NEUROFEEDBACK AS A TREATMENT TO REDUCE PAIN AND IMPROVE FUNCTION IN ADOLESCENTS WITH CHRONIC BACK PAIN

Rubén Roy Brusi

Neurofeedback as a treatment to reduce pain and improve function in adolescents with chronic back pain

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DOCTORAL THESIS

Supervised by Dr. Jordi Miró

Department of Psychology

UNIVERSITAT ROVIRA i VIRGILI

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This is to certify that:

The present dissertation: “Neurofeedback as a treatment to reduce pain and improve function in adolescents with chronic back pain”, presented by Rubén Roy Brusi, has been supervised by Jordi Miró, Professor at the Department of Psychology of the Universitat Rovira i Virgili, in fulfillment of the requirements for the degree of Doctor of Philosophy

April 27 2024, Tarragona,

Jordi Miró, PhD

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Undertaking a PhD reminds me of a phrase from Game of Thrones: “For the night is dark and full of terrors.” This quote barely scratches the surface of what PhD studies entail for most, and although it might seem like an exaggeration, for me, it has unquestionably been the most challenging experience of my life. This journey has been arduous, akin to Frodo’s quest to Mordor, yet it was made bearable by several pivotal individuals without whom I would not have reached Mount Doom.

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"Last but not least, I wanna thank me (do I?)

I wanna thank me for believing in me (laughter)

I wanna thank me for doing all this hard work (this yes)

I wanna thank me for having no days off (lie)

I wanna thank me for, for never quitting (several times)

I wanna thank me for always being a giver (not even close)

And tryna give more than I receive (I wish)

I wanna thank me for tryna do more right than wrong (close enough)

I wanna thank me for just being me at all times" (bleh)

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Abstract

Chronic back pain is a prevalent condition that can negatively impact on the wellbeing of adolescents. Previous studies have suggested the possibility that the already high prevalence of this condition might have been increasing over the last decades. Treatment recommendations for this population do not always provide adequate relief and stem from suboptimal-quality evidence. As the brain is one of the key components in the processing of pain, neurofeedback, an intervention that has been found useful to manage pain and pain-related outcomes in adults, might be an option to consider as a treatment for adolescents with chronic back pain. This thesis delves into this area of knowledge and includes three studies: (1) a secondary data analysis study to examine the trends in the prevalence of chronic back pain in adolescents (Study I), (2) a systematic review on the use of neurofeedback for managing chronic pain (Study II), and (3) a protocol study for a single-blind sham-controlled randomized pilot feasibility trial, designed to test the effects of two neurofeedback protocols as a treatment for adolescents with chronic back pain (Study III). The key conclusions that can be drawn from this dissertation are the following:

1. The prevalence of chronic back pain in adolescents has significantly increased over the last two decades, especially in older girls. In light of this, increased efforts in terms of prevention and treatment for this population are warranted.

2. Despite the fact that higher research quality is needed, neurofeedback has the potential to help decrease pain and improve function in individuals with chronic pain.

3. The results of the pilot feasibility trial will provide preliminary data on the effects of neurofeedback as a treatment for adolescents with chronic back pain, that if positive, might warrant a fully powered Randomized Controlled Trial and further research into the effects of neurofeedback for other pain problems in children and adolescents.

1. Introduction

The following pages are part of the work that I have been conducting over the past years in close collaboration with my colleagues in the ALGOS research group, nested at the Universitat Rovira i Virgili. This dissertation delves into the study of chronic back pain in adolescents and the use of neurofeedback as a potential treatment to manage pain and improve function in this population. The dissertation is divided in six sections. First, the introduction builds on both the concept of pain and chronic pain, with a particular focus on chronic back pain in adolescents, its impact, and the increase in the prevalence of chronic back pain in youths during the last decades. In this section, we also examine the brain alterations in individuals with chronic pain, the treatment options for adolescents with chronic back pain and, particularly, the potential of neurofeedback as a treatment for this population. Second, we describe the objectives of the three studies that we have carried out to advance in this area of knowledge. The aim of the first study was to examine the trends in the prevalence of chronic back pain over time in adolescents. The aim of the second study was to summarize the current state of knowledge regarding the use of neurofeedback as an intervention for pain management. The aim of the third study was to write a protocol study describing a single-blind sham-controlled randomized pilot trial to test the

feasibility, safety, acceptability and effects of two neurofeedback interventions on pain and pain related outcomes, in a sample of adolescents with chronic back pain. Third, we present an overview of the methods of each study. Fourth, the results of the dissertation are presented in the form of two studies already published and a third one that has been submitted for publication. Then, in the fifth section, we discuss the results, its implications, and consider future lines of research. Last but not least, the conclusions of this dissertation are presented, in the form of a summary of the key findings.

1.1 On the concept of pain and chronic pain

The International Association for the Study of Pain (IASP) defines pain as "*an unpleasant sensory and emotional experience associated with, or resembling that associated with actual or potential tissue damage*" (Raja et al., 2020).

In terms of duration, pain is usually dichotomized between acute or chronic. Acute pain is short in duration and a normal part of everyday life. Importantly, it has an adaptive function, as it serves the purpose of warning us that something in our body is not right, thus contributing to the maintenance of the integrity of the body (Miró, 2010; Woolf & Ma, 2007). Conversely, chronic pain (i.e., lasting 3 months or longer) does not have an

adaptive function and negatively affects the life of the individual in several ways (Turk et al., 2006; van den Berg-Emons et al., 2007). Chronic pain can be a symptom of a disease or a disease on its own (Ballantyne & Sullivan, 2022). Not only biological factors, but also psychological and social factors, contribute to the experience of pain (Barke et al., 2022). This multifactorial nature of chronic pain has been recently recognized in the IASP's new proposal of chronic pain for the 11th version of the International Classification of Diseases (Nicholas et al., 2019).

Chronic pain is a prevalent problem worldwide (Mills et al., 2019). In Spain, Dueñas and colleagues (2015) found that the prevalence of chronic pain in Spanish adults was 17%. However, chronic pain does not only affect adults, as it is also common in children and adolescents (Miró et al., 2023).

1.2 Chronic back pain in adolescents

Compared to other pain conditions, there is a dearth of evidence regarding the prevalence, the management, and the impact of chronic back pain in adolescents (Zernikow & Rathleff, 2022). Studies addressing these issues use different definitions of back pain (e.g., back pain, low back pain, chronic back pain, recurrent back pain) and/or include different chronic pain problems.

1.2.1 Prevalence of back pain and chronic back pain in adolescents

The prevalence of back pain and chronic back pain in children and adolescents is substantial (King et al., 2011; Miró et al., 2023). However, the exact prevalence is difficult to ascertain due to methodological differences in the studies conducted on this matter. The prevalence rates reported vary as a function of the definition of back pain or chronic back pain used, the sites of the pain evaluated (i.e., non-specific back pain or low back pain) the reporting period (i.e., point prevalence, monthly or more than monthly), the study population (e.g., age-related issues), and the study design (Stevens & Zempsky, 2021). Aiming to shed some light into this matter, Kamper and colleagues (2017) conducted an overview of 27 systematic reviews on the prevalence of back pain and chronic back pain in children and adolescents. This study found a monthly prevalence rate of back pain ranging from 18% to 24%, while the prevalence rates of chronic back pain ranged from 5% to 12%.

1.2.2 Impact

Back pain and chronic back pain can have a negative impact in adolescents on all function domains, including physical, psychological,

social and school-related. For example, adolescents with back pain report more visits to the doctor compared to adolescents with other pain problems (Roth-Isigkeit et al., 2005). Also, Lynch and colleagues (2006) found that children and adolescents with chronic back pain reported difficulties in the performance of daily activities, and missed an average of 2.5 days of school every month. Moreover, a recent study found that adolescents with chronic back pain have more sleep difficulties and psychological symptoms (i.e., feeling low, irritability or bad temper, feeling nervous) compared to adolescents without chronic back pain (Roman-Juan et al., 2023). Additionally, adolescents with recurrent back pain reported significantly higher odds of being bullied compared to adolescents without recurrent back pain (Madsen et al., 2023).

In addition, chronic pain in children and adolescents is associated with a high societal impact and economic burden (Groenewald & Palermo, 2015). On this issue, Espirito Santo and colleagues (2023) conducted a meta-analysis including 45 cost-of-illness studies with samples of children and adolescents with musculoskeletal complaints, and found that the annual economic burden ranged from 124$ to 69,351$.

1.2.3 The increase of adolescents with chronic back pain

King and colleagues (2011) suggested that the prevalence of pain in children and adolescents has been increasing over the last decades. In line with this idea, a couple of meta-analysis were conducted and found preliminary results suggesting that the increasing prevalence hypothesis could be true (Calvo-Muñoz et al., 2013; Potrebny et al., 2017). The first meta-analysis found that the most recent studies reported higher prevalence rates of low back pain in children and adolescents than the previous ones (Calvo-Muñoz et al., 2013). The second meta-analysis found a small increase in psychosomatic health complaints (i.e., including back pain) from 1980 to 2016 in adolescents aged 10 to 19 (Potrebny et al., 2017).

A couple of studies in Finland examined the trends over time in the prevalence of back pain among adolescents. The first one found an increase in the prevalence of low back pain from 1991 to 2001 in adolescents aged 12 to 18 (Hakala et al., 2002). However, a more recent study, found that the prevalence of low back pain in finesse adolescents aged 12 to 18 had not changed from 1991 to 2011 (Ståhl et al., 2014).

Therefore, additional research, with different samples is needed to determine whether there has been a significant increase in the prevalence of chronic back pain among adolescents.

1.3 Brain alterations in chronic pain

The brain plays a pivotal role in the onset and maintenance of pain (Chapin et al., 2012). The experience of pain is ultimately the result of an extensive cortical network that is commonly referred as the “pain matrix”, which involves several regions of the brain, including the primary somatosensory cortex, the secondary somatosensory cortex, the dorsolateral prefrontal cortex, the insula and the anterior cingulate areas (Tobimatsu, 2021). In other words, the experience of pain stems from how the brain deals with sensory input, rather than from the sensory input itself (Apkarian et al., 2011). Not surprisingly, studies have found differences in the brains of healthy individuals and those with chronic pain, not just in terms of structural and functional neurophysiological brain abnormalities (Apkarian et al., 2011; Davis & Moayedi, 2013; May, 2008), but also in the patterns of brain activity as measured by electroencephalography (EEG). The EEG is a method that records brain oscillations, which are rhythmic patterns of neural activity emerging from the synchronous activity of millions of cortical neurons in the brain (Nayak & Anilkumar, 2023). Typically, brain oscillations are classified into different bands as a function of their frequency: delta (0.5-4 Hz), theta (4-8 Hz), alpha (8-12 Hz), beta (12- 30 Hz) and gamma (30-100 Hz). Each frequency band underlies

specific neurophysiological processes and cognitive states (Diotaiuti et al., 2024), such as the experience of pain (Jensen et al., 2014).

Three systematic reviews have attempted to summarize the EEG alterations in individuals with different types of chronic pain. Two of these studies found increased theta and alpha power at rest in individuals with chronic pain (Mathew et al., 2024; Pinheiro et al., 2016), whereas the other found that individuals with chronic pain evidenced increased theta and beta power at rest (Zebhauser et al., 2023). It is important to note, however, that other studies have failed to find such features in the EEG of individuals with chronic pain (Schmidt et al., 2012; Ta Dinh et al., 2019), while others have found a different EEG pattern in individuals with chronic pain, such as an increase in beta and theta activity and a decrease in alpha activity (Jensen et al., 2009).

1.4 Treatments for adolescents with chronic back pain

As there is a paucity of high-quality research studies on the treatment of chronic pain in children and adolescents, the management of pain in pediatric population has often relied on treatment options designed for and studied in adult samples (World Health Organization, 2020).

