient group	**FMD**	**MD**	**FMD**	**MD**
n = 47	12	16	8	11
Age (mean, SD)	47.6 (6)	45.6 (15.8)	54.4 (5.7)	48.3 (12.1)
Gender, %				
Female	100 %	62.50 %	12.50 %	72.73 %
Male	-	37.50 %	87.50 %	27.26 %
Medication, %				
SSRI	100 %	100 %	87.50 %	100 %
SNRI	-	-	12.50 %	-
Bzp	91.67 %	81.25 %	62.50 %	81.82 %
AP	-	18.75 %	-	18.17 %
AE	33.32 %	18.75 %	37.50 %	27.26 %

Note: SSRI = selective serotonine reuptake inhibitors; SNRI = dual serotonin and norepinephrine reuptake inhibitor. Bzd = benzodiacepine. AP = antipsychotic. AE = antiepileptic.

4.1.2.2. EEG recording. The EEG was recorded from a 32-channel BrainAmp amplifier (Brain Products, Munich, Germany) at a sampling rate of 250 Hz. An offline 50 Hz notch filter was also applied. EOG was also recorded to correct possible artifacts. Ground was placed anteriorly to location of FCz electrode. Mastoid electrodes were used as reference channels. Electrode impedances were measured to be less than 10 kΩ. One MD patient was discarded because of a failure during the measurements.

4.1.2.3. Transcranial magnetic stimulation. Current participants are a subsample which participated in a previous study (Carretero et al., 2009), in which both patients groups (real and sham) didn't improve their depression or pain scores. The rTMS was performed with a butterfly coil of 70 mm (DANTEC, model MagPro and MagLite) connected to a stimulator. The main stimulator parameters were 20

trains at 110% of motor threshold for 60 s at 1 Hz and 45 s of inter-trials interval. Prior to the stimulation, it was established the motor threshold to lay down the stimulation area. Thus, was performed by single-pulse LF-rTMS over the left-brain area that triggered right thumb abduction. The stimulation area was in the **r**ight DLPFC, five centimeters in front of the specular point that triggered a more selective right-thumb abduction response in the left motor cortex. In the real condition, the coil was placed in direct contact with the scalp, so the middle of the coil was in the stimulation area. In the placebo condition, the coil was placed perpendicularly to the cranium at the reported stimulation point, nevertheless the coil was inclined 45º forward the axis. In this way, the magnetic field did not penetrate in the brain significantly, although the participant did hear the sound generated by the coil.

4.1.2.4. Procedure. A single-blinded study, with an external evaluator, was performed in order to examine the effects of LF-rTMS. Investigators, blinded to the treatment groups, made the evaluations pre- and post-treatment (after 4 weeks). All study participants completed the Spanish version of the Beck Depression Inventory (BDI) (Beck et al., 1961; Conde et al., 1976), and only FMD patients completed also a numerical pain rating scale, in which patients were asked about “How bad has your pain been?”, and they had to respond in a 0 to 10 point-Likert rating scale from “no pain” to “very severe pain”. Instructions given to the participants were provided by the researchers. They informed that the study was evaluating LF-rTMS as antidepressant and analgesic therapy, therefore both symptoms might improve after the treatment.

LF-rTMS was applied daily from Monday to Friday, in 20 consecutive sessions along 4 weeks. In order to assess alpha asymmetry differences due to the treatment, resting EEG was recorded during 4 minutes. Recordings of resting EEG, were registered pre- and post-treatment within the same week of the first and last LF-rTMS session, respectively. During this time, participants were instructed to remain with closed eyes.

4.1.2.5. Data reduction and analysis. Sociodemographic data (age, gender, and medication) were analyzed with non-parametric measures U de Mann-Whitney, and chi-square. Data from the questionnaires were analyzed trough repeated-measures analysis of variance (ANOVA). It was used as within factor TIME (pre vs. post). To analyze the 11-point numerical pain rating scale, the between subjects factor was TREATMENT (real rTMS vs. placebo). For the BDI scores, between subjects factors TREATMENT (real rTMS vs. placebo) and PATIENT (MD vs. FMD) were used.

Baseline EEG data was analyzed by computing power density (μV2/Hz) of the low alpha (8-10 Hz) and high alpha (10-12 Hz) bands. For this purpose, a fast-Fourier transformation (FFT) was applied with a Hanning window (10%). Data from mid-frontal (F3, F4), lateral-frontal (F7, F8), central (C3, C4), parietal (P3, P4), mid-temporal (T3, T4), lateral-temporal (T5, T6), and occipital (O1, O2) electrodes were clustered and log-transformed (log 10) to approach Gaussian distribution. An index of hemisphere asymmetry was calculated by subtracting power values of the left hemisphere from the right hemisphere at these brain locations (frontalCentral asymmetry: F4-F3, frontalLateral asymmetry: F8-F7, central asymmetry: C4-C3, parietal asymmetry: P4-P3, temporalCentral asymmetry: T4-T3, temporalLateral asymmetry: T6-T5, and occipital asymmetry: O2-O1). Data were statistically analyzed by using a randomized factorial mixed design ANOVA, with the within-subjects factors BRAIN (assym_frontalMid, assym_frontalLateral, assym_central, assym_parietal, assym_temporalMid, assym_temporalLateral, and assym_occipital), and TIME (pre vs. post), and using the between-subjects factors TREATMENT (real rTMS vs. placebo), and PATIENT (MD vs. FMD).

4.1.3. Results

4.1.3.1. Behavioral results. Non-parametric analyses (U de Mann-Whitney) reveal that FMD group had significant differences in age between treatment and placebo groups ($p<0.033$). Chi-square analysis shows that groups receiving real and

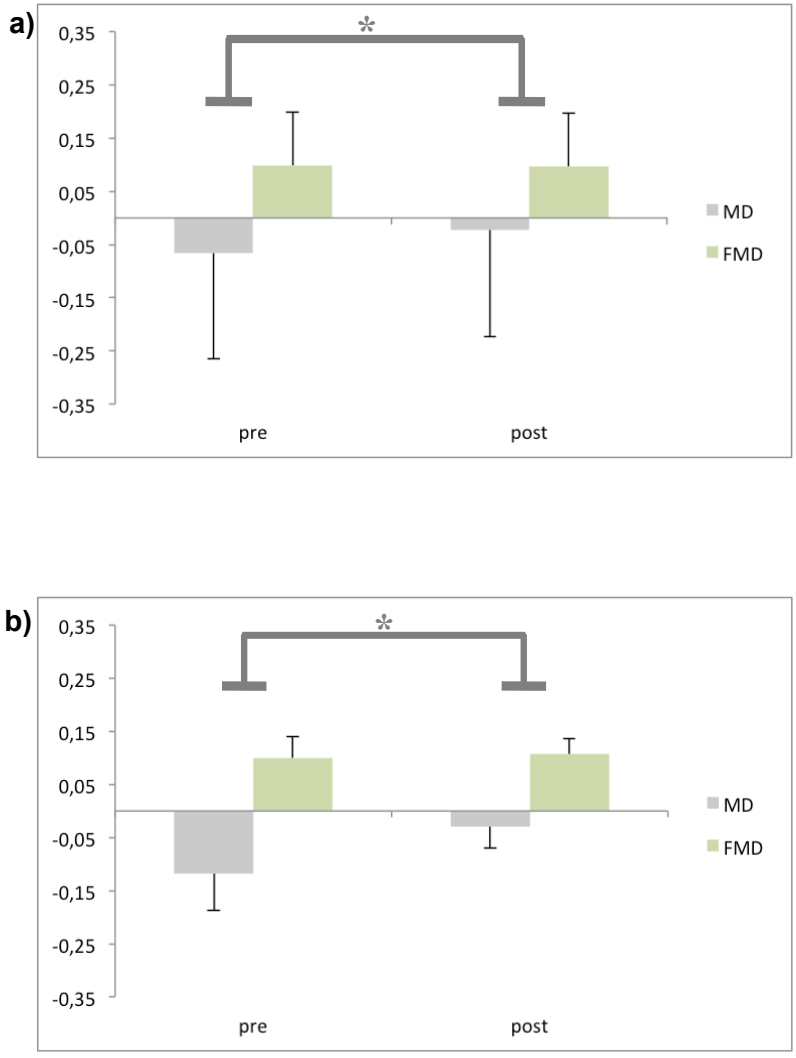
placebo treatment, both FMD and MD patients, were comparable in gender and medication intake. Analyses of BDI scores showed an effect of the TIME factor for all treatment conditions ($F(1,43)=46.3$, $p<0.001$), indicating that depression was overall reduced after the treatment. Analyses of the 11-point numerical pain rating scale reveal an effect of the TIME factor, showing also a reduction in pain rating within the FMD group, from pre- to post- treatment for both treatment groups ($F(1, 18) = 95.28$, $p< 0.001$).

4.1.3.2. EEG results. Significant effects of BRAIN ($F(6,240)=10.3$, $p<0.001$), BRAIN X PATIENT ($F(6,240)=6.2$, $p<0.001$), and TIME X PATIENT ($F(1,240)=5$, $p<0.05$) were found on the hemispheric asymmetry indexes at the low alpha band (8-10 Hz). Post-hoc mean comparison analyses revealed that after the treatment MD patients showed less asymmetry (right - left) than FMD over mid-frontal areas ($p<0.01$), but more asymmetry over lateral-temporal and central areas ($p<0.01$) (see Figure 6b).

Significant effects due to BRAIN ($F(6,240)=13.8$, $p<0.001$), BRAIN X PATIENT ($F(6,240)=7.3$ $p<0.001$), and TIME X PATIENT were found in the hemispheric asymmetry indexes for the high alpha band ($F(1,40)=4.6$, $p<0.05$). Post-hoc mean comparison analyses show equal results than in low alpha power: MD patients showed less asymmetry (right - left) than FMD over mid-frontal areas ($p<0.05$) post-treatment however, it was observed more asymmetry over lateral-temporal and central areas ($p<0.00$) (see Figure 6a).

Figure 6.

Illustrate Alpha Power Pre- and Post-Treatment in Mid-Frontal Location



Note. Mean of alpha power asymmetry (SD, error bars) of high alpha, and low alpha. *p<0.05. Figure a) depicts high alpha asymmetry in MD and FMD patients. Figure b) depicts low alpha asymmetry in MD and FMD patients. Note that treatment promoted a change in FMD patients whereas MD remain stable showing less alpha asymmetry after the treatment.

4.1.3. Discussion

To investigate the effects of LF-rTMs in brain dynamics, a single-blinded study was conducted with FMD and MD patients. The hypothesis stated that patients would improve their depressive and pain symptoms yielded by the treatment, and this

symptoms improvement would be reflected in changes in alpha asymmetry in left hemisphere after the treatment. Our results indicate that brain asymmetry changed only within the MD group, but opposite than expected. MD patients shown less alpha asymmetry over fronto-medial location compared to FMD patients, independent of the treatment group. According to the current model of hemispheric specialization associated with emotional processes (Davidson et al., 1990; Davidson, 1992), the left hemisphere asymmetry (i.e., larger activity in left than right hemisphere) is more likely to display behaviors associated with approach motivation and positive affect, while right asymmetry (i.e., greater activity in right in comparison with left hemisphere) is linked to negative affect, and the activation of avoidance-withdrawal system (Sutton & Davidson, 1997). If we consider alpha power band as inversely related to cortical activation in adults (Shagass, 1972; Lindsley, 1952), asymmetry observed in MD patients after LF-rTMS treatment may reflect either less activation of left hemisphere, or more activation of the right hemisphere after the treatment. In any case, both scenarios lead to the same conclusion: brain correlates after treatment corresponds to negative affect, according to Sutton and Davidson's theory (1997).

In fact, EEG studies reveal that depressed patients showed increased alpha activity in left than in right hemisphere (Bell et al., 1998; Gotlib et al., 1998; Henriques and Davidson, 1991; Roemer et al., 1992). This activation pattern has been frequently observed in the relative excess of alpha band activity in left mid-frontal (F3>F4), and lateral-frontal (F7>F8) locations (Debener, 2000; Henriques & Davidson, 1991; Schaffer et al., 1983). PET studies also show a hypometabolism of the left frontal cortex in depressed patients (Bench et al., 1993; Martinot et al., 1990). Some lesion studies also support this hypothesis: left frontal lobe lesions lead to decreased spontaneous verbal behavior, social withdrawal, and some instances to "catastrophic reaction" resembling depression (Kolb and Whishaw, 1996; Kolb and Taylor, 2000). It seems that asymmetry pattern is stable trough time in patients with current depression and those in remission (Allen et al., 2004; Blackhart et al., 2006; Hagemann et al., 2002; Tomarken et al., 1992; Vuga et al., 2006), which could be

explaining our post-treatment results. In accordance to these findings, brain asymmetry could be a trait marker for the disposition toward negative affect.

Furthermore, our results also indicate the expected results, reducing depression and pain scores, but the effect was unspecific of the treatment (real rTMS vs. placebo). Post-treatment depression index and subjective pain ratings were both reduced for real treatment and placebo groups, revealing a placebo response to the rTMS manipulation. Placebo response can be triggered by cognitive factors like relief expectancy (Krummenacher et al., 2010), which could explain our results. Indeed, our participants were told that the treatment would reduce their pain and depressive symptoms, enhancing relief expectancy, and hence a placebo response. Our results are in agreement with previous studies were also was found a pain reduction for treatment and placebo groups (Atlas et al., 2019). However, in this study it was applied LF-rTMS either to the left DLPFC or to the left primary motor cortex, finding greater improvement in the treatment groups for pain and depressive symptoms. In this line, a recent meta-analysis (O'Connell et al., 2018) concludes that rTMS over prefrontal cortex does not apear to be more effective than placebo for chronic pain management. Nevertheless, in a recent study not included in the previous meta-analyses, Phillips et al. (2018) found depression and pain reduction ratings, in depressive patients resistant to treatment with comorbid pain, after high-frequency rTMS over left DLPFC.

In summary, LF-rTMS with positive verbally induced expectations was as effective as placebo in the reduction of pain and depression observed in the subjective scales,.However, brain correlates (in this case, left alpha asymmetry) remain with a negative affect pattern, which seems to be a biomarker of depression.

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4.2. Study 2: Brain correlates of placebo analgesia in chronic back pain patients compared with healthy subjects

4.2.1. Introduction

Placebo analgesia represents an example of antinociception, exerting powerful descending control of pain under certain conditions (Bingel et al., 2006; Stein et al., 2012). The descending modulatory system is the principal pathway to change pain perception by means of cognitive and contextual features (Tracey, 2010). In this line, placebo analgesia can be very specific and it can be modulated by several cognitive, emotional, and situational factors (e.g., expectation, beliefs, learning, meaning, context, verbal instructions, level of pain) (Benedetti et al., 2006; Shapiro & Shapiro, 1997). Placebo analgesia depends on automatic conditioning responses and cognitive modulation based on experience (Kong & Benedetti, 2014). Indeed, several studies have pointed out expectancy and conditioning as the main mechanisms mediating placebo effects (Amanzio & Benedetti et al., 1999; Klinger et al. 2007; Price et al., 1999).

Regarding psychological mechanisms involved in placebo analgesia, it exist a debate about the major contribution in placebo analgesia of expectations or conditioning. In this line, Klinger et al. (2007) designed a study to reveal mechanisms of placebo analgesia testing differences between expectancy and classical conditioning in patients with atopic dermatitis. Results indicate that conditioning without placebo instructions may trigger a placebo response; moreover, the placebo instruction alone could not generate placebo response. The authors suggest that expectation and conditioning are needed to elicit a placebo response; however, classical conditioning may be more important regard to the maintenance of the placebo responses. Furthermore, conditioning was proved as the only factor leading to a pain reduction consistent with placebo analgesia response (Colloca et al., 2008). In addition, conditioned responses tend to be more long-lasting and robust (Colloca & Benedetti, 2006). Therefore, according to these authors,

conditioning seems to be a main contributor to generate and maintain placebo response. Nevertheless, new evidence reveals that a combination of both is required to elicit placebo effects (Wager & Atlas, 2015).

Besides the psychological mechanisms above described, placebo analgesia is also correlated with different brain structures and can modulate specific brain areas. For instance, the PFC) has been widely associated with placebo response (Tracey, 2010). Benedetti et al. (2006) conducted an EEG study with Alzheimer disease (AD) patients that revealed the important role of the PFC to achieve a placebo analgesia response. In this experiment, expectations were manipulated while applying lidocaine to alleviate pain after venopuncture, in both AD patients and controls. The study revealed that AD patients showed less analgesia in the placebo condition than controls, and this lower placebo response was positively correlated with poor performance on neuropsychological tasks related to frontal lobe function. Furthermore, authors conclude that reduced placebo analgesia was also associated with reduced connectivity of the PFC with the rest of the brain in these patients, which may be responsible to the vanishing of placebo analgesia response. It has also been shown, by voxel-based morphomertry, that gray matter density in the dorsolateral PFC (DLPFC), as in nucleus accumbens (NAc) and insula, was correlated with greater placebo analgesia response (Schweinhardt et al., 2009). Actually, different authors agree that is in the DLPFC where the placebo analgesia response is initiated (see Medoff & Colloca, 2015).

Intriguingly, there is considerable evidence for functional and structural alterations in the PFC of chronic pain patients, specially in the case of chronic back pain (CBP). CBP is the most widespread chronic pain syndromes, with prevalence in Spain about 60.53% of the pain population (National Health and Wellness Survey [NHWS], 2010, extracted from Langley et al., 2011). Baliki et al. (2006, 2011) observed in CBP patients that pain intensity seems to be maintained by sustained activation of PFC (Baliki et al., 2006, 2011). Moreover, it has been shown that CBP patients display a significant atrophy in cortical gray matter in the DLPFC, which it is related to pain perception (Apkarian et al.,

2004). Given that the DLPFC is implied in the top-down pain control, it has been argued that plastic changes in PFC may lead to a disruption in the top-down mechanisms to control pain (Apkarian et al., 2004).

Moreover, it has been observed that chronic pain patients exhibit aberrant activity in the brain frequency domains (Kisler et al., 2020). In particular, regarding alpha, it has been observed slowness of peak alpha frequency, and increased alpha oscillations (see Kisler et al., 2020). Event-related desynchronization (ERD) of alpha frequency band (8-12 Hz) represents an important aspect of top-down regulation of incoming sensory information (Klimesch et al., 2007). Alpha ERD seems to be a correlate of cellular excitability in the thalamo-cortical system (Ferracuti et al., 1994) and predict subjective evaluation of pain intensity (Babiloni et al., 2006). Moreover, it has been argued that alpha ERD may be reflecting the transfer of sensory information through sensoriomotor thalamo-cortical and cortico-cortical pathways such as it happens in attentional processes (Klimesch, 1999; Pfurtscheller & Lopes da Silva, 1999). In the pain field, alpha band power decrease has been associated with the presentation of noxious stimuli (Chen & Rappelsberger, 1994; Dowman et al., 2008; Huber et al., 2006).Conversely, other studies suggest that subjective experiences of pain lead to higher peak alpha frequencies (Nir et al., 2010).

Nevertheless, little is known about the alpha implications in placebo analgesia. For instance, Hunneke and cols. (2013), conducted a response conditioning protocol with verbal suggestions, to asses changes in alpha during resting-state in healthy controls. The authors observed alpha band decreases in the control condition, whereas alpha power was increased in the post-conditioning recording for the placebo group. However, they recorded EEG before, during and after procedure, so they did not have results of the stimulation periods. In contrast, Li's group (2016), conducted an experiment with healthy subjects were EEG was recorded also during processing of noxious stimuli to assess placebo analgesia effect. For this purpose, it was injected to participants either an isotonic saline (innocuous) or a hypertonic saline (painful), and they went through

four conditions along two sessions (control, pain, control+placebo, pain+placebo). Authors observed that, for the first condition, during noxious processing, alpha power decreased whereas no differences were found in the second condition; however, the fourth condition revealed an alpha desynchronization, but smaller than in the second condition. Nevertheless, all the studies found were conducted in healthy subjects therefore we have no data of alpha functioning during placebo analgesia in CBP patients.

According with the previous findings, we were aimed to explore anticipation and painful stimulation. We hypothesized that CBP patients will show lower placebo response than healthy controls. This might be reflected on subjective ratings, as well as by changes on brain dynamics. Specifically, we expect that CBP will show an enhancement of alpha power on frontal cortex in comparison with healthy controls in the test phase (placebo response).

4.2.2. Methodology

4.2.2.1. Participants. The study included 20 patients diagnosed with persistent back pain, lasting more than 6 months (10 women and 10 men) and 20 healthy controls (10 women and 10 men). Nevertheless, three of them were excluded because of technical reasons. Therefore, 37 volunteers were included in the final analyses (see Table 3). CBP patients were recruited from the Kovacs Clinic (Palma, Spain), a specialized centre for CBP. Exclusion criteria included the presence of neurological disease, high blood pressure, or opioid consumption in the last 2 weeks. Table 3 also displays medication intake in both groups. A specifically designed information leaflet was given to all subjects, and after agreeing to participate, individual written consent was provided. Prior to the experiment, questionnaires assessing emotional state of the participants, State and Trait Anxiety Inventory (STAI) (Seisdedos, 1982; Spielberger et al., 1970) and the Beck Depression Inventory (BDI) (Conde et al., 1976; Beck et al., 1961), were also

provided. The study was in accordance with the Declaration of Helsinki (1991) and was approved by the Ethics Committee of the Universitat de les Illes Balears (Spain).

Table 3.