Despite the advances in the management of chronic pain in children and adolescents, it could be argued that still, little is known about which treatment options work better for different pain conditions. There are three significant contributions in this area that are worth mentioning. First, a Cochrane review concluded that psychological therapies are efficacious to decrease pain intensity and pain frequency for children and adolescents with headache and mixed chronic pain conditions (Fisher et al., 2018). Second, and concerning medication, an overview of systematic reviews found that there is no high-quality evidence for delivering any pharmacological intervention to children or adolescents with chronic pain. This does not mean, however, that medication is not used in this population. As physicians cannot deny access to pain relief, it is actually common practice to use medication to manage pain in children and adolescents, often in the form of off-licence prescribing (Eccleston et al., 2019). Last but not least, a World Health Organization (WHO) systematic review and meta-analysis on the efficacy (and safety) of pharmacological, physical and psychological interventions to manage chronic pain in children was published recently (Fisher et al., 2022). In short, this review found that all three types of interventions may decrease pain intensity and/or frequency in different pain conditions, but underlined that it is psychological therapies, in particular Cognitive Behavioral Therapy (CBT),

the option with more robust evidence (Fisher et al., 2022). Despite these recommendations and the fact that there are treatment options available for this population, additional research is needed to provide children and adolescents with adequate pain relief.

In relation to back pain, a recent study produced an evidence-based guideline focusing on the treatment of non-specific back pain and chronic back pain in children and adolescents (Frosch et al., 2022). In this program, physical therapy (i.e., physical activity) and psychological therapy (i.e., CBT) were recommended to treat non-specific back pain in pediatric populations. For those with chronic non-specific back pain, when unimodal treatments were not effective, the guidelines recommended intensive interdisciplinary treatment programs.

In addition, this same study discouraged pharmacological interventions or invasive treatments and endorsed education and physical activity to prevent chronic back pain in children and adolescents. Noticeably, these aforementioned recommendations were based on suboptimal-quality evidence or indirect evidence (e.g., some recommendations were based on studies that included a wide range of chronic pain conditions). Therefore, additional high-quality research on treatments for children and adolescents with back pain and chronic back pain is warranted.

1.4.1 Neurofeedback as a potential treatment for adolescents with chronic back pain

Previously, we have mentioned that the brain is inextricably involved in the maintenance of pain, and that the brain of individuals with chronic pain is different from those of healthy individuals. However, the brain abnormalities that characterize individuals with chronic pain may be reversible (Flor, 2014; May, 2008). Therefore, a treatment option that targeted and aimed to modify brain activity directly, such as neurofeedback, might have the potential to influence pain experience and should be considered as a potentially viable option to help manage chronic pain (Jensen et al., 2014).

Neurofeedback is a type of biofeedback intervention that aims to change brain activity (Hammond, 2011). This non-invasive neuromodulatory treatment provides real-time information to the individual about her or his brain activity, facilitating the individual's ability to change it in ways that are associated with improved wellbeing. It consists of a brain-computer interface, including a method to acquire the brain activity, an amplifier to increase the signal and a computer that process this signal and returns it to the subject in the form of video, audio or their combination (Jensen et al., 2014).

The brain activity can be measured by EEG, functional Magnetic Resonance Imaging (fMRI) or both (Ciccarelli et al., 2003), although EEG-based neurofeedback is the method that has been used and studied the most (Marzbani et al., 2016). Among EEG-based neurofeedback, there are several types, that have been described in Study I. For the purpose of this dissertation, we will only focus on brain oscillation power-based neurofeedback.

As an intervention to help manage chronic pain, the aim of neurofeedback can be twofold: to reduce brain activity that is hypothesized to be associated with the processing of nociceptive information (i.e., beta oscillations in the 13 – 21 Hz frequency range) and/or to increase brain activity that is hypothesized to be associated with reduced pain processing and increased relaxation (i.e., alpha oscillations in the 8-12 Hz frequency range; Jensen et al., 2014). There are different training sites, that often include electrode placements in the frontal regions (F3, F4, FP1 and FP2 in the 10-20 system; Stokes & Lappin, 2010), the central site (Cz, C3 and C4 in the 10-20 system; (Jensen, Gertz, et al., 2013; Siniatchkin et al., 2000), or temporal locations (T3 and T4, in the 10-20 system; (Jensen, Sherlin, et al., 2013), although other electrode placements have been used (Jensen et al., 2007).

Several studies have evaluated the use of NF as a treatment for chronic pain in adults, and most have shown positive results in terms of pain reduction and improvements in pain-related outcomes (Farahani et al., 2014; Hasan et al., 2015; Jacobs & Jensen, 2015; Jensen, Gertz, et al., 2013; Jensen, Sherlin, et al., 2013; Kayıran et al., 2007, 2010; Kravitz et al., 2007; A. Mathew et al., 1987; Miltner et al., 1988; Prinsloo et al., 2018, 2019; Stokes & Lappin, 2010; Walker, 2011). Importantly, and to the best of our knowledge, only one study has evaluated the effects of neurofeedback as a treatment for children with chronic pain (Siniatchkin et al., 2000). This study examined the effects of 10 sessions of neurofeedback in a sample of 10 children with migraine without aura, and found a significant reduction in the number of days with migraine per month and the duration of migraine episodes but no improvements in the intensity of the migraine headaches, the use of headache medications or other migraine-related symptoms. Given the generally positive results, additional studies assessing the effects of neurofeedback as a treatment for chronic pain in youths is warranted.

Despite the preliminary support, neurofeedback has been questioned as to whether it can produce any therapeutic effect for pain or other health problems over and above placebo (Thibault et al., 2017). Thus, a summary of the current available evidence regarding the effects of

neurofeedback to manage pain is required to better understand the state of knowledge regarding this potentially promising pain intervention.

2. Objectives

This doctoral dissertation studies the situation of chronic back pain among adolescents and the potential use of neurofeedback as an intervention to help manage chronic back pain in this population.

2.1 Objective 1

To study the prevalence of chronic back pain in adolescents and examine its trend over time. For this aim, a secondary analysis of international data was conducted and is presented in Study I.

2.2 Objective 2

To learn about the current state of knowledge regarding the use of neurofeedback as a treatment for chronic pain. To do so, a systematic review was conducted and is presented in Study II.

2.3 Objective 3

To develop a study protocol of a neurofeedback intervention as a treatment for adolescents with chronic back pain. To achieve this aim, we developed a study protocol describing a single-blind sham-controlled randomized pilot trial to test the feasibility, safety, acceptability and effects

of two neurofeedback interventions on pain and pain-related outcomes, in a sample of adolescents with chronic back pain (Study III).

3. Methods

Three studies were conducted and are presented in this dissertation: a research article examining the trends in prevalence of chronic back pain using secondary data (Study I), a systematic review on the use of neurofeedback for pain management (Study II), and a study protocol for a neurofeedback intervention for adolescents with chronic back pain (Study III). As the methods are reported in full in each of the articles included in this dissertation (i.e., see the Results section), only a brief description of the methods is included here.

3.1 Procedure

In Study I, a secondary data analysis study was conducted. Data from four consecutive waves (2001/02, 2005/06, 2009/10 and 2013/14) of the Health Behavior among School-aged Children (HBSC) study was used. The HBSC study is a cross-sectional international study, promoted by an international alliance of researchers in collaboration with the WHO, and conducted in several countries and regions. Every four years, 11-, 13- and 15-year- old boys and girls are surveyed about health behaviors, health indicators and contextual variables. Noteworthy, the HBSC study provides

nationally representative samples of the participating countries warranting representation by sex, age and school type.

For Study II, a systematic review was conducted and reported following the Preferred Reporting Items for Systematic reviews and Meta-Analyses for protocols (PRISMA-P; Moher et al., 2015), and preregistered at the PROSPERO International Prospective Register of Systematic Reviews (https://www.crd.york.ac.uk/prospero/; registration number CRD42018115335).

In study III, a protocol study was drafted according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist (Chan et al., 2013). The protocol study describes a single-blind controlled randomized pilot feasibility trial.

3.2 Participants

In Study I, the final sample consisted of 650,841 adolescents from 33 countries. In regard to sex, 51% of the total sample were girls (n=334,130). The mean age of the adolescents was 11.6, 13.6 and 15.6 years for the 11-, 13- and 15-year groups.

For Study II, the systematic review, six databases were searched from inception through September 2019: PubMed, Ovid, Embase, Web of Science, PsycINFO and Scopus. The search strategy was based on a

combination of key terms concerning all pain conditions and types of neurofeedback. The full Pubmed Strategy can be found at https://www.crd.york.ac.uk/PROSPEROFILES/115335_STRATEGY_20181031.pdf. As a result, 24 studies were included in the review.

For Study III, the protocol study, as described, a total sample of 45 adolescents aged 11 to 18 with chronic back pain will be recruited, as deemed appropriate to achieve the aims of the pilot. Participants will be randomly assigned to receive one of the two active conditions (15 participants each group) or the sham intervention (i.e., control group; 15 participants).

3.3 Measures

In Study I, only a few of the available variables that the HBSC study covers were selected. Specifically, the survey year (i.e., 2001/02, 2005/06, 2009/10 and 2013/14), sex, age groups (11-, 13- and 15-year-olds), and the presence of chronic back pain. This last variable is derived from one of the items of the HBSC symptoms checklist. This item asks the participant how often she or he has experienced having back pain during the past 6 months, and the possible answers are: “About every day”, “More than once a week”, “About every week”, “About every month” and “Rarely or never”. The presence of chronic back pain was deemed positive for those

adolescents who reported having back pain weekly or more often for the past 6 months. The HBSC symptoms checklist has been found to provide reliable and valid measures of subjective health complaints (Haugland & Wold, 2001), and the dichotomization of this item has been succesfully used in previous studies using the HBSC data (Gobina et al., 2019).

For Study II, no measure was needed. However, the included studies are synthesized with respect to different characteristics: year of publication, condition (e.g., active group, active control group, waiting list), sample size, age of the participants (i.e., mean or range), sex, pain problem (e.g., migraine, fibromyalgia, multiple sclerosis), study design, neurofeedback type, type of neurofeedback protocol, number of sessions, length of the sessions, the inclusion of follow-up, pain change (i.e., pain intensity mean, number of pain episodes), and effects in brain activity (e.g., EEG, changes in BOLD activity).

For Study III, a selection of variables was selected to measure the feasibility, safety and acceptability of two neurofeedback protocols, as well as their effects on pain and pain related outcomes. In short, the study includes questions about demographic characteristics (i.e., sex, age, and school grade), variables measuring feasibility, safety and acceptability and variables assessing the study outcomes. The outcome measures are the following: pain intensity, pain frequency, the presence of chronic back

pain, pain-related interference, physical function (i.e., sleep disturbance, mobility, and fatigue), psychological function (i.e., anxiety, depression and cognitive function), and resting-state EEG.

For further details, a more detailed explanation can be found within the methods section of each article.

4. Results

The three articles included in this dissertation are provided in this section:

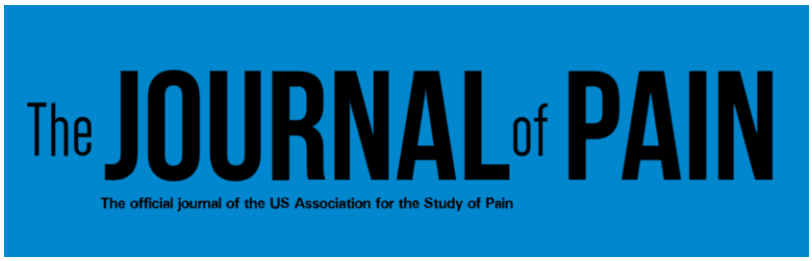
Study I. Roy, R., Galán, S., Sánchez-Rodríguez, E., Racine, M., Solé, E., Jensen, M. P., & Miró, J. (2022). Cross-national trends of chronic back pain in adolescents: results from the HBSC study, 2001-2014. *The Journal of Pain*, 23(1), 123-130. doi.org/10.1016/j.jpain.2021.07.002

Study II. Roy, R., de la Vega, R., Jensen, M. P., & Miró, J. (2020). Neurofeedback for pain management: A systematic review. *Frontiers in Neuroscience*, 14, 532534. doi.org/10.3389/fnins.2020.00671

Study III. Roy, R., Román-Juan, J., Jensen, M. P., & Miró, J. A neurofeedback-based intervention to reduce pain intensity and improve function in adolescents with chronic back pain: study protocol for a single-blind controlled randomized pilot feasibility trial. *Submitted to BJPsych Open.*

4.1 Study I

Cross-national trends of chronic back pain in adolescents: results from the HBSC study, 2001-2014.