Sociodemographic and Clinical Data

	Healthy controls (n=18)	**Chronic back patients** (n=19)
Age (mean, SD)	48.6 (8.7)	48.3 (8.2)
Gender (n)		
Male	8	9
Female	10	10
Medication (%)		
Antidepressants	11.1	33.3
Analgesics/muscle relaxants/NSAIDs	16.6	83.3
Anxiolytics	5.5	39
STAI (0-60)		
State	19.3	29.7
Trait	20.4	30.7
BDI (0-63)	5.4	15.1

Note: NSAIDs = non-steroidal anti-inflammatory drugs.

4.2.2.2. Conditioning task. The paradigm used to assess placebo effects was a response conditioning design (Wager and Atlas, 2015), with context enrichment associative cues. In this type of paradigm it is combined instructions with reinforcement to promote placebo response. In our particular case, heat stimuli corresponding with three different intensities (high, medium and low) were applied during three different phases: baseline, placebo conditioning, and test (see Figure 7a). During the first phase (baseline), three heat stimuli (one of high-, one of medium-, and one of low-intensity) were delivered to the left (50%) and to the right wrist (50%), following a pseudorandomized order. The intensities of the high-, medium- and low-intensity heat stimuli during this condition were 42ºC, 40ºC and 38ºC, respectively (see Table 4). The intensity levels of heat stimuli used in the present study were obtained from previous

experiments in healthy volunteers (data not shown). Nevertheless, patients were asked to rate the pain elicited just after each stimulus using a numerical scale (0= no pain, 10=unbearable pain) implemented on a computer keyboard, in order to ensure that they could differentiate between intensities.

Table 4.

Temperatures in the Three Phases for Control, and Placebo Conditions

Phase	Cream	Temperatures (°C)		
		High	*Medium*	*Low*
phase 1	no cream	42	40	38
		42	40	38
phase 2	control	42	40	38
	placebo	**39**	**37**	**35**
phase 3	control	42	40	38
	placebo	42	40	38

Note. Phases correspond to conditioning trials, where phase 1 corresponds to the baseline trial, phase 2 to the conditioning trial, and phase 3 to the test trial.

In the second phase (placebo conditioning), two innocuous creams were applied to the inner wrist before heat stimuli were delivered. Both creams were composed of a thick ointment (o/w emulsion q.s. 50g), with slight mint smells produced by methyl salicylate-menthol 0.5% in the placebo cream or 0.25% in the control cream, in order to enhance their expectations. In the same line, creams were packed in two different labelled tubes, and participants were instructed that one tube contained a “moisture” cream used to control the moisturizing effects on the skin, whereas the other one contained a cream for pain relief. In half of participants, the moisture cream was applied to the left wrist and the analgesic cream to the right wrist. After the application of the creams, 30 heat stimuli of different intensities (10 of high-, 10 of medium-, and 10 of low-intensity) were again delivered to the right (50%) and to the left wrist (50%), following a pseudorandomized order. In order to enhance expectations of pain relief and increase the placebo response, during this condition, intensities of heat stimuli were surreptitiously reduced when they were delivered to the wrist with the “analgesic” cream.

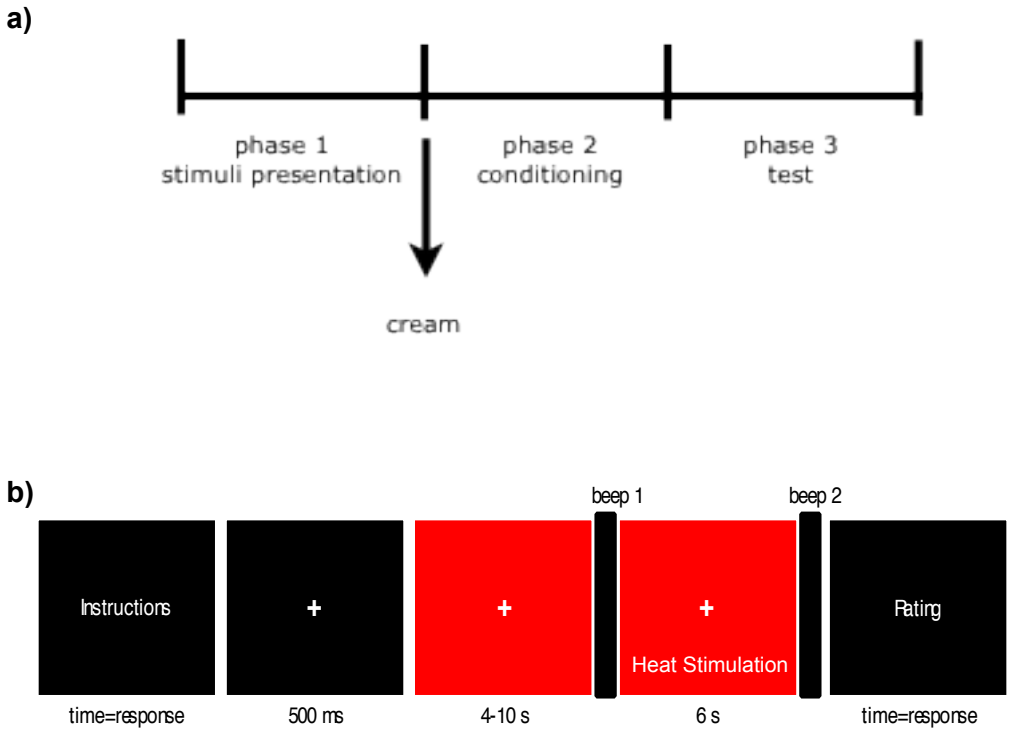
Thus, stimulus intensities of 42ºC (high), 40ºC (medium) and 38ºC (low) were used when delivering heat to the wrist with the moisture cream, whereas stimulus intensities of 39ºC (high), 37ºC (medium) and 35ºC (low) were used when delivering heat to the wrist with the placebo cream. Participants were again asked to rate the pain elicited by each stimulus using the same numerical scale as in the baseline condition.

The third phase (test) runs next to the placebo conditioning phase, just after a brief pause (decided by the participant). Participants were told that the third phase was designed in order to test long-term effects of the cream. For this purpose, 15 heat stimuli (five of high-, five of medium-, and five of low-intensity) were delivered to the left (50%) and to the right wrist (50%) as during baseline. The intensities of the high-, medium- and low-intensity heat stimuli during this condition were identical as during baseline. Patients were asked to rate the pain elicited by each stimulus using the same numerical scale as in the previous conditions.

Trial presentation was controlled by a computer with Presentation software 15.0 (Neurobehavioral Systems, Berkley, USA, https://www.neurobs.com/), connected to a thermal stimulator with a peltier, were volunteers placed the cubital wrist (one cm2). All the trials followed an identical structure in the three conditions (see Figure 7b). The trial started with a fixation cross on a black screen during 500 ms, and it followed by a colour cue signalling the intensity level of the upcoming heat stimulus (a red screen for a high-intensity stimulus, an orange screen for a medium-intensity stimulus, and a yellow screen for a low-intensity stimulus). After a random interval (from four to ten seconds), there was a beep requesting the participants to put cubital wrist on the peltier. After six seconds (fixed interval), participants were requested to remove their wrist from the peltier surface and to rate their pain.

Figure 7.

Experimental Procedure (a) and Run Structure of One Trial (B).



Note. Figure (a) displays the phase and cream application order, and (b) shows the trial structure.

4.2.2.3. EEG recording and materials. The EEG was recorded from a QuickAmp amplifier (Brain Products, Munich, Germany) at a sampling rate of 1.000 Hz, using a 64 electrodes cap placed in accordance with the International 10-20 System (Electro-Cap international Inc., Ohio, USA). Electrooculogram (EOG) was also recorded in order to correct possible ocular artifacts. Ground was placed anteriorly to location of FCz electrode and common reference was used. Electrode impedances were measured to be less than 5 kΩ, and a 50Hz Notch filter was applied during data acquisition. Besides the EEG cap was placed already during the stimuli presentation, this time was used to stabilize participants. EEG data was recorded only during placebo conditioning and test phases. In addition, electromyography was acquired from the surface (40x50 mm) of the extensor digitorum muscle in both arms to visually control that participants follow the

procedure during the experiment (i.e., to check they actually move and place the wrist on the peltier were the subjects placed the cubital wrist).

4.2.2.4. Procedure. The experiment was conducted in a room from of the Pain Unit of Hospital Son Espases (Palma de Mallorca, Spain), to adequate the context to medical procedures, and besides enrich associative cues. Participants where told that they were part of a study designed to understand the brain processing during analgesia. After written informed consent, participants completed the previously detailed questionnaires. Then, participants were seated on a chair from 1,5 m eye distance from the computer screen (LCD 21.5”), and EEG was placed. The instructions of the experiment were delivered to the volunteers in paper format, with the aim of influence the less in the participants.

4.2.2.5. Data reduction and analysIs. For the statistical analyses of the clinical data, it was conducted an univariate analysis of variance (ANOVA), in which the between subjects factor was GROUP (CBP, HC). Furthermore, in order to examine pain ratings of the three different intensities of thermal stimulation presented, phase 1 was analyzed with a 2x2x3 ANOVA with the between subject factor GROUP (CBP, HC), and the within subjects factors CREAM (A, B), and INTENSITY (High, Medium, and Low). After a first analysis of pain ratings, we observed no significant differences for low intensities, so it was selected as baseline and subtracted to the medium and high intensities of phases 2 and 3. The new computed variables were used for the statistical analyses, a 2x2x2 ANOVA, with the between subjects factor GROUP (CBP, HC), and the within subjects factors CREAM (A, B), and INTENSITY (H-L, M-L).

The EEG data from second and third phases was offline filtered with high and low pass filter setting at 2 Hz and 40 Hz, respectively. Data were segmented in epochs based on the marker of the cue for high, medium, and low temperatures. Afterwards, it was selected the segment between the first beep, to the second beep (from 1000 ms to 6000 ms, to avoid movement artifacts the first second was removed from the analysis).

Then, the previously segmented data were again segmented in epochs of one second. Ocular movements were corrected using a standardized regression method (Gratton et al., 1983). In addition, an artifact rejection protocol with following criteria was applied: maximal allowed voltage step/sampling point 200 μV, minimum allowed amplitude -200 μV, maximal allowed amplitude 200 μV, and maximum allowed absolute difference 200 μV. Fast Fourier Transform (FFT) was computed for the theta (3-8 Hz), alpha (8-12 Hz), and beta (12-30 Hz) bands. FFT power density (μV2/Hz) was corrected with a Hanning window (10%), and exported with a resolution of 0.1 Hz.

For the statistical analyses electrodes were pooled in fronto-central (Fz, F1, F2, F3, F4, FCz, FC1, FC2, FC3, FC4, Cz, C1, C2, C3, C4) and centro-parietal (Pz, P1, P2, P3, P4, CPz, CP1, CP2, CP3, CP4); and subjected to appropriate transformations to approach Gaussian distribution (log 10). Thereafter, the power of the different bands was analyzed by means of ANOVA (2x2x2) for each intensity level in test phase. The between subject factor was GROUP (CBP, HC), and the within subjects factors CREAM (A, B), and LOCATION (FC, CP). Afterwards, alpha, beta, and theta ERD during anticipation period were analysed by using the resting time of 500 ms of fixation cross previous to display the cue as a baseline (BL). ERD was calculated following the formula used by Babiloni et al. (2006): ERD%= (Stimuli-BL/BL)*100. Then, ERD% data was analyzed following the above-indicated ANOVA.

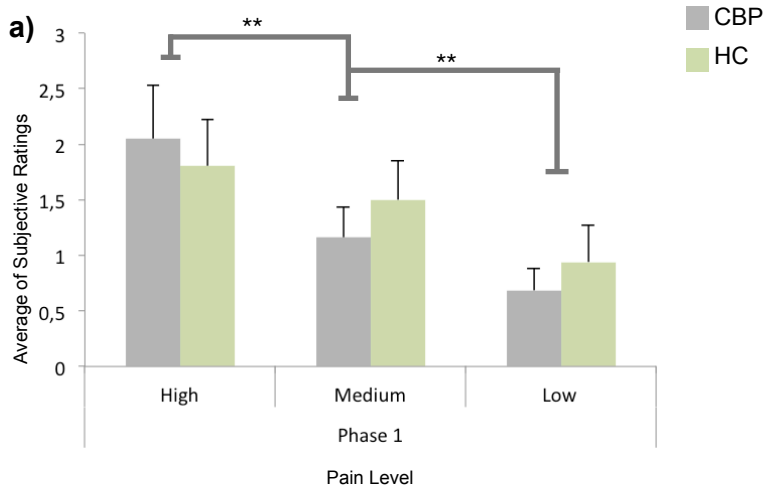
4.2.3. Results

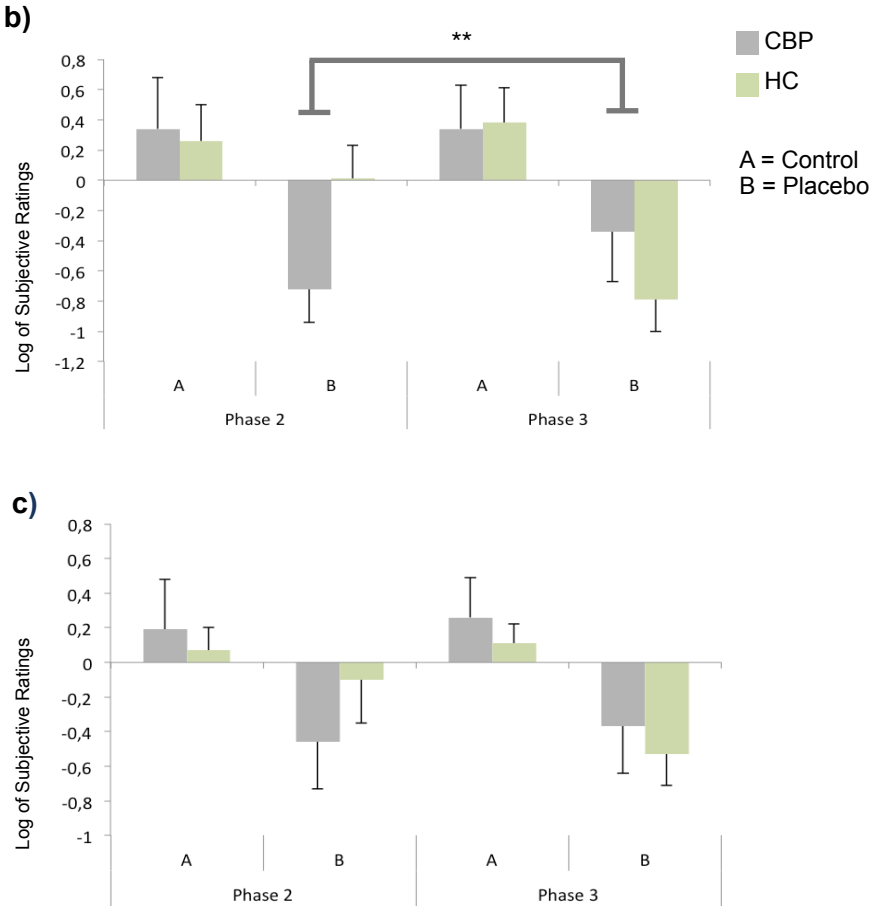
4.2.3.1. Clinical and Behavioral results. The statistical results of clinical data, bring to light a significant effect in the factor GROUP both for STAI and BDI: STAI-S $F(1,34) = 7.4$ $p<0.01$; STAI-T $F(1,34) = 7$ $p<0.012$; BDI $F(1,34) = 13.8$ $p<0.001$. Further analysis suggest that CBP show larger emotional distress than HC. Whereas CBP may be situated around the quantile 70, HC would be situated below quantile 50, in both trait and state anxiety. Data is revealing anxiety disorders within the CBP group. In addition, CBP score higher in BDI revealing mild depressive symptoms.

The statistical analyses of the subjective pain ratings of the presentation phase (phase 1) revealed a significant effect in the factor INTENSITY ($F(2,70)=21.3$, $p<0.001$). Further analyses showed that all the participants rated the high intensity stimulus as more painful than the medium, and medium as more painful than the low ones ($p<0.01$). In the second ANOVA (conditioning and test phases), it was significant the factor CREAM ($F(1,35)=8.5$, $p<0.01$), and the interactions PHASE X GROUP ($F(1,35)=10.3$, $p<0.01$), PHASE X CREAM X GROUP ($F(1,35)=7.6$, $p<0.01$), and PHASE X INTENSITY X GROUP X CREAM ($F(1,35)=5.6$, $p<0.05$). Post-hoc analyses revealed that in phase 2 CBP patients rated the control cream condition as more painful than the placebo one, whereas HC showed no differences. Within the test phase, both groups rated the control cream condition as more painful than the placebo one (CBP $p<0.05$; HC $p<0.01$). However, only for the high intensity HC rated the control cream condition as more painful than the placebo one ($p<0.01$), while no differences were found for the CBP patients. This last effect reveals that, the placebo effect appeared mainly for the HC group, in the high intensity condition (see Figure 8).

Figure 8.

Subjective Ratings Results





Note: Mean (SD, error bars) (a) subjective ratings average on phase 1 (temperature presentation). (b) Subjective ratings transformations in the High-Low condition. (c) Subjective ratings transformations in the Medium-Low condition for conditioning (phase 2) and test (phase 3) trials. **p<0.01.

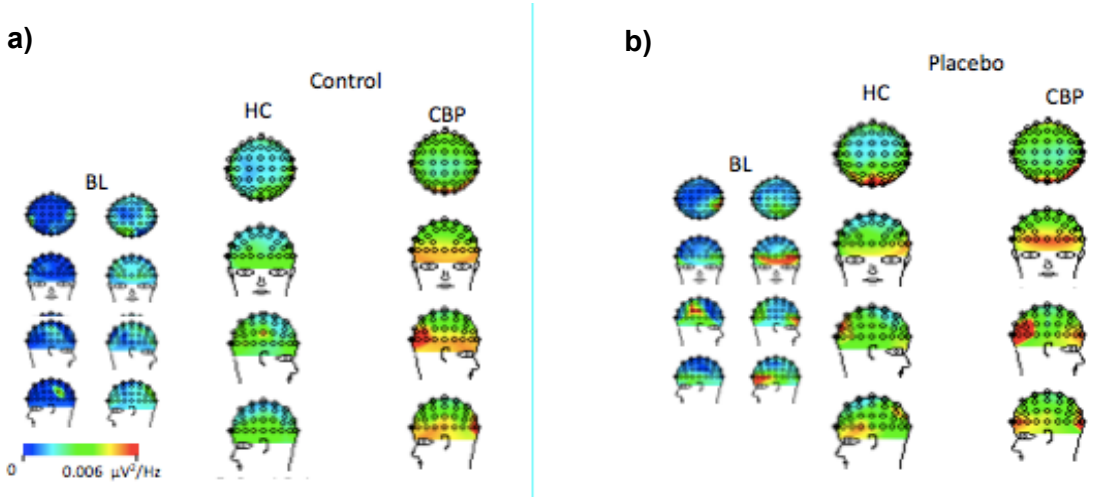
4.2.3.2. EEG results

4.2.3.2.1. Anticipation period. ERD analysis was performed for the anticipation period, and analyzed into three ANOVAs according to the three pain intensities. During this period, alpha power reveals a significant effect, only for the high intensity, in the interaction factors CREAM X GROUP ($F(1,35)=6.7$, $p<0.05$), LOCATION X CREAM X GROUP ($F(1,35)=4.9$, $p<0.05$). Post-hoc analyses expose that ERD was greater for placebo than control condition just for CBP ($p<0.05$) at fronto-central and centro-parietal locations. The ANOVA conducted on the theta and beta power did not reveal significant results at any condition.

4.2.3.2.2. Heat stimulation. In the test phase, alpha band showed significant effects in the high intensity for the factor LOCATION ($F(1,35)=8.5$, $p<0.01$), and the interaction factors LOCATION X GROUP ($F(1,35)=5.9$, $p<0.05$), LOCATION X CREAM ($F(1,35)=9.5$, $p<0.005$), LOCATION X CREAM X GROUP ($F(1,35)=5.6$, $p<0.05$). In the post-hoc analyses it was observed that during the test phase, CBP patients within the placebo condition, showed alpha power enhancement compared to the control condition in fronto-central location ($p<0.05$), and it was also greater for CBP compared to healthy controls in both conditions (see Figure 9).

Figure 9.

FFT Power Density of Alpha Distribution in the Test Condition During Heat Stimulation



*Note***.** The figures display the significant interaction effect of LOCATION X CREAM X GROUP. BL = Base line, HC = healthy controls, CBP = chronic back pain.

In turn, at centro-parietal location, the control condition exhibits greater alpha power in CBP patients ($p<0.05$), whereas there was no difference for the placebo condition. For the medium intensity, it was found significant the factor LOCATION ($F(1,35)=4.4$ $p<0.05$), and the interaction LOCATION X CREAM X GROUP ($F(1,35)=6$, $p<0.05$). Further analyses expose that for medium intensities CBP patients exhibit more alpha power than healthy controls in fronto-central location ($p<0.05$). For the CBP group, the control condition showed no differences. Nevertheless, in the placebo condition CBP

displayed greater alpha power than healthy controls ($p<0.05$). Finally, in the low intensity no significant results were found.