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Cross-National Trends of Chronic Back Pain in Adolescents: Results From the HBSC Study, 2001-2014

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Abstract: **Chronic back pain is a common problem that negatively impacts the wellbeing of many adolescents. Prior research suggests that the prevalence of chronic back pain has increased over the last decades, but research on this issue is scarce, single country-based, and has yielded inconsistent results. This study aimed to examine trends in the prevalence of chronic back pain over time in adolescents aged 11, 13 and 15, using data from the Health Behavior in School-aged Children (HBSC) survey. We conducted a secondary analysis of data from 650,851 adolescents, retrieved from four waves (2001/02, 2005/06, 2009/10 and 2013/14) of HBSC data from 33 countries or regions. The prevalence of back pain was higher (1) in each successive survey over time (18.3% in 2001/02, 19.3% in 2005/06, 20.4% in 2009/10 and 21.6% in 2013/14), (2) in girls (21.9%) compared to boys (17.8%), and (3) in older adolescents compared to younger ones (14.5% in 11-year-olds, 19.6% in 13-year-olds and 25.5% in 15-year-olds). The increase in prevalence from 2001/02 to 2013/14 was more marked in older girls compared to younger girls, and in older boys compared to younger boys, and it ranged between 1% for 11-year-old boys and 7% for 15-year-old girls. More resources should be allocated to the prevention and treatment of chronic back pain in adolescents, especially for older girls.**

Perspective: ***The prevalence of chronic back pain in adolescents has increased from 2001-2002 to 2013-2014, especially in older adolescent girls. These findings underline the need of further research to understand the reason behind the increasing trend, and what programs are better suited to prevent chronic back pain among adolescents.***

Key words: *Chronic back pain, prevalence, adolescents, trends, multivariate model.*

Back pain is a common chronic pain problem in adolescents.[20,22] Moreover, back pain and chronic back pain in children and adolescents is associated with lower levels of well-being, higher medical care requirements and costs, and functional limitations.[1,12,13,28,33,35] A review of 27 systematic reviews on back pain in children and adolescents found that its monthly prevalence ranges from 18% to 24%. In most, but not all, of the reviews, the prevalence of back pain was higher for girls than boys, and increased with age.[23]

It has been suggested that there has been an increase in the prevalence of pain problems in young people over the last decades.[24] For example, a meta-analysis reported a slight increase of psychosomatic health complaints

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Conflict of interest statement

The authors declare no financial or other relationships that might lead to a conflict of interest related to this study.

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from 1980 to 2016, including back pain, in adolescents aged 10 to 19.[31] Also, a different meta-analysis on the prevalence of low back pain in children and adolescents found that the most recent studies reported higher prevalence rates than the oldest ones.[6] To our knowledge, only two studies, both conducted in Finland, have examined trends over time in the prevalence of back pain among adolescents. One of them found that the prevalence of low back pain in adolescents aged 12 to 18 had increased from 1991 to 2001, and that this increase in prevalence was similar for both sexes and all ages considered (i.e., there was not a significant interaction between sex or age and the survey year).[14] However, the second and most recent study found that the prevalence of low back pain in adolescents aged 12 to 18 remained stable from 1991 to 2011.[37]

As these studies reached contradictory conclusions and only considered the Finnish population of adolescents with low back pain, there is a need for additional studies looking at changes in the prevalence of chronic back pain in adolescents across time in other countries. Therefore, we sought to examine the prevalence of chronic back pain in adolescents aged 11, 13 and 15, using four waves of a large nationally representative survey conducted mainly in Europe and North America from 2001 to 2014. Based on previous research findings, we hypothesized that: (1) the overall prevalence rate of chronic back pain would show a linear trend of increasing prevalence over time; (2) girls would have a higher overall prevalence of chronic back pain compared to boys; and (3) older adolescents would have a higher overall prevalence of chronic back pain compared to younger adolescents. In addition, we explored the potential moderating effects of sex and age on the hypothesized time effect (i.e., change in global prevalence rate over time with each wave of the survey) on chronic back pain.

Methods

Design, Setting and Sample

This study uses data from the Health Behavior among School-aged Children (HBSC) study.[8] The HBSC study is a cross-sectional international study conducted in several countries or regions of Europe, North America and Israel by an international alliance of researchers in collaboration with the World Health Organization. Every 4 years, the HBSC study assesses health behaviors (e.g., smoking, exercising), health indicators (e.g., health problems, use of health services) and contextual variables (e.g., relationships with family and peers, school environment) in 3 different age groups and for both sexes, using self-reported measures administered in classrooms. The HBSC study provides nationally representative samples of 11-, 13- and 15-year-old boys and girls for each participating country, using a cluster sampling method (with the school classes as the primary sampling unit) and ensuring representation by sex, age and school type. The three age groups were selected to represent the "onset of adolescence, the challenge of physical and emotional changes, and the middle years when important life and career decisions are beginning to be made".32, p. 143 Further information regarding the HBSC study methods is available elsewhere.32

To address the aims of this study, secondary data from 801,648 adolescents were retrieved from 4 consecutive waves (2001/02, 2005/06, 2009/10 and 2013/14) of the HBSC study. Ethical consent was obtained and granted by researchers in each participating country.

Variables and Measures

Variables regarding time of assessment, sociodemographic information and data from the HBSC symptoms checklist (HBSC-SCL) were used. The information regarding time of assessment was the survey year (i.e., 2001/02, 2005/06, 2009/10 and 2013/14). Sociodemographic information included both sex (boys *vs.* girls) and age group (11-, 13-, and 15- year-olds). The presence of chronic back pain was extracted from one of the items of the HBSC-SCL, an 8-item symptom checklist which has been found to provide reliable and valid measures of subjective health complaints.[16] This item reads: "In the last six months, how often have you had backaches?" The possible responses are: "About every day", "More than once a week", "About every week", "About every month" and "Rarely or never". The presence of chronic back pain was deemed positive for those adolescents who reported having back pain weekly or more often for the past 6 months. This dichotomization has been previously used in articles also using items from the HBSC-SCL.[11,16]

Missing Data

Although the number of missing values was small (3%, n = 20,243), we examined the possibility that missing data might bias the results using multiple imputation, a procedure that replaces missing values by several predicted and simulated values. In particular, we used the multivariate imputation by chained equations procedure, as it allows to specify models for different types of variables. A logistic model was used to replace missing data regarding the presence of chronic pain, and an ordered logistic model to impute missing age data. A total of 20 imputed datasets were created and analyzed with a multiple logistic regression containing the same variables used in the complete case analysis. We then planned to compare the findings from these analyses. If the results differed significantly, we planned to provide the multiple imputation model results. If not, we planned to provide the complete case results.

Data Analyses

In order to perform the planned analyses, we first eliminated data belonging to participants from countries that did not provide data for each of the four survey years (i.e., Albania, Armenia, Bulgaria, Iceland, Luxembourg, Malta, Republic of Moldova, Romania, Slovakia, Turkey and the United States of America). We then created two different datasets: one without any missing data for complete case analysis and another for the multiple imputation analyses.

For the complete case analysis, we removed data from those respondents who did not provide answers to all the study variables. For the multiple imputation analysis, we imputed data for those participants with missing information. For descriptive purposes, we first computed the number and percentages for categorical variables and means and standard deviations for continuous variables for the sample as a whole. To test the study hypotheses, we conducted two three-stage hierarchical multiple logistic regression with the presence of chronic back pain as the criterion variable, one with the complete case analysis data and another one with the imputed data. The results of these analyses were used to ascertain which subgroups should be considered in order to report accurate estimates of the prevalence of chronic back pain (i.e., either by year of survey, by sex, by age groups, by year of survey and sex, by year and survey and age group, by sex and age group, or by year of survey, sex, and age group altogether). To test the study hypotheses, we entered variables reflecting time, sex, and age as a block in step 1. All these predictors were entered dummy coded (i.e., being surveyed in 2001/02, being female and being 11 years old as the reference categories, respectively). A significant time effect at this step, with an associated increase in the prevalence of chronic back pain over time, would support hypothesis 1. In the same way, a significant sex or age effect at this step, with girls reporting a higher rate of chronic back pain than boys or higher rates in older participants than younger participants, would support hypothesis 2 and 3, respectively. We then entered interaction terms in steps 2 and 3; the Time X Sex, Time X Age and Sex X Age (two-way) interactions terms in step 2 and the Time X Sex X Age (three-way) interaction term in step 3. If any of these interactions emerged as significant, we planned to compute stratum-specific estimates of the prevalence of chronic back pain by the significant effect modifiers. For example, if the three-way interaction was significant, we planned to compute and examine the prevalence rates (%) at each time point separately for boys and girls in each of the three age groups. If the three-way interaction was not significant, we planned to follow up any significant two-way interaction effects by examining the prevalence rates for boys and girls in each of the three age groups (if a significant sex moderating effect on age was identified), the prevalence at each time point separately (1) for boys and girls (if a significant sex moderating effect on time was identified) and (2) for each of the three age groups (if an age moderating effect on time was identified). The adequacy of the final regression model was evaluated using the Hosmer-Lemeshow goodness-of-fit test. Statistical significance was set at $P < .05$. The statistical analyses were conducted using STATA 14 (Stata Corp., Texas, USA). The command *svyset* and survey weights were used to account for the complex sampling method.

Results

Participant Characteristics

We first removed data belonging to participants from the 11 countries that did not participate in the four waves that are the focus of the current study (n = 130,564) and from those respondents who had not provided answers to all the study variables (n = 20,243). The final sample for the complete case analysis consisted of 650,841 adolescents from 33 countries or regions. The mean age of participants was 13.6 years (SE = 0.002; Range = 9.8 − 17.3). The mean age of respondents was 11.6, 13.6 and 15.6 years for the 11-, 13- and 15-year groups, respectively. The two sexes, the three age groups and the four survey waves had a similar sample size (please see Table 1). The final sample for the multiple imputation analyses consisted of 671,084 adolescents.

Regression Analyses

To test the hypotheses of our study, we performed two multiple logistic regression analyses with chronic back pain as the criterion variable, one using the complete case data and the second using imputed data. Step 1, representing the main effects, step 2, representing the two-way interactions, and step 3, representing the three-way interaction between predictors, were all significant. The results using the multiple imputation data were similar to those using the complete case analysis data (please see Supplementary Table 1). We therefore present the results from the complete case analysis here (see Table 2). The Hosmer-Lemeshow goodness of fit statistic was $\hat{C} = 0.01$ (df = 8, p = 0.999), indicating that there was a good fit for the final model including the three-way interaction.

All three study hypotheses were supported, given that time, sex, and age were significantly associated with the presence of chronic back pain in step 1. That is, the global prevalence was higher (1) in each following year of survey (18.3% in 2001/02, 19.3% in 2005/06, 20.4% in 2009/10 and 21.6% in 2013/14), (2) in girls (21.9%) compared to boys (17.8%), and (3) in older adolescents compared to younger ones (14.5% in 11-year-olds, 19.6% in 13-year-olds and 25.5% in 15-year-olds).