4.2.4. *Discussion*

The aim of the present study was to investigate the brain response during placebo analgesia in CBP patients, and to assess differences in placebo effect between CBP and HC. For this purpose, a response conditioning design with verbal suggestion, and rich associative cues (hospital setting and creams formulation) was conducted. In our study, an inert cream was used as placebo (B) and control (A), however, participants were told that cream B has an analgesic effect in order to enhance positive expectancy. To generate more robust placebo analgesia response, conditioning was performed by surreptitiously reducing pain intensity of thermal stimulation in the placebo condition during conditioning phase. In the test phase, pain intensities were adjusted to the initial ones (presentation phase), and it was the same for placebo and control conditions. EEG was analyzed during the processing of painful stimulation, and during anticipation period, in absence or presence of a placebo manipulation.

The analysis of anxiety and depression scores revealed that CBP patients exhibit more negative affect than healthy subjects. Results are in accordance to previous studies revealing that patients with musculoskeletal pain have more risk to suffer from mild to severe symptoms of depression and anxiety, which have an important role modulating pain perception (Arola et al., 2010), or even also resulting in less cognitive flexibility (Jones et al., 2013). On the other hand, affective research has pointed out that alpha enhancement could be involved in emotional modulation of perception and attention via cortical inhibition (Uusberg et al., 2013). PFC is also involved in the belief of self-control of pain, limiting fear of pain, cognitive reappraisal via inhibition of limbic system or generating new emotions (for review, see Tracey, 2010). Morton et al. (2009) proposed that the reduction of anxiety generated by optimist expectations of relief could be an important factor in the placebo analgesia response. Actually, one year later, the

same authors found out that reductions in anxiety were associated to reduction in anticipatory processes in placebo analgesia experiment (Morton et al., 2010). Research also suggests that increase endogenous opioid tone may potentiate placebo analgesia (e.g., after exercise), but anxiety reduces this endogenous effect (van Hecke et al., 2013). Therefore, data suggest that enhanced anxiety scores could be interfering in the placebo analgesia response in CBP patients.

The analyses of pain ratings from the first phase reveal that participants could perfectly distinguish the three different pain intensities presented. Regarding to the test phase, we observed that both groups showed reduced pain scores in the placebo condition, reflecting placebo analgesia effect. As consequence, our data are in agreement with a previous studies conducted in patients with irritable bowel syndrome and CBP (Klinger et al., 2017; Price et al., 2009), revealing that patients may also achieve placebo analgesia responses. However, for the highest intensity in the placebo condition, only HC showed a significant decrease in pain ratings. Therefore, as expected, CBP patients showed less reduction in pain ratings, hence less placebo-induced analgesia response, but only for high intensities.

In order to assess anticipation processes in our study, stimuli were preceded by a cue indicating the intensity of the following heat. According to Brown et al. (2008), under certain conditions, anticipation was a predictor of pain processing, and certain expectations of high pain would increase pain perception. Indeed, Babiloni and cols. (2006) put forward that alpa ERD predicts subjective evaluations of pain; in fact, the greater the alpha suppression, the higher the pain perception. In this line, our EEG results about the anticipation period, reveal a greater decrease of alpha over frontal and centro-parietal locations in response to placebo in CBP compared to HC. Therefore, the alpha desynchronization observed in our experiment could reflect cognitive processing of the cue, generating expectancy about pain intensity in CBP. In this line, studies suggest that attention, semantic memory, and action planning lead to alpha desynchronization (Klimesch, 1999; Uusberg et al., 2013), whereas alpha

synchronization accompanies voluntary top-down inhibition of motor responses (Hummel et al., 2002; cited in Uusberg et al., 2013). It has been argued that alpha synchrony might represent top-down control of sensory inputs, and it could reflect reduced attention to external stimuli and focus in internal expectations (Klimesch et al., 2007). Considering that, it can be argued that CBP reflected greater self-focusing in their own expectations previous noxious stimulation.

During noxious stimulation in the placebo condition during both conditioning and test phases, HC did not reveal any significant change in the studied bands, while processing medium and high stimuli intensities. Besides, alpha power was lower than for CBP along the conditions. Our results are in agreement with previous research. In this line, the most widespread finding assumes that under any painful stimulation, HC would display a decrease of alpha power (Bromm & Lorenz, 1998; Chen & Rappelsberger, 1994; Dowman et al., 2008, Huber et al., 2006), whereas chronic pain patients show increased frontal alpha power (Jensen et al., 2013). Indeed, it is argued that exists a positive correlation between the subjective pain intensity and alpha power (Nir et al., 2010). Results in healthy subjects, are also in agreement with the only found study assessing alpha band and placebo condition (Li et al, 2016), in which an alpha desynchronization during placebo analgesia were observed.

During noxious stimulation in the placebo condition of test phase, CBP show an enhanced alpha power over frontal locations while processing medium and high stimuli intensity. In fact, CBP patients seem to show different alpha power distribution and topography than HC, which is consistent with previous research (e.g., Jacobs et al., 2010). Some authors have explained the observed increase of frontal alpha power in patients with relation to drowsiness (Jensen et al., 2013). They argue that frontal locations may play a role in pain suppression, and enhanced frontal alpha would reflect less success in suppressing pain by top-down processes. Based in previous studies, it is possible to argue that in our study, frontal alpha enhancement in CBP could be reflecting a deficit in retrieving memories reflected in a lack of frontal activity during pain

processing. It could be argued that CBP patients are not able to recall memories of pain reduction (Jones et al., 2013). Thus, it may induce to a disruption in learning placebo responses, and hence an abnormal pain processing via disrupted top-down pain regulation.

In summary, our data are in agreement with previous studies where placebo conditioning, plus verbal suggestions and associative cues (in this case, hospital setting and creams formulation), may induce placebo analgesia responses. Furthermore, placebo manipulations affect brain processing in CBP patients by enhancing alpha power, leading patients to not achieve proper placebo analgesia response, demonstrating a lack of ability inhibiting ascending nociceptive inputs under certain conditions. These results have clinical implications due to the fact that every therapy have a placebo component, and is possible that these patients may not benefit of it, with the result of greater pain perception. To our knowledge, there is not another study addressing alpha power during placebo analgesia in CBP patients.

5. GENERAL DISCUSSION AND CONCLUSIONS

Both studies included in the present thesis were aimed to investigate neuroplasticity mechanisms involved in top-down modulation of chronic pain and how they could affect clinical treatments. The general hypothesis of this thesis is that chronic pain lead to neurobiological changes that affect clinical treatment outcomes, and they can be altered by learning and expectancy processes, as the biopsychosocial model of pain predicted, that will be reflected in EEG and behavioral abnormalities. For this purpose, two studies were conducted in clinical samples, FM and CBP, in which EEG recordings were analyzed. Results from both studies support the main hypothesis, as we will discuss below. The fist three objectives are fulfilled by the first study, and the following two by the second study.

The first objective of the present thesis was to assess the effectivity of LF-rTMS over rDLPFC in reducing depressive and pain symptoms in patients with a clinical history of MD and FMD patients. According to literature, negative emotions can be a predisposing factor to develop chronic pain (Lerman et al., 2015, Meints & Edwards, 2018), and indeed depression and chronic pain are shared in 80% of patients (Poole et al., 2009). This high comorbidity could be reflecting a shared pathophysiology, because oftentimes antidepressant drugs are prescribed to chronic pain patients, demonstrating analgesic effects (Kleiber et al., 2005). LF-rTMS over rDLPFC has been revealed as a probable useful therapeutic tool for depression management (Lefaucheur et al., 2020) and it even has been approved by the FDA for the treatment of resistant depression (Philips et al., 2018). Conversely, it did not show effectiveness for pain management (O'Conell et al., 2018), remaining unclear whether pain response is depending on negative emotions. The results of the first study indicate an overall subjective reduction in pain and depressive symptoms, in both treatment groups (placebo and real LF-rTMS). Therefore, our study failed to replicate a previous study in which was applied LF-rTMS over rDLPFC and authors found a reduction in depression and pain after treatment (Lee et al., 2012). However, our data is a sub-sample of the study from Carretero et al. (2009),

in which no differences were found between sham and real stimulation in depression and pain. In this line, a recent meta-analysis conducted to assess rTMS validity in pain treatment shown the inefficacy of LF-rTMS over DLPF for pain treatment (O'Connell et al., 2018). Taken all together, we can conclude that LF-rTMS over rDLPFC is not more effective than sham stimulation as comorbid pain and depression treatment.

The second objective was to explore neuroplasticity induced by LF-rTMS. It was observed that, despite of the behavioral improvements, brain dynamics do no reflect that change. Within the MD group, results of alpha asymmetry are in agreement with previous studies showing frontal asymmetry in depressive patients as a possible biomarker (Davidson, 1995; Henriques & Davidson, 1990, 1991; Roemer et al., 1992). Nevertheless, it changes slightly after the treatment, showing that rTMS somehow affected their neural plasticity. However, in our study we cannot explain if left frontal increase in alpha power could have been caused either by a decrease in right or increase in left hemisphere. In this line, depressed patients treated with placebo exhibit EEG changes in PFC particularly in the right hemisphere (Benedetti & Amanzio 2011). Therefore, it is possible that these changes observed in our study may be due to a decrease in right hemisphere. On the other hand, in the FMD group no changes were observed in alpha asymmetry post-treatment, showing a stable asymmetry pattern with more alpha activity over the right hemisphere reversed to the one showed by depressive patients. Although both group of patients share MD diagnosis, their brain dynamics are way different. Other possible explanation of the absence of asymmetry change in FMD relies on a study conducted by Goffaux et al. (2009), which demonstrate that FM patients treated with placebo show spinal hyperexcitability even if pain ratings were reduced, so its is possible that spine keep the brain tone stable through the procedure.

The third objective of this thesis was to better understand the induction of positive expectations during a clinical trial. In the first study, participants in a clinical trial were told that the treatment was performed to alleviate depression and pain, therefore both variables could have been affected by the positive expectation induction. Our results are

in accordance with previous studies, showing the implication of expectations in treatment outcomes. For instance, Jakovljevic' (2014) revealed that depressive patients have been proved to be highly responsive to placebo suggestions. Moreover, Goffaux et al. (2007) said the same regarding pain, stating that the endogenous pain inhibitory systems can be also modulated by expectations affecting active drug's efficacy. According to some authors, expectation of pain level represents up to 77% of the variance in post-treatment pain ratings (Vase & Wartolowska, 2019). Therefore, expectations could have mediated behavioral results, affecting rTMS treatment outcomes. In addition, according to some authors, nocebo responses, or lack of placebo responses, can be observed in clinical trials and practice as discontinuation of participation, need of higher dosis, and lack of treatment adherence (Colloca, 2019; Jakovljevic', 2014). In our study, thirteen subjects did not finish the clinical trial, possibly due to nocebo responses.