Regarding the interactions, two out of the three two-way interactions (Time X Age and Sex X Age) and the three-way interaction (Time X Sex X Age) emerged as statistically significant. The significant Time X Sex X Age interaction indicates that the rate of increase in the prevalence of chronic back pain from 2001/02 to 2013/14 was moderated by both the sex and age of the adolescent. Table 3 displays the prevalence rates at each time point separately for boys and girls in each of the three age groups, as well as the changes in the prevalence of chronic back pain from 2001/02 to 2013/14 for each considered stratum. As can be seen, all subgroups considered showed an increase in the prevalence of chronic back pain from 2001/02 to 2013/14, which ranged between 1% for 11-year-old boys and 7% for 15-year-old girls. There was an increase of 3% in the global prevalence of chronic back pain in the 12-year period of study considered.

For further details, Table 4 displays the odds ratios (OR) for chronic back pain in 2013/14 compared to the reference year 2001/02, for boys and girls in each of the three age groups. The odds of having chronic back pain in 2013/14 compared to 2001/02 were all significant,

Table 1. Weighted Numbers and Percentages of Participants by Study Variables

		Number	
Variable	Categories	n	%
Sex	Girls	334,130	51%
	Boys	316,711	49%
Age	11-year-olds	210,953	32%
	13-year-olds	222,471	34%
	15-year-olds	217,417	33%
Year of survey	2001/02	151,538	23%
	2005/06	163,154	25%
	2009/10	167,639	26%
	2013/14	168,510	26%
Country or region of residence	Austria	17,332	3%
	Belgium (Flemish)	18,866	3%
	Belgium (French)	18,100	3%
	Canada	37,965	6%
	Croatia	20,791	3%
	Czech Republic	19,001	3%
	Denmark	17,841	3%
	England	18,947	3%
	Estonia	16,599	3%
	Finland	22,857	4%
	France	26,603	4%
	Germany	23,460	4%
	Greece	16,327	3%
	Greenland	3,926	1%
	Hungary	15,992	2%
	Ireland	16,148	2%
	Israel	19,078	3%
	Italy	16,969	3%
	Latvia	17,083	3%
	Lithuania	22,042	3%
	Macedonia	16,849	3%
	Netherlands	16,994	3%
	Norway	16,976	3%
	Poland	20,368	3%
	Portugal	15,507	2%
	Russia	25,337	4%
	Scotland	22,768	4%
	Slovenia	19,340	3%
	Spain	29,475	5%
	Sweden	22,062	3%
	Switzerland	21,867	3%
	Ukraine	18,965	3%
	Wales	18,406	3%

and higher in girls compared to boys and in older adolescents compared to younger ones.

Discussion

Chronic back pain is a common health problem which has been found to negatively impact the lives of those with this condition, including adolescents.[23,29,40,41] In addition, prior research suggests the possibility that the prevalence of chronic back pain might have been increasing among adolescents over the past few decades.[14,24] The findings from the current study not only confirmed this observation across many countries, but also identified higher prevalence ratings in (1) girls compared to boys, and (2) older adolescents compared to younger adolescents. We also found that the increase in prevalence over time was significantly higher in older girls compared to younger girls, and in older boys and compared with younger boys.

To date, only two studies have examined trends in the prevalence of back pain among adolescents over time. These studies, which focused on the evolution in the prevalence of low back pain among Finish adolescents, reported conflicting results. Hakala and colleagues[14] found an increase from 1991 to 2001, whereas Ståhl and colleagues[37] found that the prevalence of low back pain had not changed significantly over a period of time twice as long, specifically from 1991 to 2011. Our results are consistent with the former study, as we found an

Table 2. Multiple Logistic Regression Analyses: Significance of Steps, Interactions and Overall Model

Variables	*Wald* F	*df*	*p*
Step 1	10192.894	6	<.001
Sex	8.64	1	<.01
Age Group	844.30	2	<.001
Survey year	21.35	3	<.001
Step 2	301.56	11	<.001
Time X Sex	1.77	3	.621
Time X Age	100.40	6	<.001
Sex X Age	7.94	2	.019
Step 3	16.56	6	.011
Time X Sex X Age	16.56	6	.011
Overall model	10734.30	23	<.001

Table 3. Trends in 6-Months Prevalence of Chronic Back Pain (2001/02-2013/14)

	2001/02	*2005/06*	*2009/10*	*2013/14*	
Subgroup					*Change*
11-year-olds					
Girls	14.6	15.1	15.7	16.1	Up 1.5%
Boys	13.0	13.5	13.9	13.8	Up 0.8%
13-year-olds					
Girls	20.0	20.7	21.4	24.4	Up 4.4%
Boys	16.8	17.3	17.8	18.1	Up 1.3%
15-year-olds					
Girls	24.9	26.8	29.5	32.2	Up 7.3%
Boys	20.9	21.5	23.0	23.7	Up 2.8%
Total	18.3	19.3	20.4	21.6	Up 3.3%

NOTE. Change computed considering the 2001/02 and 2013/14 waves.

increasing trend in the prevalence of chronic back pain among adolescents from 2001 to 2014. One potential reason for the conflicting results is the different periods of time considered by the three studies. Another possible explanation for the different results might be differences in the study participants; our analyses used a sample that was representative of the adolescent population of a total of 33 countries and regions of Europe, North America and Israel, whereas the other two studies were conducted only with Finish adolescents.

Table 4. Odds Ratios for Chronic Back Pain in 2013/14 Relative to 2001/02

Subgroup		*p-Value*
11-year-olds		
Girls	1.10 (1.05-1.16)	<.001
Boys	1.07 (1.01-1.12)	0.014
13-year-olds		
Girls	1.29 (1.24-1.34)	<.001
Boys	1.10 (1.05-1.15)	<.001
15-year-olds		
Girls	1.44 (1.38-1.49)	<.001
Boys	1.19 (1.14-1.24)	<.001

Abbreviations: CI, confidence interval; OR, odds ratio.

Although a few national studies have failed to find sex differences in the prevalence rates of back pain among adolescents,[21,26,30,38] most national studies (e.g.,[24,43,44,46]) have found higher prevalence rates in girls compared to boys, and a review of systematic reviews of back pain prevalence concluded that these prevalence rate differences are reliable.[23] Our findings are consistent with this latter body of research, as we found that chronic back pain was significantly more prevalent in girls compared to boys. Also consistent with the findings from previous research,[26,30,38,42,43] we found that older adolescents had a higher overall prevalence of chronic back pain compared to younger adolescents.

To date, and to the best of our knowledge, only one study has tested the moderating effects of sex and age on the increase of prevalence of back pain over time. Hakala and colleagues,[13] who examined data from a sample of Finish adolescents, did not find a significant moderating effect of sex or age on the increase in the prevalence of back pain. However, we not only found that sex and age separately moderated the increase in

the prevalence of chronic back pain, but also that the effect of time on the prevalence varied as a function of both sex and age. That is, the rate of increase was not only higher in girls compared to boys, and in older adolescents compared to younger ones, but also in older girls compared to younger girls, and in older boys compared to younger boys.

These findings have important financial and clinical implications. There is a consensus that chronic pain conditions in children and adolescents result in a significant economic burden to society.[12,19,36] If our findings are replicated in future studies, and if the prevalence continues to increase over time, we could anticipate that the economic burden associated with chronic back pain in adolescents will only worsen. Also, if the current findings regarding the role of sex on prevalence rates are replicated in future studies, this would suggest that older female adolescents are particularly at risk for developing chronic back pain. This would support the need for research to understand the reasons for this effect (e.g., the role of biological, psychological, and social factors), the findings from which could inform the development of interventions that could reduce the risk of chronic pain development in adolescents in general, and perhaps in girls in particular. Moreover, if this finding is confirmed in other studies, this would support the need for providing greater resources to this segment of the population.

In addition, a number of studies have found that having back pain or low back pain during mid-adolescence significantly increases the odds of having low back pain later on, either in later adolescence[34] or in adulthood.[5,15,18,22] Thus, an increased incidence of this problem in adolescents might translate in more individuals having or developing chronic pain during adulthood. And chronic back pain in adults is already one of the most serious global public health problems.[45]

Considering all the factors discussed above, it stands to reason that some preventive efforts and early interventions for those adolescents who have back pain need to be implemented. Landry and colleagues[27] discuss some potential treatment and preventive measures for adolescents with low back pain, based on physical activity, physical therapy exercise, and postural education and hygiene. Also, preventive interventions could be implemented in earlier ages, when the back pain problem is less likely to have evolved into a chronic disabling condition. Along these lines, an educational intervention aiming to improve eight-year-old's knowledge on the prevention and management of low back pain proved successful.[25] Adopting and implementing these and similar measures could potentially reduce the risk that back pain will become chronic and, to some extent, decrease the number of cases of adolescents whose chronic back pain will persist into adulthood.

To date, we have no clear data-driven explanations for the increase in the prevalence of chronic back pain in adolescents, let alone why this increase has been more marked for older female adolescents. A possible explanation for such an increase might be related with the increase in the incidence of the risk factors for back pain. Despite mixed evidence and some inconsistencies in the research around this topic (e.g, screen time, low physical activity, obesity, etc.), Kamper and colleagues found that psychological distress, smoking, low socioeconomic status, and taller height increase the risk of back pain in children and adolescents.[23] Another review on potential risk factors for back pain in children and young adults added later pubertal status, positive family history of back pain, increased growth spurt and a history of back pain to the list of potential risk factors.[2] For example, the rates of mental health problems among children and adolescents have increased in the last decades.[7,10] Further studies should investigate whether this higher incidence in psychological problems or a higher incidence of any of the other risk factors might account for the increase in the prevalence of chronic back pain over time. Another potential explanation might be related to society's increased emphasis on academic success, which translates into increased school pressure. This might also explain why the increase in the prevalence of chronic back pain has been higher in girls, as school stress is higher in girls compared to boys.[20] Further research on these issues is warranted.

This study has a number of important limitations. First, as the HBSC study is conducted mostly in countries from Europe, the extent to which the findings generalize to other countries outside of Europe is not known. Second, the definition and measurement of pain in the survey/s was based solely on the presence (or not) of back pain; the findings do not speak to the relative magnitude or severity of pain, or pain interference, in the study sample.[21] Future surveys should include measures of pain severity and interference if possible, to determine the rate and extent of disabling chronic pain.[17,39] Third, the HBSC study did not measure gender in addition to sex. This precluded our ability to evaluate gender as a factor that might moderate the presence of chronic back pain. Future studies would benefit from the inclusion of a measure of gender, in addition to the measure of sex, as the role that gender plays in the presence of chronic back pain remains to be thoroughly explored,[4] especially in children and adolescents.[3] Fourth, the regression model did not include other covariates that might have been associated with the presence of chronic back pain, such as the socioeconomic status. Finally, and due to the surveying method, students who were absent on the day when the surveying process took place were not accounted for. This could have biased the findings, as adolescents with health problems are more likely to be absent from school.[9]

Despite the study's limitations, to our knowledge this is the first study to report the increase in prevalence of chronic back pain over time in adolescents with data from different countries and regions. Future studies are needed to determine if the increasing trend in the prevalence of chronic back pain continues in future waves of the HBSC study (or in other studies with separate assessment periods over time), as well as to identify the possible reasons for the changes in rates of pain over time and also, the reasons that rates are moderated by both age and sex. Additional research is also needed to study

what programs are more suited to prevent chronic back pain among adolescents and whether the results are also dependent on the age and sex of the adolescents. Finally, as an accurate understanding of the trend in adolescent's incidence of chronic back pain is critical for determining population health priorities, future studies should assess if this increasing pattern also occurs with other chronic pain problems.

Perspective

The prevalence of chronic back pain in adolescents has increased from 2001/02 to 2013/14, especially in older adolescent girls. These findings underline the need of further research to understand the reason behind the increasing trend, and what programs are better suited to prevent chronic back pain among adolescents.

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Supplementary data

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4.2 Study II

Neurofeedback for pain management: A systematic review.