According to neuroimage studies, expectations for pain impairment frequently correlate with brain activation changes related with PA (Schafer et al., 2018). Even though specific areas involved in PA expectations are not yet identified (Schafer et al., 2018), a vast literature support the idea that areas related the most with PA expectations are prefrontal areas, such as ACC and PFC, and PAG (Bingel et al., 2006; Goffaux et al., 2007, 2009; Petrovic et al., 2010; Lorenz et al., 2005; Vase & Wartolowska, 2019), but also thalamus, insula, AMG and somatosensory cortex. Intriguingly, in our study we applied LF-rTMS, which inhibits cortical activity of the right DLPFC, therefore it would not be expected a placebo response due to the inhibition on the area, as occur in the Krummenacher et al. (2010) study, which found a PA reduction leaded by Lf-rTMS over DLPFC. In that study it was performed a conditioning paradigm (unlike ours, that we just induced positive expectations via verbal suggestions).Therefore, a possible explanation is that the applied neurostimulation technic did not affect the expectation pathway, as does with the conditioning one. According to the dual-process model of Schafer et al. (2018), PA would rely on two separate but connected processes: accumulative and dynamic. The first one would be related to conditioned responses, and the last one

would be in charge of the PA depending on expectations. Therefore, the divergence with the Krummenacher et al. study could be explained by these two different processes used to generate the PA response, supporting the dual-process model.

Deriving from the third objective, the forth objective was to know if there exist differences in PA response in experimental pain between healthy volunteers and CBP patients. Plenty of studies using chronic pain populations indicate that they are able to achieve a PA response (see Colloca, 2019). However, to our best knowledge, no other studies were conducted about differences with healthy subjects in their response. In addition, placebo seems to be modulating the efficacy and tolerability of analgesic treatments, and it may be also contributing to the lack of adherence to treatments among patients (Bingel, 2014; Jakovljevic', 2014), revealing a major clinical implication. Indeed, it is hypothesized that the ineffectiveness of treatments in chronic pain may be related to the lack of capabilities to activate proper learning mechanisms to readjust pain mechanisms altered in chronic pain (Ingvar, 2015). Our study revealed, in line with previous studies, that CBP achieve PA; nevertheless, their response, for highest administered pain, was reduced compared to healthy participants. Following the assumptions of the biopsychosocial model of pain, and according to literature, several factors could be explaining this effect, such as emotions, cognition, and biological differences.

Emotions can contribute to pain modulation, as we learnt in previous sections. In line with the first study, it was observed that chronic pain patients show more negative affects than healthy volunteers, that may have contributed to pain maintenance due to its rol of integration of sensory pain with other sensory system's information (Wagner et al., 2009). Though in the presented experiment it was not possible to assess if negative emotions were a consequence of chronic pain or an underlying factor, some studies point it to be a predisposing factor to develop and maintain chronic pain (Lerman et al., 2015, Meints & Edwards, 2018). Moving to PA field, Kosek et al. (2017) found that placebo responders show less depressive symptoms and catastrophizing thoughts than

not responders. Therefore, negative emotions observed in the CBP sample could also have interfered with the placebo response, thus collaborating to their pain maintenance.

Cognitive factors could have also mediate the abnormal PA response in CBP. Previous research indicates that placebo responses are mainly mediated by learning mechanisms and cognitive expectancy (Coleshill et al., 2018; Colloca, 2014). Patients have way more experience in medical situations than healthy subjects, and prior therapeutic experiences modulate PA response (Colloca, 2019; Vase & Wartolowska, 2019). Indeed, conditioning, observational, and instructional learning are supposed to combine generating as well positive or negative expectations, and conditioned responses (Colloca, 2014).

Among biological factors explaining results, we fulfill our fifth objective, that was to explore whether brain frequencies would be affected by chronic pain patients while processing PA. Neuroanatomical and neurofunctional abnormalities in chronic pain patients can contribute to the reduced PA response. For instance, some authors stated that pain intensity is maintained by sustained activation of PFC (Baliki et al., 2006, 2011), and patients display a significant atrophy in cortical gray matter in the DLPFC (Apkarian et al., 2004). Moreover, chronic pain patients exhibit aberrant activity in the brain frequency domains (Kisler et al., 2020). Chronic pain patients also show alterations in endogenous systems, such as the endocannabinoid and opioid systems. In that regard, growing evidence points to the endocannabinoid system as the biological substrate for affective and painful comorbidity, showing disrupted endocannabinoid signaling in both chronic pain and depressive patients, also pointing to a regulatory role on opioid transmission (Fitzgibbon et al., 2015; Huang et al., 2016). Regarding endocannabinoid system, patients show reduced serum levels of endocannabinoids, and genetic alterations in CB1 receptor and FAAH (Fitzgibbon et al., 2015).

In this line, in our study, HC did not show alpha power changes during the anticipation (or expectation) period, whereas CBP showed alpha power reduction in

frontal locations, and so an increase in frontal activity. As mentioned above, placebo expectations are associated with greater activity in left ACC, right precentral PFC, and left PAG (Vase & Wartolowska, 2019). One explanation of the results could be that the learning of the effectiveness of the placebo during the conditioning phase must be matched with the incoming input, and the mismatch activates PFC to retrieve memories and maintain the belief about the treatment (Watson et al., 2009), activating learned mental schemas involved in the dynamic process, as stated by the dual process model. That process might have an abnormal functioning in CBP patients, reducing the attention to external stimuli and focusing in their own expectations (Klimesch et al., 2007), that can be altered by previous learning. On the other hand, the alpha enhancement observed during pain processing in the placebo condition, in CBP unlike HC, could be reflecting a lack of top-down pain control. As it was previously mentioned, CBP patients present neuroanatomical and functional impairments that could explain the PA disfunction, due to the the relation of the impaired areas with top-down mechanisms of pain control (Apkarian et al., 2004; Baliki et al., 2004, 2006; Grachev et al., 2000). In this line, it has been proved that placebo responders have better cognitive performance in processing speed than non-responders, demonstrating the implication of frontal lobes in placebo (Benedetti & Amanzio, 2011). Indeed, a recent study conducted with patients with neurocognitive disorders revealed that PA is related functionally with executive functioning, and anatomically with the medial-PFC (in particular, the medial-cingulate cortex), concluding that the greater the atrophy, the lower placebo response (Palermo et al., 2019). Hence, the soft placebo response observed in CBP patients, in addition to frontal alpha enhancement during pain processing, could be interpreted as an impairment of frontal mechanisms involved in the placebo effect.

In a nutshell, the results of the present thesis are in accordance with a recent meta-analysis (O'Connell et al., 2018) and confirm that LF-rTMS over rDLPF is not an effective therapy for pain management. Furthermore, it may even interfere with endogenous pain control mechanisms (Krummenacher et al., 2010). Despite of subjective reduction in depressive symptoms and pain ratings after rTMS treatment,

brain asymmetry remains steady in FMD patients. Moreover, in the second study, brain frequencies of CBP depict abnormalities both in expectation and noxious stimulation processing, revealing differences in pain processing. Maybe, these abnormalities (i.e., stable and dysfunctional alpha asymmetry and different alpha power distribution in PA response) are leaded by neuroplasticity changes induced by chronic pain states, revealing alpha asymmetry as a plausible candidate as a biomarker for chronic pain. Therefore, we can assume that chronic pain leads to neurological changes that affect treatment outcomes. Moreover, expectations can interfere with clinical treatment outcomes. In fact, it was observed that the expectation-induced PA is not reversed by LF-rTMS, as occur when it is induced by conditioning, revealing a different pathway for both processes, supporting the dual-process model. Derived from our data, we can infer that expectations in chronic pain patients do not depend on areas located in rDLPFC, because the applied LF-rTMS was not able to inhibit its action. In the second study, it was also observed that chronic pain seem to lead to different expectation processing. According to the dual-process model, expectations are formed by a dynamic process in which new information is analyzed to be placed in the mental schema of that very situation, so it is possible that CBP patients, because of their greater medical experience, may require a bigger effort to set the new information in their situational schema, needing more frontal functioning implication than healthy people. Furthermore, it was revealed that despite of chronic pain patients can achieve PA, their response is lower than healthy controls. CBP patients show reduced PA response compared with healthy subjects, and it could be mediated by brain abnormalities. Brain frequencies may be manipulated with PA paradigms, but chronic pain patients show brain abnormalities, negative emotions, and cognitions, reflected in impairments of learning processes associated to pain control, that may be influencing the maintenance of pain and the ineffectiveness of therapies, interacting with the ongoing therapies, and either decreasing its efficacy.

5.1. Conclusions

1. LF-rTMS over rDLPFC is not an effective therapy for chronic pain management.

2. Expectations about the treatment outcomes may generate PA in a clinical trial, altering the results. Therefore, it is important to control for expectations in clinical trials by asking participants about them.

3. LF-rTMS over rDLPFC does not inhibit PA induced by expectations, generated via verbal suggestions.

4. Chronic pain patients respond to PA procedures, including or not conditioning, but their response is lower than healthy subjects.

5. Chronic pain patients show greater anxiety and depression scores, compared with healthy subjects, which could interfere in the PA response.

6. During PA processing, chronic pain patients show alpha desynchronization during anticipation, and alpha enhancement in frontal cortex during painful stimulation.

7. Chronic pain patients show neurobiological alterations derived from neuroplasticity mechanisms, which in turn affect PA response.

8. The biopsychosocial model seem a good model to explain PA, however the dual-model process is more accurate in describing underlying processes in PA.

5.2. Limitations

There exist some critics about how is induced the placebo condition in rTMS controlled studies, due to the fact that placing the coil at 45º is also giving some stimulation, and is capable to evoke potentials (Lisanby et al., 2001; Loo et al., 1999, 2000). This effect of the placebo condition could also be causing the lack of differences between both groups of patients (placebo vs real LF-rTMS). In the first study, age differences observed in placebo and treatment groups were not included in the analyses as covariable, neither the pre- treatment base line differences between FMD and MD. Furthermore, thirteen subjects did not finish the clinical trial, and therefore our sample was smaller than expected.

In none of the studies were asked the subjective expectation level of participants, and it could have be used as a controlling factor (Colloca, 2019). Interactions of emotions and treatment were not assessed in the second study. In the second study, frontal assessment in the participants (either anatomical or neuropsychological) would have also been useful to correlate placebo analgesia response with frontal function.

6. FUTURE DIRECTIONS

The results of the presented studies, and the observed limitations, aim to continue researching in pain control procedures for chronic pain patients resistant to pharmacological treatments. The field of research I am working in nowadays is cannabis, pain and quality of life, in which we are conducting two different studies in collaboration with the *Universitat de València* and the *Observatorio Europeo de Cultivo y Consumo de Cannabis*. Moreover, I was asked from the *Revista Española de Drogodependencias* to write an editorial paper about cannabis and pain (Annex II).

The dual-process model for PA states that expectations of relief are mediated by the opioid system (dynamic process), whereas conditioning is mediated by the endocannabinoid system (accumulative process), and they should be processed in different brain areas, but this is not yet clearly defined (Schafer et a., 2018; Coleshill et al., 2018). The presented studies show that despite of chronic pain patients show PA response, they are not leveraging the full benefits of top-down pain control. However, it is still unknown how this lack of effects are mediated.