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SYSTEMATIC REVIEW
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Neurofeedback for Pain Management: A Systematic Review

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Background: Chronic pain is a significant global health issue. For most individuals with chronic pain, biomedical treatments do not provide adequate relief. Given the evidence that neurophysiological abnormalities are associated with pain, it is reasonable to consider treatments that target these factors, such as neurofeedback (NF). The primary objectives of this review were to summarize the current state of knowledge regarding: (1) the different types of NF and NF protocols that have been evaluated for pain management; (2) the evidence supporting each NF type and protocol; (3) if targeted brain activity changes occur with NF training; and (4) if such brain activity change is associated with improvements on treatment outcomes.

Methods: Inclusion criteria were intentionally broad to encompass every empirical study using NF in relation to pain. We considered all kinds of NF, including both electroencephalogram- (EEG-) and functional magnetic resonance imagining- (fMRI-) based. We searched the following databases from inception through September 2019: Pubmed, Ovid, Embase, Web of Science, PsycINFO. The search strategy consisted of a combination of key terms referring to all NF types and pain conditions (e.g., neurofeedback, rt-fMRI-NF, BOLD, pain, migraine).

Results: A total of 6,552 citations were retrieved; 24 of these that were included in the review. Most of the studies were of moderate quality, included a control condition and but did not include a follow-up. They focused on studying pain intensity (83%), pain frequency, and other variables (fatigue, sleep, depression) in samples of adults (n = 7–71) with headaches, fibromyalgia and other pain conditions. Most studies (79%) used EEG-based NF. A wide variety of NF types and protocols have been used for pain management aiming to either increase, decrease or regulate brain activity in certain areas theoretically associated with pain.

Conclusions: Given the generally positive results in the studies reviewed, the findings indicate that NF procedures have the potential for reducing pain and improving other related outcomes in individuals with chronic pain. However, the current evidence does not provide definitive conclusions or allow for reliable recommendations on which protocols or methods of administration may be the most effective. These findings support the need for continued – but higher quality – research in this area.

Keywords: systematic review, neurofeedback, neuromodulation, pain management, treatment outcome

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INTRODUCTION

Rationale

Chronic pain is a major global health issue (Goldberg and Mcgee, 2011), affecting about one in four adults (Schopflocher et al., 2011; van Hecke et al., 2013; Nahin, 2015) and a similar number of youths (Huguet and Miró, 2008; King et al., 2011). Chronic pain has a number of negative physical, psychological and social consequences in the life for those with this condition (Institute of Medicine (U.S) Committee on a National Agenda for the Prevention of Disabilities, 1991; Bair et al., 2003; Finan et al., 2013; De Ruddere and Craig, 2016). The costs of chronic pain to society are enormous, and include both direct (e.g., medical expenses) as well as indirect costs [e.g., expenses associated with work absenteeism, hiring somebody to take care of the patients, or travel costs to receive treatment (Gaskin and Richard, 2012; Groenewald et al., 2014)]. For most individuals with chronic pain, the available treatments do not provide adequate relief and are generally unable to prevent new episodes (Williams et al., 2012).

The brain, an organ influenced by biological, psychological, and social factors, plays a central role in the onset and maintenance of pain (Chapin et al., 2012). For example, a growing body of evidence indicates that there are structural and functional neurophysiological brain abnormalities in individuals with chronic pain (May, 2008; Apkarian et al., 2011; Davis and Moayedi, 2013). Likewise, individuals with chronic pain evidence patterns of brain activity (as measured by electroencephalography; EEG) that differ from those without chronic pain (Pinheiro et al., 2016). It is possible that some of these brain abnormalities may be reversible with treatment (May, 2008; Flor, 2014). Thus, it would be reasonable to consider treatments that target brain activity directly as viable interventions for reducing the severity and impact of chronic pain.

Neurofeedback (NF) is a non-invasive treatment that targets brain activity. It is a type of biofeedback that provides real-time information to patients about their brain activity, allowing them to learn how to directly change this activity in ways that may lead to improved health and comfort. NF can be performed either by using brain activity measured via EEG or functional Magnetic Resonance Imaging (fMRI). The EEG approach is used much more often, because EEG biofeedback technology is more accessible and less expensive. With EEG-based NF, one or more electrodes are placed on the patient's scalp to measure the amplitude (also referred to as "power") of oscillatory activity in different frequency bandwidths. The raw electrical signal represents the collective activity of millions of neurons in the cortex, just below the electrode. This signal is analyzed and aspects of that electrical brain activity are fed back to the patient (Jensen et al., 2014). Normally, EEG-based NF targets a change in the power of activity in specific oscillation bandwidths whereas fMRI-based NF targets changes in the blood oxygen-level dependent (BOLD) activity in regions of interest in the brain (Sulzer et al., 2013; Thibault et al., 2018).

Whether NF is conducted with EEG or fMRI, measured changes in brain activity are fed back to the patient. Often, but not always, the feedback is provided via a game. For example, a program might allow the patient to "fly" a plane when he or she makes a change in the targeted brain activity (e.g., an increase in alpha power as measured over the sensory cortex). The plane will fly smoothly as long as the targeted brain activity is in the direction of the training criteria established by the therapist, whereas the plane might drop or otherwise malfunction if the brain activity falls outside of the training range. This feedback influences and progressively helps the patient learn to change brain activity via operant conditioning (Heinrich et al., 2007; Sherlin et al., 2011). It is important to note that although operant conditioning is the principle underlying the most common NF treatments, there are some types of NF that operate via different principles (Sherlin et al., 2011). Also, changes in brain activity often take a relatively long time to occur with NF treatment; a full course of NF treatment is normally comprised of 15–50 sessions of 20–40 min each (Heinrich et al., 2007; Hammond, 2011).

In the context of pain treatment, NF aims to change brain activity that is thought to underlie or influence the experience of pain (Ibric and Dragomirescu, 2009). The findings from a number of research studies provide preliminary support for the efficacy of NF for reducing pain in clinical samples (Jensen et al., 2014; Miró et al., 2016). However, some investigators have questioned whether NF has any beneficial effect for pain or other problems over and above placebo or outcome expectancy effects (Thibault et al., 2017). Thus, a critical summary of the available evidence regarding the efficacy of NF interventions targeting pain as an outcome is needed in order to better understand the current state of knowledge regarding this potentially promising pain intervention.

Objectives

Given the considerations discussed above, the primary objectives of this review were to summarize the current state of knowledge regarding (1) the efficacy of NF for reducing pain and (2) the effects of NF on pain-related brain activity in individuals experiencing pain.

Research Questions

Specifically, we aimed to: (1) describe the different types of NF and NF protocols, and how NF has been used for pain management; (2) summarize the evidence regarding the efficacy of each type of NF and different NF protocols for modulating pain and for improving pain-related outcomes; (3) determine the level of evidence regarding the effect of NF training on measures of brain activity thought to be related to pain, and if changes in measures of this brain activity are associated with improvements in pain-related outcomes; and (4) asses the quality of the studies included in the review.

METHODS

Study Design

The current systematic review was conducted and reported following the Preferred Reporting Items for Systematic reviews and Meta-Analyses for Protocols 2015 (PRISMA-P 2015) guidelines (Moher, 2015) and was preregistered at the PROSPERO International Prospective Register of

Systematic Reviews (https://www.crd.york.ac.uk/prospero/; with registration number CRD42018115335).

Participants, Interventions, Comparators

We included studies using samples of children or adults, either healthy or with clinical pain conditions, where neurofeedback was used to influence pain outcomes. The inclusion criteria were intentionally broad in order to include in the review every empirical study using NF to treat pain. All types of studies were included, regardless of sample size or study design. We also considered all kinds of NF, both EEG- and fMRI-based NF, and included studies combining the use of NF with other interventions or using NF to enhance the efficacy of other pain treatments. We also aimed to include studies on all types of pain, including chronic pain, acute pain, and laboratory (induced) pain. Any study that assessed at least pain intensity or pain frequency was included. The only exclusion criterion was if a given paper under consideration was written in a language other than Spanish or English.

We considered studies that included the assessment of pre- to post- treatment changes in pain intensity and/or pain frequency, as measured using questionnaires or rating scales with support for their reliability and validity (Jensen and Karoly, 2001). When available, we also examined the extent to which any changes noted after NF training did or did not maintain at follow-up.

When assessed, we noted the effects of NF on pain-related outcomes, including fatigue, sleep problems/sleep quality, psychological function (anxiety or depression), perceived health-related quality of life and pain-related interference or disability. We also considered pre- to post-treatment changes in measures of brain activity; that is, pre- to post-treatment changes in the power of different brain oscillation bandwidths or pre- to post-treatment changes in BOLD activity. When possible, we also examined if any pre- to post-treatment improvements in these outcomes maintained at follow-up.

Search Strategy

We searched the following databases from inception through September 2019: PubMed, Ovid, Embase, Web of Science, PsycINFO and Scopus. The search strategy consisted of a combination of key terms referring to all neurofeedback types and pain conditions (e.g., neurofeedback, rt-fMRI-NF, pain, migraine, fibromyalgia). To see the full Pubmed strategy please see https://www.crd.york.ac.uk/PROSPEROFILES/115335_STRATEGY_20181031.pdf. We also searched the reference lists of all articles reviewed in order to identify any additional studies to include. In addition, we performed a search of ClinicalTrials.gov to identify ongoing or completed studies with unpublished results and asked the corresponding authors to allow us to include their results in the review. Finally, we attempted to contact the authors of any papers included in the review that did not provide all the data needed for our synthesis to request these data.

Data Sources, Studies Sections, and Data Extraction

Two of the authors (RR and RdlV) independently assessed the eligibility of the articles retrieved after the database search for inclusion in the review. If any disagreement emerged, they were resolved in consultation with a third author (JM). Next, a deduplication process was conducted via a reference manager (Mendeley). Once a final list of selected articles was identified, their reference lists were reviewed to identify additional studies that could be of interest.

We extracted the following study characteristics from each article identified for inclusion: article title, author(s), publication year, country, sample characteristics (sample size, age, sex, education level, household income, pain problem), intervention protocols (i.e., scalp positions and bandwidths targeted for EEG-based NF, brain regions being targeted in fMRI-based NF, number, duration and frequency of sessions), primary study outcomes (i.e., pain intensity, pain frequency), and secondary outcomes (i.e., fatigue, sleep quality, psychological function [anxiety, depression], perceived health-related quality of life and pain-related disability). If available, we extracted EEG or BOLD activity in whichever way it was reported.

When more than one measure was used to assess the same construct, we planned to inform about the one that is reported most often in the literature as the primary outcome for that study. If data from the same study were reported in different papers, we only retrieved the data from the paper that was published first, unless there was a subsequent study that added additional participants or provided additional data.

Data Analysis

Given the paucity of research on the topic, as evidenced by preliminary searches as well as the disparity of methods and outcomes reported, we anticipated that a meta-analytical approach would not be feasible. As this was confirmed after the search, here we present a systematic narrative synthesis summarizing the characteristics and findings of the studies included in the review. We included all studies identified irrespective of their risk of bias. In addition, we organized the narrative synthesis by study design, starting with those with stronger designs and continuing from there to the studies using lower-quality designs. We describe separately EEG-based NF (and its subtypes) and fMRI-based NF. We report on the outcomes (clinical and neurophysiological) as a function of the type of NF (EEG- or fMRI-based) and protocol used. We also summarize the different uses of NF in pain management. Next, we summarize NF's effects on pain intensity and pain frequency, as well as on measures of the pain-related variables mentioned above. We also note whether the studies provided EEG- or fMRI-assessed physiological data, and if they reported changes in measures of physiological activity following NF. If so, we assessed whether these changes in brain activity were associated with changes in the brain activity targeted by the intervention. If presented by the study authors, we also report on the extent to which changes in measured brain activity change were associated with observed improvements in treatment outcomes.

In addition, we rated and describe study quality using the Quality Assessment Tool for Quantitative Studies from the Effective Public Health Practice Project [EPHPP; (Thomas et al., 2004)], as this tool allows for a comparison of study quality between studies using different designs. The EPHPP tool consists of six quality components to be rated as "strong" (coded as "1") "moderate" (coded as "2"), or "weak" (coded as "3"): selection bias, study design, confounders, blinding, data collection methods, and withdrawals and drop-outs. We did not compute a final score for each study as relevant methodological aspects of the studies appear to be better assessed individually (Jüni et al., 1999). Again, two authors (RR and RdlV) conducted this evaluation independently. In the event of any disagreements, these were resolved in consultation with a third author (JM).

RESULTS

Study Selection and Characteristics

Our initial search retrieved 6,552 citations. After eliminating duplicates, 3,560 articles were assessed based on their title and abstract. A total of 3,513 articles were excluded because they did not meet the inclusion criteria and 47 were read in full. A total of 11 authors were contacted for additional data. However, only one of these responded to us, and this author did not provide the additional data needed. One completed project that could be potentially eligible was found in ClinicalTrials.gov. We contacted the corresponding author for that project but did not receive an answer. The final number of studies included in the review was 24. See **Figure 1** for a flow diagram of the article selection process.

The vast majority of the studies we identified for inclusion in this review were conducted in the last decade. A plurality of the studies ($k = 12$, 50%) were conducted in the United States, four (17%) were conducted in Germany, and the rest were conducted in six other countries. The quality of the study designs was rated as "moderate" for the most part. Two studies (9%) were case series, 19 (79%) were non-randomized trials, and only three (13%) were randomized controlled trials (RCTs). The sample sizes in the studies that were not case series ranged from $n = 7$–71. Only seven (29%) studies included follow-up assessments. Most of the studies (19, 79%) included only adults, four (17%) included both adults and youths, and one (4%) used a pediatric sample only. The pain type most frequently studied was headache (including migraines; $k = 5$, 21%). The rest of the studies evaluated the effects of NF in individuals with a variety of pain conditions: fibromyalgia (two studies), spinal cord injury (SCI) and chronic pain (three studies), a variety of chronic pain problems (two studies), pain associated with radiation therapy for cancer (one study), chemotherapy-induced peripheral neuropathy (CIPN; one study), postherpetic neuralgia (one study), Complex Regional Pain Syndrome Type I (CRPS-I; one study), and chronic paraplegia (one study). Two studies (8%) used NF to enhance hypnotic analgesia in individuals with multiple sclerosis. Also, a total of four studies (17%) assessed the effects of NF on laboratory (induced) pain in healthy individuals.

In addition to pain intensity ($k = 20$, 83%) and pain frequency ($k = 4$, 17%), the studies assessed a number of other pain-related outcomes such as: fatigue ($k = 6$, 25%), sleep quality/problems ($k = 3$, 13%), anxiety ($k = 2$, 8%), depression ($k = 2$, 8%), and pain-related interference ($k = 4$, 17%). Seventeen (71%) of the studies assessed changes in brain activity after the intervention. Of these, 11 (46%) performed analyses to determine if pre- to post-treatment changes in measures of brain activity were associated with pre- to post-treatment changes in one or more study outcomes.

Regarding the NF type, most studies ($k = 19$; 79%) used EEG-based NF; five ($k = 5$, 21%) used fMRI-based NF. Among the studies that were conducted with EEG, 15 (63%) used brain oscillation power-based NF, two (8%) used surface and/or low-resolution electromagnetic tomography (LORETA) Z-score NF, and two (8%) used event related potentials (ERPs) NF. A total of 21 studies (88%) used NF as a single intervention, one (4%) used it in addition to other interventions and two (8%) used it to enhance the effects of another intervention.

A variety of control conditions were used in the controlled studies: one study (4%) tested NF provided to a clinical sample against the same NF intervention provided to a control sample of healthy individuals and a waitlist-control condition, one (4%) used an active control condition and a waitlist-control condition, two (8%) used a waitlist-control condition, one (4%) used a sham condition, four studies (17%) used an active control condition, one (4%) used three active control conditions and a sham condition, and one (4%) used four sham control groups and one active control condition.

Participants in the studies reviewed received between one to 98 sessions. For those who received more than one session, frequency ranged from once a week to daily, and duration ranged from 16–120 min. See **Tables 1**, **2** for details about the interventions and participants in the studies reviewed.

Synthesized Findings

Description of the Different NF Types and NF Protocols

A variety of NF types and protocols have been used for pain management. Most of them attempted to decrease brain activity hypothesized to be associated with the processing of nociceptive information (Siniatchkin et al., 2000; Emmert et al., 2014) and/or increase brain activity hypothesized to be inconsistent with pain information processing (Mathew et al., 1987; Jensen et al., 2014). Others aimed to normalize brain activity, relative to available normative data on brain activity (Koberda et al., 2013; Prinsloo et al., 2019). Here, we briefly describe the main characteristics of each type of NF used before discussing their effects on treatment outcomes.

We identified five different types of NF: four EEG-based and one fMRI-based. EEG-based NF asses and aim to modify the power of brain oscillation activity in different bandwidths from electrodes placed on the scalp. Brain oscillations are traditionally grouped in different bandwidths, expressed in cycles per second (Hz). The traditional bandwidths most often used for bandwidth classification, from slower to more rapid are: delta (δ, 0.5–4 Hz), theta (θ, 4–8 Hz), alpha (α, 8–13 Hz), beta (β, 13–30 Hz), and gamma (γ, 30+ Hz). Other bandwidths that are sometimes used in NF studies are most often subclassifications of these primary ones, such as low β (12–15 Hz) and high β (21-30 Hz) (Marzbani

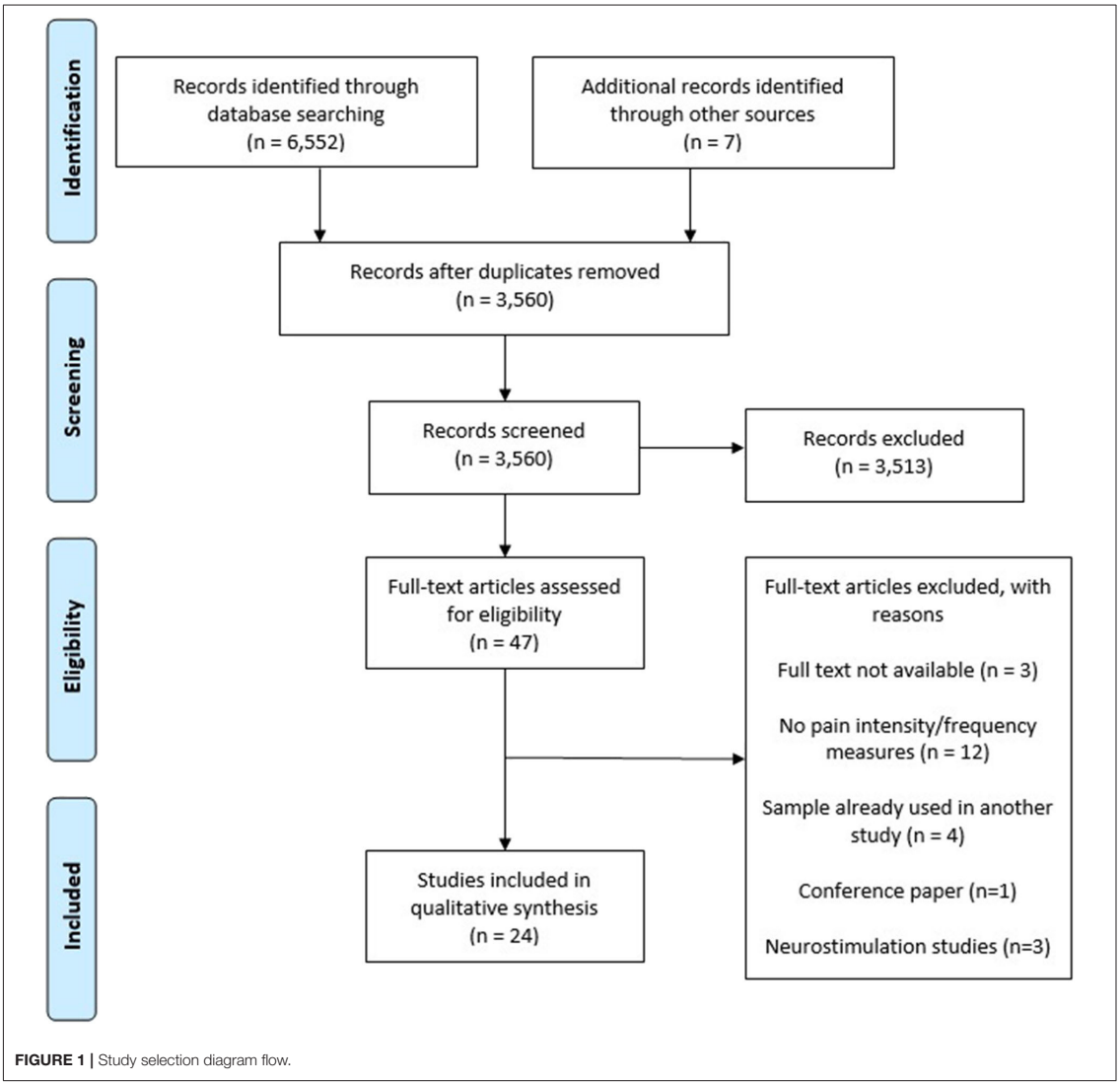

FIGURE 1 | Study selection diagram flow.

et al., 2016). Another common bandwidth used in NF studies is called "sensorimotor rhythm" (SMR) frequency (12–15 Hz). The SMR bandwidth is the same frequency as low β, but is a common frequency found in the sensorimotor areas of the cortex (Hoedlmoser et al., 2008).

Brain oscillation power-based NF

This type of NF that has been used most frequently in research in this area (Krigbaum and Wigton, 2014). This approach aims to increase or decrease the power of specific oscillation bandwidths as assessed from electrodes placed on different parts of the scalp. There is a large variety of protocols that have been used when treating patients with this procedure; in fact, we were unable to identify any studies that used the same NF protocol. That said, many of the protocols were quite similar. The protocols are often named based on the frequencies they seek to alter (e.g., an "alpha protocol" would be one seeking to alter – often increase – α power). This approach normally involves three electrodes: one for the active training site, one for the reference site, and one for ground. Some protocols using this approach are theory-based; that is, they intend to alter a frequency theorized to be associated with a behavioral outcome [e.g., increased α is associated with increased relaxation; (Hammond, 2011)]. Other protocols are data-based; that is, based on an initial

TABLE 1 | Description of participant characteristics.