Growing literature put forward the implication of the endocannabinoid system in chronic pain and negative affects, such as anxiety and depression (Boychuck et al., 2015; Hillard & Liu, 2014). Since the dual process model exposes that learning mechanisms mediating PA would be relaying on cannabinoid system, it is possible that the observed disfunction of the endocannabinoid system could interfere the accumulative process and mediate in the lack of top-down mechanisms of pain control observed in chronic pain patients, and until now this is also an unsolved question.

On the other side, molecular studies pointed to genetic differences related to endocannabinoid signaling in placebo responders and not responders (Peciña et al., 2013), exposing a down regulation of CB1 receptors as a possible cause of the reduced placebo responses (Peciña & Zubieta, 2015). Chronic pain patients show alterations in

CB1 and CB2 receptors and FAAH (Fitzgibbon et al., 2015). In addition, growing literature supports the idea of the role of the endocannabinoid system in depression/ anxiety and pain comorbidity. Therefore, there is a disruption of endocannabinoid signaling in chronic pain populations that would be affecting their emotions and the top-down regulation of pain control. Literature back that exogenous cannabinoids alleviate pain and depressive symptoms (Huang et al., 2016), so it is possible that cannabis acts over the neural circuits in charge of top-down regulation of pain and emotions. Threrefore, solving all these questions will have important clinical implications.

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ANNEX I

Table 1. List of conditions gathered in the axial system.

Axis I - Painful regions
Head, face and mouth Cervical region Upper shoulder and upper limbs Thoracic region Abdominal region Lower back, lumbar spine, sacrum and coccyx Lower limbs Pelvic region Anal, perineal, and genital region
Axis II - Systems involved in pain
Nervous system (central, peripheral, and autonomic) and special senses; physical disturbance or dysfunction. Nervous system (psychological and social). Respiratory and cardiovascular systems. Musculoskeletical system and connective tissue Cutaneous and subcutaneous and associated glands (breast, apocrine, etc.) Gastrointestinal system Genito-urinary system Other organs or viscera (e.g., thyroid, lymphatic, hemopoietic) Unknown
Axis III - Pain pattern
Single episode, limited duration Continuous or nearly continuous, nonfluctuating Continuous or nearly continuous, fluctuating severity Recurring irregularly Recurring regularly Paroxysmal Sustained with superimposed paroxysms
Axis IV - Subjective pain intensity
Mild Medium Severe
Axis V - Etiology of pain
Genetic or congenital disorders Trauma, operation, burns Infective, parasitic Inflammatory, immune reactions Neoplasm Toxic, metabolic, radiation Degenerative, mechanical Dysfunctional (including psychophysiological) Unknown Psychological origin

Table 2. General taxonomy of pain syndromes

Relatively generalized syndromes (e.g., peripheral neuropathy, phantom limb, central pain, fibromyalgia, etc.)
Relatively localized syndromes - head and neck
Neuralgias of the head and face Craniofacial pain of musculoskeletical origin Lesions of the ear, nose, and oral cavity Primary headache syndromes, vascular disorders, and cerebrospinal fluid syndromes Pain of psychological origin in the head, face, and neck Suboccipital and cervical musculoskeletical disorders Visceral pain in the neck
Spinal pain (spinal and radicular pain syndromes) cervical and thoracic
Cervical spinal or radicular pain syndromes Thoracic spinal or radicular pain syndromes
Local syndromes of the upper limbs and relatively generalized
Pain in the shoulder, arm, and hand Vascular disease of the limbs Collagen disease of the limbs Vasodilating functional disease of the limbs Arterial insufficiency in the limbs Pain of psychological origin in the lower limbs
Visceral and other syndromes of the trunk apart from spinal and radicular pain
Visceral and other chest pain Chest pain of psychological origin Chest pain referred from abdomen or gastrointestinal tract Abdominal pain of neurological origin Abdominal pain of visceral origin Abdominal pain syndromes of generalized diseases Abdominal pain of psychological origin Diseases of the bladder, uterus, ovaries, and adnexa Pain in the rectum, perineum, and external genitalia
Spinal pain (spinal and radicular pain syndromes) lumbar, sacral and coccygeal
Lumbar spinal or radicular pain syndromes Sacral spinal or radicular pain syndromes Coccygeal pain syndromes Diffuse or generalized spinal pain Low back pain of psychological origin with spinal referral
Local syndromes of the lower limbs
Local syndromes in the leg or foot: pain of neurological origin Pain syndromes of the hip and thigh of musculoskeletal origin Musculoskeletal syndromes of the leg

Note. Merskey & Bogduk, 1994

ANNEX II

Editorial

Cannabis y dolor ¿Podremos ver el bosque tras los árboles?

Cannabis and pain Will we be able to see the woods behind the trees?

Noemí Sánchez Nàcher

Universitat de les Illes Balears

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Palabras Clave

Cannabis medicinal; Manejo del dolor; Dolor crónico; Cannabis Sativa.

Key Words

Medical cannabis; Pain management; Chronic pain; Cannabis Sativa.

INTRODUCCIÓN

En los últimos años, la planta de *Cannabis Sativa L.*, sus derivados y componentes están generando mucha atención en diferentes ámbitos, en parte, derivada de su legalización para usos terapéuticos en al menos 30 países (como, por ejemplo, Canadá, Australia, Uruguay, Israel), así como en la mayoría de estados de Estados Unidos (33 estados, por el momento). Este hecho, ha incentivado a que la comunidad científica comience a mostrar mayor interés por las propiedades del cannabis, viéndose reflejado en el asombroso aumento de estudios relacionados, existiendo casi la misma producción científica en los últimos 10 años que en toda la historia previa. Curiosamente, este incremento de producción científica se ha generado pese a las dificultades existentes para investigar con cannabis, al encontrarse actualmente dentro de la Lista I de la Convención Única de 1961 sobre estupefacientes. Este estatus legal de la planta no permite, o dificulta en demasía, la experimentación, con lo que es muy difícil encontrar ensayos clínicos

– Correspondencia a:
Noemí Sáqnchez Nàcher
Email: n.s.nacher@gmail.com

controlados que evalúen su efectividad, aunque sí con algunos de sus cannabinoides, ya que no tienen el mismo estatus legal. De hecho, en nuestro país, la Agencia Española del Medicamento y Productos Sanitarios aprobó el medicamento *Sativex,* el cual contiene una combinación 1:1 de Dronabinol (THC1 sintético) y extracto de CBD2 de la planta de cannabis, con indicación aprobada para el tratamiento de la espasticidad en la esclerosis múltiple (aunque se receta de forma compasiva para otras indicaciones).

Pese a que los tratamientos cannábicos comienzan a introducirse en la farmacopea, la confusión y el estigma creados alrededor de esta planta están generando mucha controversia mediática, política y legal respecto a sus propiedades terapéuticas y, por ende, la posibilidad de su legalización o regulación (ni que decir tiene la mayor controversia en sus usos recreativos). Sin embargo, aparentemente existe poca o ninguna en los ámbitos científicos, o sociales en el uso medicinal y principalmente en caso concreto del manejo del dolor. Como ejemplos relevantes en el ámbito científico podemos encontrar los informes de la *National Academies of Sciences y el Comité de Expertos en Dependencia a Drogas*. En concreto, la *National Academies of Sciences* publica en su informe de 2017 que "existe evidencia sustancial" de que el cannabis es un tratamiento efectivo para el manejo del dolor crónico, entre otras patologías. Por otro lado, tras la 40ª reunión del Comité de Expertos en Dependencia a Drogas, celebrada en junio de 2018, se emitió una serie de recomendaciones para la Organización Mundial de la Salud, en las que concluye que el CBD no debería encontrarse en los tratados internacionales sobre drogas al no ser considerado como tal. Respecto a la planta, sus extractos, THC e isómeros consideran que existe suficiente evidencia como para realizar una revisión crítica sobre su estatus legal. Cambiando este estatus sería posible la realización de ensayos clínicos controlados sobre la efectividad de la planta, hecho que haría avanzar enormemente nuestro conocimiento sobre sus propiedades. Respecto al ámbito social, según la última encuesta del CIS de noviembre de 2018, el 84% de las personas encuestadas se decantaron a favor de *"la venta de marihuana en establecimientos y en determinadas condiciones"* para uso médico, con lo que la opinión pública parece estar bastante posicionada a favor del uso terapéutico de la planta.

DOLOR CRÓNICO Y CANNABIS

El dolor se puede definir como una percepción subjetiva resultante de la transducción, transmisión y modulación de la información sensorial filtrada a través de la propia genética e historia de aprendizaje, que además es modulado por el estado psicológico y emocional, así como el contexto sociocultural (Turk y Monarch, 2002). Asimismo, cuando el dolor se cronifica suele ir acompañado de depresión, ansiedad, insomnio y problemas sociales (van Hecke et al., 2013), los cuales agravan la situación de la persona que lo padece. El 17,25% de la población española padece algún tipo de dolor crónico, sin embargo, es interesante observar que las personas con dolor moderado tomen más medicación que aquellas con dolor severo y que el 51,22% de las personas con dolor crónico no tengan prescripciones de medicamentos para tratar el

dolor (*National Health and Wellness Survey* [*NHWS*], 2010). De los datos extraídos de esta encuesta se observa que pese a la alta prevalencia de población con dolor, no existe una adherencia a los tratamientos médicos al uso equivalente, y esta circunstancia se agrava en el caso de las personas con dolor severo. Observando una necesidad de búsqueda de nuevas estrategias para el manejo del dolor, ya que los datos muestran que las existentes no están funcionando para todas las personas.

En el estado español no existen datos publicados sobre el número de pacientes con dolor crónico que utilicen cannabis, dada su condición de ilegalidad, pero en otros países como, por ejemplo, Estados Unidos, sí podemos obtener una instantánea. De hecho, según estudios recientes, el dolor crónico es la patología por la que más recurren los estadounidenses al cannabis, representando el 67% del total de los pacientes con licencia (Boehnke et al., 2019; Kosiba et al., 2019). Aunque existen diferencias, dependiendo del estatus legal que tiene el cannabis en cada estado y las aplicaciones médicas que le han concedido, el dolor crónico y, en concreto, el dolor severo (Park y Wu, 2017), siempre se mantiene en primera posición en los requerimientos de licencias de cannabis medicinal. Asimismo, los autores no encuentran diferencias de género en las razones aludidas para utilizar cannabis.

Teniendo en consideración los datos epidemiológicos previamente presentados sobre adhesión a tratamientos en el estado español, aquellas personas con dolor severo a quienes los tratamientos convencionales no les han dado resultado, intentarán paliar su dolor de algún modo, y no es descabellado pensar que, del mismo modo que las personas estadounidenses, tienen la posibilidad de hacerlo mediante cannabis.

¿Es realmente efectivo el cannabis en el tratamiento y/o manejo del dolor crónico?