Authors (year)	Condition	Sample size	Age M (SD or Range)	Sex (% female)	Sample condition
Caro and Winter (2011)	E: NF	15	66.7 (12.3)	93	Fibromyalgia
	C: TAU	63	50.5 (13.9)	79	
DeCharms et al. (2005)	E: NF or biofeedback	12	36.7 (31–38)	33	Chronic pain
	C: Healthy control group	36	23.5 (18–37)	44	Healthy sample
Emmert et al. (2014)	E: NF (lAIC)	14	27.6 (2.1)	50	Healthy sample
	E: NF (ACC)	14	27.4 (2.6)	50	
Farahani et al. (2014)	E: NF	15	37.6 (7.5)	47	Headache
	E: TENS	15	40.7 (10.1)	40	
	C: WL	15	37.3 (9.4)	47	
Guan et al. (2015)	E: NF	8	58.5 (2.4)	37	Postherpetic neuralgia
	C: Sham NF	6	61.3 (3.4)	50	
Hasan et al. (2015)	E: NF	7	50 (4)	14	Central neuropathic pain and chronic paraplegia
Jacobs and Jensen (2015)	E: NF	4	NR (14–56)	50	Variety of chronic pain problems
Jensen et al. (2018)	E: NF + Hypnosis	12	57.5 (10.6)	75	Multiple sclerosis with either chronic pain, fatigue or both
	E: Mindfulness + Hypnosis	10			
	C: Hypnosis	10			
Jensen et al. (2013a)	E: NF	10	46.1 (12.6)	30	Spinal cord injury and chronic pain
Jensen et al. (2016)	E: NF + Hypnosis	10	49.2 (11.26)	63	Multiple sclerosis and chronic pain
	E: Relaxation + Hypnosis	9			
Jensen et al. (2007)	E: NF	18	40.8 (17–56)	89	CRPS-I
Jensen et al. (2013b)*	E: NF	30	49.2 (22–77)	27	Spinal cord injury and chronic pain
	E: tDCS	28			
	E: Hypnosis	29			
	E: Concentration meditation	30			
	C: Sham tDCS	30			
Kayiran et al. (2010)	E: NF	18	31.8 (6.2)	100	Fibromyalgia
	C: Escitalopram	18	32.4 (6.7)	100	
Koberda et al. (2013)	E: NF	4	NR (46–59)	50	Variety of chronic pain problems
Mathew et al. (1987)	E: NF	8	NR (18–40)	NR	Tension headache
	C: WL	4			
Miltner et al. (1988)	E: NF	10	NR (21–46)	0	Healthy sample
Prinsloo et al. (2019)	E: NF	14	56 (35–76)	21	Patients with head and neck cancer undergoing radiation therapy
Prinsloo et al. (2018)	E: NF	35	62 (9.6)	89	Chemotherapy-induced peripheral neuropathy
	C: WL	36	63 (11)	86	
Rance et al. (2014a)	E: NF	10	27.8 (4.7)	60	Healthy sample
Rance et al. (2014b)	E: NF	10	29 (6.4)	40	Healthy sample
Siniatchkin et al. (2000)	E: NF	10	10.5 (1.5)	20	Migraine
	C: Healthy control group	10	9.9 (0.6)	30	Healthy sample
	C: WL	10	11.6 (2.6)	20	Migraine
Stokes and Lappin (2010)	E: NF	37	NR (9–79)	78	Migraine
Vučković et al. (2019)	E: NF	15	50.6 (14.1)	20	Central neuropathic pain and chronic spinal cord injury
Walker (2011)	E: NF	46	NR (17–62)	NR	Migraine

*NR, not reported; E, Experimental; C, Control; NF, neurofeedback; TAU, Treatment as usual; WL, Wait-list control group; TENS, Transcutaneous electrical nerve stimulation; CRPS-I, Complex regional pain syndrome type I; TBI, Traumatic brain injury; CIPN, Chemotherapy-induced peripheral neuropathy. lAIC, Left anterior insular cortex; ACC, Anterior cingulate cortex; tDCS, transcranial Direct Current Stimulation. *In this study the same participants received up to a single session of all four active procedures and the sham control procedure.*

TABLE 2 | Description of study and intervention characteristics.

Authors (year)	Country	Study design	NF type	Monotherapy (Yes / No)	Number of sessions	Length of sessions (minutes)	Follow-up
Caro and Winter (2011)	USA	Cohort analytic	Frequency NF	Y	Varied $M = 58$ range (40–98)	NR	None
DeCharms et al. (2005)	USA	Cohort analytic	rt-fMRI NF	Y	1	13 to 39	None
Emmert et al. (2014)	Switzerland	Cohort	rt-fMRI NF	Y	1	16	None
Farahani et al. (2014)	Iran	RCT	Frequency NF	Y	15	30	None
Guan et al. (2015)	China	Cohort analytic	rt-fMRI NF	Y	1	NR	None
Hasan et al. (2015)	UK	Cohort	Frequency NF	Y	Varied range (2–40)	45	1 month
Jacobs and Jensen (2015)	USA	Case series	Frequency NF	Y	Varied range (22–41)	30	None
Jensen et al. (2018)	USA	Cohort analytic	Frequency NF	N	6	30	1 month
Jensen et al. (2013a)	USA	Cohort	Frequency NF	Y	12	NR	Varied (3 months)
Jensen et al. (2016)	USA	Cohort analytic	Frequency NF	N	4	30	1 month
Jensen et al. (2007)	USA	Cohort	Frequency NF	N	1	30	None
Jensen et al. (2013b)	USA	Cohort analytic	Frequency NF	Y	1	20	None
Kayiran et al. (2010)	Turkey	RCT	Frequency NF	Y	20	30	None
Koberda et al. (2013)	USA	Case series	Surface Z-score and LORETA NF	Y	Varied range (10–65)	30	None
Mathew et al. (1987)	India	Cohort analytic	Frequency NF	Y	20	30	None
Miltner et al. (1988)	Germany	Cohort	ERP-based NF	Y	1	120	None
Prinsloo et al. (2019)	USA	Cohort	Z-score LORETA NF	Y	Varied range (1–6)	20	None
Prinsloo et al. (2018)	USA	RCT	Frequency NF	Y	20	45	1 month 4 months
Rance et al. (2014a)	Germany	Cohort	rt-fMRI NF	Y	4	40	None
Rance et al. (2014b)	Germany	Cohort	rt-fMRI NF	Y	4	40	None
Siniatchkin et al. (2000)	Germany	Cohort analytic	ERP-based NF	Y	10	72	None
Stokes and Lappin (2010)	USA	Cohort	Frequency NF	N	Varied $M = 40$ (30 NF + 10 pir-HEG)	30	Varied (3–24 months)
Vučković et al. (2019)	UK	Cohort	Frequency NF	Y	Varied $M = 14$ range (3–48)	25 to 30	None
Walker (2011)	USA	Cohort analytic	Frequency NF	Y	Varied M = 24 range (12–32)	30	None

NR, not reported; NF, neurofeedback; RCT, randomized controlled trial; fMRI, functional magnetic resonance imaging; ERP, event related potential; LORETA, low-resolution electromagnetic tomography.

quantitative electroencephalogram (qEEG) assessment of the patient that is then used to select the electrode positions and bandwidths to be targeted. Using the data-based approach, the participant is first administered a qEEG assessment to evaluate his or her unique EEG pattern, relative to a normative database. "Excesses" (power at bandwidths that are substantially greater than normative values) or "deficits" (power at bandwidths that are substantially lower than normative values) for any bandwidth activity at specific electrode sites are then identified, relative to healthy individuals. Once this assessment is conducted, an individualized treatment protocol is then designed to target any EEG "abnormalities" (i.e., deviations from the norm). The goal is to "normalize" the brain activity.

Surface Z-score NF and LORETA Z-score NF

To discuss the LORETA Z-score NF approach it is necessary to explain what LORETA imaging is. LORETA is a functional imaging procedure that seeks to estimate EEG bandwidth activity in deeper (intracranial) regions of the brain, based on data collected from surface electrodes (Pascual-Marqui et al., 1994, 2002). Similar to EEG data collected from specific electrodes, data from LORETA imaging can be compared with normative

LORETA data, and then used to develop a treatment protocol (e.g., to reduce θ power in the thalamus, if a specific patient's pretreatment LORETA assessment indicates excessive thalamic θ). Alternatively, it is possible to simply determine that more (or less) power of a specific bandwidth at a certain intracranial site might decrease an individual's pain and, based on that information, to develop a protocol to use LORETA Z-score NF to alter activity in that bandwidth at that location. It is also possible to use a "normalizing" protocol in real time, such that the qEEG or LORETA-based data are compared to the norms directly, allowing to reinforce responses in the direction of the normative database. The use of qEEG and LORETA data in real time NF are commonly referred to as "surface Z-score NF" and "LORETA Z-score NF," respectively (Wigton, 2013).

ERP-based NF

Event-related potential (ERP) assessments allow the study of stereotypical brain activity responses that occur at different specific time points following a specific stimulating cognitive, sensory or motor event (such as a response to an aversive stimuli; Luck, 2014). These time-locked brain responses to the aforementioned events are called components, which are believed to reflect the activity of postsynaptic potentials produced when thousands or millions of pyramidal neurons fire in synchrony while processing information (Sur and Sinha, 2009). ERP-based NF seeks to alter these components. One common ERP-based NF approach targets slow cortical potentials (SCP), which are slow event-related electrical shifts in the EEG of less than 1 Hz, that alternate between being electrically positive and negative (Wyckoff and Strehl, 2011; Krigbaum and Wigton, 2014). A distinctive component central to SCPs is the contingent negative variation (CNV), a negative potential that is recorded from the scalp during response anticipation, while the subject is anticipating and preparing for task performance (i.e., when they are told to press a button when a warning appears on the monitor). The aim of SCPs NF is to either increase or suppress the CNV by means of feedback, in order to regulate the excitation threshold (Strehl, 2009). Increased negativity is related to increased neural activity and a lower excitation threshold, whereas increased positivity is related to less neural activity and a higher excitation threshold (Strehl et al., 2006). Another ERP-based protocol that has been used for pain management targets changes in the amplitude of the N150-P260 complex, as this complex is sensitive to nociceptive stimulation (Miltner et al., 1988). The N150 is an early negative component that occur 150 milliseconds after the presentation of a stimulus, whereas the P260 is an early positive component that can be observed 260 milliseconds after the presentation of a stimulus.

Real-time fMRI NF

rt-fMRI NF allows patients to regulate brain activity in specific brain areas (including deeper areas of the brain) by targeting changes in the BOLD activity in the regions of interest. The most commonly used procedure in this type of NF involves an anatomical scan combined with a localizer task to identify the voxels of the region of interest to be trained (Sulzer et al., 2013; Thibault et al., 2018). Following this, the level of BOLD activity in the targeted area is fed back to the patient in order to facilitate their ability to increase or decrease that activity, as appropriate. The goal is to teach the individual to deliberately control the activation of the brain areas thought to be involved in pain perception and regulation.

Evidence Regarding the Effects of EEG-Based NF

Brain Oscillation Power-Based NF

We identified 15 articles that evaluated the effects of brain oscillation power-based NF on pain and pain-related outcomes. In the first of these, a RCT was conducted to evaluate the efficacy of a SMR protocol in individuals with fibromyalgia (Kayiran et al., 2010). Participants were randomly allocated to either the NF group ($n = 18$) or an active control group ($n = 18$) receiving 10 mg of escitalopram per day for 8 weeks. The NF treatment was comprised of 20 30-min sessions aiming to increase SMR bandwidth activity assessed over the right-central area of the scalp (C4 in the international 10-20 system). In addition to assessing pain intensity, the authors assessed resting state EEG activity in the participants who received NF during an eyes-open condition at baseline, 2 weeks, 4 weeks (end of treatment), 8 weeks (1-month follow-up), 16 weeks (3-month follow-up) and 24 weeks (5-month follow-up) after treatment started. Although they found no changes in the mean amplitudes of resting state bandwidth power over time, there was a statistically significant decrease in the θ/SMR ratio at the end of the treatment, compared to baseline. Participants in both treatment conditions reported significant pre- to post-treatment reductions in pain intensity (measured with a 10-cm Visual Analog Scale), fatigue, anxiety and depression. The improvements were maintained at all the follow-up assessment points (i.e., up to 5 months after treatment started, or 4 months after treatment ended). In the NF group, the maximum reductions in both pain intensity and fatigue were reached at the 4th week of treatment (i.e., at the end of NF treatment), whereas in the active control group the greatest reduction in pain intensity was reported at the 8th week of treatment (i.e., at the end of active treatment for the control group). Moreover, the improvements in pain intensity, fatigue, anxiety and depression were significantly greater for the NF group than the control group at every assessment point. See **Tables 3**, **4** for a summary of the pain and brain activity outcomes for all the studies.

In another RCT, a sample of 71 cancer survivors with CIPN were randomly allocated to the NF group ($n = 35$) or to a wait-list control group ($n = 36$) (Prinsloo et al., 2018). A qEEG was conducted and used to develop patient-specific NF protocols to normalize EEG-assessed oscillation power. The NF treatment consisted in 20 45-min sessions. The average pain intensity and pain interference ratings for the NF group were significantly lower at the end of the treatment compared to the wait-list control group; these differences were still statistically significant at 1-month and 4-month follow-up assessment points. Although there was also a significant difference in fatigue ratings between groups at the end of treatment, these differences were no longer statistically significant at 1-month and 4-month follow-up. There

TABLE 3 | Pre-treatment, post-treatment and follow-up pain intensity and frequency ratings.