El sistema endocannabinoide es un sistema biológico complejo y ubicuo que posee múltiples funciones fisiológicas. Dicho sistema, se expresa prácticamente a lo largo de todo el organismo (por ejemplo, sistema nervioso, sistema digestivo, aparato reproductor, músculos, sistema inmune), teniendo una gran presencia en las vías nociceptivas. Se ha descubierto que el sistema endocannabinoide representa un importante sistema endógeno de control del dolor, el cual funciona paralelamente al sistema opioide, siendo ambos cruciales en la resolución de estados de dolor, así como de los aspectos afectivos y cognitivos del mismo (Woodharms et al., 2017). Este hecho ha propiciado que dicho sistema sea visto como una prometedora diana terapéutica, dada la presente crisis de opioides y la falta de herramientas para el manejo del dolor crónico severo.

La evidencia clínica, es decir, la experiencia subjetiva que informan las personas usuarias, sumado a la historia de la medicina, sugieren que existen numerosas propiedades terapéuticas en la planta, como es el caso del manejo del dolor. Sin embargo, los estudios de revisión y meta-análisis revelan una marcada disparidad en cuanto a la eficacia de los cannabinoides. En un reciente estudio de revisión de Campbell y colaboradoras (2019), se ponen de relieve diferentes limitaciones de los ensayos clínicos llevados a cabo con terapias cannábi-

cas, entre los que se encuentran la selección y tamaño de la muestra, y la limitada duración de los ensayos. Otra limitación observada en las revisiones es el hecho de mezclar y tratar como iguales diferentes terapias cannábicas como son el *cannabis medicinal* y las *medicinas basadas en cannabis* (Lynch et al., 2015). El primer término hace referencia al uso de la planta de cannabis, o extractos de la misma, mientras el segundo hace referencia a cannabinoides sintéticos o extractos depurados de algún cannabinoide específico, siendo por el momento THC y/o CBD los más utilizados. Este hecho de agrupar diferentes tipos de terapias cannábicas es un error, ya que la planta, además de los dos cannabinoides famosos, posee más de 400 compuestos (siendo más de 100 de ellos cannabinoides) los cuales interactúan entre sí modulando su acción fisiológica. Por esta causa, en principio, la planta completa debería tener diferente efecto que la extracción o síntesis de THC o CBD en solitario, debido a su mayor complejidad química. De hecho, se muestran importantes diferencias en la farmacocinética dependiendo de la fuente del cannabinoide, el perfil de cannabinoides e incluso las vías de administración (Campbell et al., 2019), con lo que si se mezclan todas estas variables no es posible obtener un resultado objetivo del efecto del tratamiento sobre el dolor crónico. Otra cuestión a tener en cuenta es la caracterización misma del dolor crónico, ya que pese a tener igual manifestación clínica, la fisiopatología de cada tipo es muy diferente; pero, a menudo, tanto para realizar ensayos como en las revisiones, se agrupan todas las tipologías en un doloroso cajón desastre. También la misma valoración del dolor puede conducir a resultados sesgados, ya que como se indica al inicio del apartado, el dolor crónico es multidimensional, así que no es realista únicamente medir la variación en la intensidad del dolor sino que se deberían incluir otros aspectos de tipo psicológico como la percepción de calidad de vida o bienestar. En esta línea, en un ensayo clínico no aleatorizado con cannabis medicinal, donde se analizó el efecto de la coadministración de cannabis en decocción junto con el tratamiento convencional, en un amplio abanico de pacientes con dolor crónico no oncológico (véase: fibromialgia, radiculopatía, dolor de cabeza, artritis reumatoide, dolor neurológico, otros síndromes con dolor crónico) se observó que el tratamiento redujo levemente la intensidad del dolor, sin embargo, mejoró significativamente el funcionamiento diario, así como permitió una reducción en los síntomas de ansiedad y depresión (Poli et al., 2018). Este último estudio pone de relieve que la intensidad de dolor puede permanecer casi invariable (como ocurre en otros ensayos clínicos controlados), sin embargo si se analizan otros parámetros relacionados con el dolor, como la calidad de vida y bienestar personal, se observa una mejora significativa. Sin embargo y pese a las limitaciones descritas, existe cierto consenso científico en la utilidad del cannabis para el manejo del dolor crónico, aunque no para todos los tipos (Romero-Sandoval et. al., 2017).

Según los ensayos clínicos y estudios de revisión consultados, los mayores efectos y con mayor evidencia científica en la reducción de la intensidad del dolor se encuentran en el dolor crónico de origen neuropático (Romero-Sandoval et. al., 2017; Müche et al., 2018; Poli et al., 2018; Urits et al., 2019a

y b). En particular, en un reciente análisis de *"datos de la vida real"*, muestra que las medicinas basadas en cannabis no sólo palian el dolor mediante la reducción de la intensidad misma del dolor, sino que parece apuntar hacia una mejora significativa en otros parámetros relacionados como mejora en las actividades de la vida diaria, sueño, estado anímico, bienestar, así como calidad de vida tanto física como psicológica. Estos resultados se mostraron más significativos en las personas con dolor neuropático en comparación a los grupos de dolor mixto o nociceptivo (Ueberall et al., 2019).

En relación al dolor musculoesquelético parecen no existir ensayos clínicos controlados, pese a ser una de las condiciones con mayor prevalencia en dolor crónico (Campbell et al., 2019). Respecto al dolor de tipo oncológico, los ensayos clínicos realizados con medicinas basadas en cannabis, especialmente nabiximoles (*Sativex*), muestran una efectividad cuestionable en la reducción de la intensidad del dolor (Romero-Sandoval, 2017; Häuser et al., 2019), aunque parece mejorar el sueño en estos pacientes (Urits et al., 2019b).

En el caso del dolor de tipo reumático, existen ensayos clínicos que muestran que los nabiximoles son efectivos en la reducción del dolor generado por artritis reumatoide (Urits et al., 2019b), mientras otros dicen lo contrario (Romero-Sandoval, 2017). Los estudios con fibromialgia muestran el mismo patrón de resultados también causado, en parte, por la escasez de ensayos clínicos controlados de alta calidad de evidencia (Fritzcharles et al., 2016). Sin embargo, en un reciente estudio observacional llevado a cabo con cannabis medicinal para el tratamiento de la fibromialgia, se observa una mejora significativa en los síntomas asociados a esta patología, así como en su calidad de vida (Sagy et al., 2019). En esta línea el profesor Ethan Russo (2001, 2016) presentó una *teoría de deficiencia clínica endocannabinoide* como base fisiológica de esta patología (así como otros síndromes resistentes a tratamiento como migraña y colon irritable), que ha sido citada ampliamente, aunque no ha sido estudiada en profundidad.

Pero siendo el cannabis una *"droga"*, ¿es seguro el uso de terapias cannábicas?

Opino que debemos intentar eliminar el estigma de *"droga"* creado durante décadas sobre esta planta el cual se está interponiendo en el completo desarrollo y conocimiento científico. De hecho, en el estudio antes citado de Poli y colaboradores (2018), se indica que hasta 38 pacientes no fueron incluidos en el estudio, ya que no quisieron tomar cannabis dado el estigma que acarrea, y otros 87 no pudieron conseguir su medicación, ya que no disponían de ella en la farmacia (por el estigma de los farmacéuticos). Estos hechos serían impensables en un ensayo clínico con cualquier otra sustancia.

Se plantean dos problemas principalmente respecto a las terapias cannábicas: el primero guarda relación con los efectos secundarios y el segundo con la posibilidad de usos problemáticos o adicción. Los ensayos clínicos realizados con medicinas basadas en cannabis consultados muestran efectos secundarios de tipo leve a moderado como mareo, sequedad de boca, confusión, cambios de humor y trastornos cognitivos, entre otros. Estos efectos suelen estar asociados a mayores concen-

traciones de THC y son más consistentes en personas que nunca han sido expuestas al cannabis en comparación con personas con experiencia previa (ver Campbell et al., 2019). Mientras en alguna revisión se llega a cuestionar si la mejora clínica puede ser superada por los daños potenciales (Mücke et al., 2018), en otros estudios y revisiones se muestran las terapias como seguras y tolerables, incluso en estudios longitudinales, además se alude a que los efectos beneficiosos superan los adversos (ver Poli et al., 2018, Ueberall et al., 2019; Urits, et al., 2019a y b). Pese a los efectos secundarios descritos, los fitocannabinoides nunca han sido relacionados con sobredosis o efectos fatales, tanto en uso terapéutico como recreativo, posiblemente a causa de que no existen receptores cannabinoides en el tronco cerebral (Maroon y Bost, 2018) y de que los preparados utilizados de forma medicinal suelen contener a su vez CBD el cual mitiga los efectos del THC. Respecto al segundo problema planteado, se ha observado, principalmente mediante encuestas, que las personas que utilizan cannabis de forma terapéutica en comparación a aquellas que lo utilizan de forma recreativa, son personas de mayor edad, muestran una mayor historia de uso, menores problemas relacionados con el uso del cannabis, no lo utilizan en mayores cantidades o frecuencia y muestran preferencia por variedades de cannabis ricas en CBD (como el *Cannabis indica*) (Cohen et al., 2016). Además, el patrón de consumo en estas personas se asemeja más a una pauta de medicación (Sznitman, 2017).

Un beneficio secundario aludido al uso de terapias cannábicas como analgésico, es el potencial para reducir la cantidad de opioides prescritos, principalmente dada la actual epidemia opioide existente, donde 142 personas mueren al día derivado del abuso de este analgésico (Nájera, 2017). Los estudios preclínicos, ecológicos y epidemiológicos sugieren la posibilidad de que las terapias cannábicas puedan reducir la cantidad de opioides o incluso sean un remplazo (Capmbell et al., 2019). De hecho, se ha llegado a observar una reducción del 47% en la toma de opioides, incluso el cese de la prescripción en el 40% de los pacientes con dolor crónico involucrados en un programa de cannabis medicinal (Vigil et al., 2017).

La información consultada apoya la posibilidad de utilización del cannabis como herramienta para el manejo del dolor, ya sea en mayor o menor medida, bien en su forma herbal como sintética, sin embargo, se necesita de más investigación para trazar los perfiles de eficacia para cada síndrome. Pero no podremos avanzar libremente en el conocimiento sobre esta planta y sus compuestos, si se sigue manteniendo su estatus legal, ya que existen muchas restricciones para la investigación con humanos. Asimismo se deben abolir los prejuicios y estigmas entorno a la planta, y las personas que la utilizan, para de ese modo eliminar barreras y que las personas sean totalmente libres a la hora de elegir su tratamiento.

*ABREVIATURAS:

1. THC: delta-9 tetrahidrocannabinol, fitocannabinoide reconocido con efectos psicoactivos y efectos medicinales.
2. CBD: cannabidiol, fitocannabinoide reconocido que no posee efectos psicoactivos, pero sí efectos medicinales.

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