Authors (year)	Condition	Pain pre M (SD)/[SEM]	Pain post M(SD)/[SEM]	Pain follow-up M (SD)/[SEM]
Kayiran et al. (2010)	E: NF	I: 8.9 (0.18)	I: 1.6 (0.21)	I (1 m): 1.9 (0,27) I (3 m): 2.4 (0.34) I (5 m): 2.6 (0.36)
	C: Escitalopram	I: 9.1 (0.23)	I: 4.7 (0.48)	I (1 m): 3.3 (0.27) I (3 m): 4.5 (0.34) I (5 m): 5.3 (0.30)
Prinsloo et al. (2018)	E: NF	I: 4.9 (0.35)	I: 2.7 (0.38)	I (1 m): 2.7 (0.51) I (4 m): 3.8 (0.48)
	C: WL	I: 4.4 (0.44)	I: 4.5 (0.35)	I (1 m): 4.6 (0.58) I (4 m): 4.6 (0.40)
Farahani et al. (2014)	E: NF	F (w): 4 (2.6)	F (w): 2.6 (1.77)	NA
	E: TENS	F (w): 5.4 (3.33)	F (w): 3.3 (1.68)	NA
	C: WL	F (w): 4.6 (4.43)	F (w): 4.4 (1.53)	NA
Stokes and Lappin (2010)	E: NF	F (m): 7.6 (5.1)	NA	F (3 m to 2 y): 2.9 (2.8)
Walker (2011)	E: NF	NR	F: 93% of participants > 50% reduction in migraine frequency.	NA
	C: Anti-migraine drug	NR	F: 8% of participants > 50% reduction in migraine frequency.	NA
Mathew et al. (1987)	E: NF	I: 6.2 (1.07)	I: 2.1 (1.23)	NA
	C: WL	I: 5.7 (1.71)	I: 3.9 (0.49)	NA
Caro and Winter (2011)	E: NF	NR	I: 39% reduction on average.	NA
	C: TAU	NR	I: No significant reduction on average.	NA
Jensen et al. (2007)	E: NF	I: 5.49 (2.24)	I: 3.2 (2.72)	NA
Hasan et al. (2015)*	E: NF	I: 7.3 (5.1)	I: 5.1 (1.46)	I: Reduced intensity compared to baseline but increased 1 to 2 points compared to last session.
Vučković et al. (2019)[T]*	E: NF	6.0	4.1	NA
Jensen et al. (2013a)	E: NF	I: 5.95 (1.7)	I: 5.4 (1.67)	I (3 m): 5.7 (1.90)
Jensen et al. (2013b)	E: NF	I: 4.61 (1.93)	I: 4.4 (2.09)	NA
	E: tDCS	I: 4.19 (2.02)	I: 3.9 (2.21)	
	E: Hypnosis	I: 4.27 (2.08)	I: 3.7 (2.16)	
	E: Concentration meditation	I: 4.44 (2.16)	I: 4.0 (1.97)	
	C: Sham tDCS	I: 4.39 (2.07)	I: 4.2 (2.02)	
Jacobs and Jensen (2015)	E: NF	All four participants reported significant pain intensity reductions.		
Jensen et al. (2016)	E: NF + Hypnosis	I: 5.3 (1.27)	I: 4.4 (0.71)	I (1 m): 4.0 (0.86)
	C: Relaxation + hypnosis	I: 5.2 (1.96)	I: 4.3 (1.9)	I (1 m): 4.3 (1.96)
Jensen et al. (2018)	E: NF + Hypnosis	I: 3.6 (1.17)	I (after NF): 2.6 (0.67) I (after hypnosis): 2.6 (1.20)	I (1 m): 2.4 (1.23)
	E: Mindfulness + Hypnosis	I: 3.8 (1.35)	I (after mindfulness): 2.8 (2.07) I (after hypnosis): 2.3 (2.42)	I (1 m): 3.3 (1.28)
	C: Hypnosis	I: 5.3 (1.57)	I (after hypnosis): 4.5 (2.61)	I (1 m): 4.5 (2.17)
Prinsloo et al. (2019)	E: NF	93% of the participants achieved significant reductions in pain intensity at either session 1 or 3.		
Koberda et al. (2013)	E: NF	All four patients reported reductions in pain intensity <50%.		
Miltner et al. (1988)	E: NF	6.4 (NR)	I (Increase N150-P260): 5 (1.62) I (Decrease N150-P260): 5.2 (1.63)	NA
Siniatchkin et al. (2000)	E: NF	I: 5.3 (1.4) F (m): 3.9 (2.5)	I:4.8 (2.3) F (m): 1.7 (1.8)	NA
	C: Healthy control	NA	NA	
	C: WL	I: 5.6 (1.8) F (m): 3.8 (3.6)	I: 6.0 (1.8) F (m): 4.0 (3.3)	
DeCharms et al. (2005)	*Individuals with* chronic pain E: NF C: Autonomic biofeedback	44% reduction in pain intensity in the NF group, which was three times larger than for those in the biofeedback group.		NA

(Continued)

TABLE 3 | Continued

Authors (year)	Condition	Pain pre M (SD)/[SEM]	Pain post M(SD)/[SEM]	Pain follow-up M (SD)/[SEM]
	Healthy individuals E: NF (rACC) C: 4 control groups with no feedback from rACC	In the experimental group, increasing or decreasing the BOLD activity in the rACC resulted in the noxious stimuli to be rated as more or less painful, respectively. The changes in pain intensity in the experimental were significantly larger than for any of the four control groups.		
Guan et al. (2015)	E: NF	I: 4.13 [0.55]	I (Up-training): increase in NRS scores of 1.8 [0.31] points. I (Down-training): decrease in NRS scores of 1.5 [0.33] points	NA
	C: Sham NF	I: 5.0 (0.52)	I (Up-training): increase in NRS scores of 0.1 [0.01] points. I (Down-training): decrease in NRS scores of 0.5 [0.22] points.	
Emmert et al. (2014)*	E: NF (IAIC)	I: 7.7 (1.20)	I: 6.0 (1.63)	NA
	E: NF (ACC)	I: 7.0 (1.15)	I: 6.2 (1.76)	
Rance et al. (2014a)	E: NF	None of the four conditions reported a significant decrease in pain intensity.		NA
Rance et al. (2014b)	E: NF	None of the two conditions reported a significant decrease in pain intensity.		NA

*E, Experimental; C, Control; NF, neurofeedback; NA, Not assessed; NR, Not reported; TAU, Treatment as usual; WL, Wait-list control group; TENS, Transcutaneous electrical nerve stimulation; I, Intensity, F, Frequency; W, week; M, month; Y, year; [SEM] standard error of the mean; IAIC, Left anterior insular cortex; ACC, Anterior cingulate cortex; BOLD, blood oxygen-level dependent. * Pain intensity scores calculated from participants individual's data presented in the study. [T] Average pre- and post-session scores.*

were no significant between-group differences in sleep quality or sleep disturbances at any assessment point. Results showed that brain activity, that is, the EEG frequencies targeted in the scalp positions chosen by the protocol, changed significantly from pre- to post-treatment toward a more "normal" EEG activity and that it was significantly different for the NF group compared to the waitlist group. Specifically, the NF group showed a significant increase in α relative power and a significant decrease in β relative power as averaged over all the electrodes.

Another RCT compared the efficacy of NF and transcutaneous electrical nerve stimulation (TENS) in a group of 45 healthcare practitioners with primary headaches (Farahani et al., 2014). Participants were randomly allocated to either a NF group ($n = 15$), a TENS group ($n = 15$) or a waitlist-control group ($n = 15$). The NF treatment consisted of 20 30-min sessions and aimed to increase SMR and decrease θ and high β over the right and left temporal cortex (T3 and T4 in the international 10–20 system). Both the NF and TENS groups experienced significant reductions in headache frequency compared to the waitlist-control group. However, the NF group achieved a significantly greater reduction in headache frequency than the TENS group.

In an uncontrolled study (Stokes and Lappin, 2010), 37 patients with migraine were treated with a combination of NF, passive infrared hemo-encephalography (pIR-HEG; a form of neurofeedback based on thermal outputs in response to changes in blood flow dynamics rather than brain electrical activity Carmen, 2004), and thermal biofeedback (i.e., a type of biofeedback that aims to change body temperature). The treatment consisted of an average of 40 sessions and included an average of 30 frequency-based NF sessions and an average of 10 pIR-HEG or hand-warming biofeedback sessions. NF training aimed to reduce the amplitude of the frequencies which were assessed at baseline and determined to be "excessive;" that is, treatment was tailored to each participant and was not standardized. The scalp positions where NF was conducted were primarily 5 sets of homologous sites (including over the prefrontal, frontal, temporal, central and parietal areas; FP1-FP2, F3-F4, T3-T4, C3-C4, and P3-P4 in the international 10–20 system). Compared with baseline scores, patients reported a significant reduction in the number of migraines per month at follow-up (a post-treatment assessment was not conducted), which was conducted three months to two years after the end of the treatment.

Walker studied the effects of NF as a treatment for recurrent migraine headaches (Walker, 2011). Of the 76 individuals entering the study, 46 chose to follow the NF treatment and 25 chose to remain with anti-migraine medication (the specific medication used by the study participants was not reported). The qEEG analysis at baseline showed an excess of power in the high β frequency band at a number of electrode sites – excesses that were most pronounced in the frontal, central and parietal regions. The NF protocol consisted in five 30-min sessions targeting a reduction in high β activity and an increase in 10 Hz activity at each electrode where an excessive high β activity had been identified. At post-treatment, 98% and 32% of the participants in the NF and control condition reported reductions in headache frequency, respectively. Specifically, in the NF group, 54% experienced a complete cessation of migraine headaches, 39% experienced a reduction in migraine headaches greater than 50, and 4% experienced a reduction of <50%. In the control group, none of the participants experienced a complete cessation of migraine headaches, 8% experienced a reduction in migraine headaches greater than 50, and 20% experienced a reduction of less than 50%.

The oldest study included in this review (Mathew et al., 1987) assessed the efficacy of NF as a treatment for

TABLE 4 | Brain activity outcomes.

Authors (year)	NF protocol	Effects in brain activity (pre- to post-treatment or during)	Association between brain activity change and pain improvements
Kayiran et al. (2010)	↗ SMR at C4.	No changes in the mean amplitudes of EEG rhythms. A significant decrease in the θ/SMR ratio at the end of the treatment compared to baseline.	NA
Prinsloo et al. (2018)	Normalize EEG at several unreported scalp locations.	After treatment, the NF group significantly increased α activity and decreased β activity.	NA
Farahani et al. (2014)	↗ SMR, ↘ θ and high β at T3 and T4.	NA	NA
Stokes and Lappin (2010)	NF, pir-HEG, hand-warming biofeedback. NF: normalize EEG at several scalp locations, mainly at: T3, T4, C3, C4, F3, F4, FP1, FP2, P3, P4.	NA	NA
Walker (2011)	↘ high β and ↗ 10 Hz activity at each electrode with excessive high β.	NA	NA
Mathew et al. (1987)	↗ α at one or more unreported scalp locations.	The NF group showed an increase in the amount of time spent with a preponderance of α activity. In the NF group, there was no change in overall α amplitude. The wait-list control group did not evidence any significant brain activity change after treatment.	NA
Caro and Winter (2011)	↗ SMR, ↘ θ and high β at Cz.	NA	NA
Jensen et al. (2007)	Tailored to each patient and adapted depending on patient's improvement. Normally started by ↗ SMR at T3 and T4.	NA	NA
Hasan et al. (2015)	First part: ↗ α at Oz. Second part: combination of 4 protocols: A: ↗ SMR, ↘ θ and high β at Cz. B: ↗ α, ↘ θ and high β at P4. C: ↗ α, ↘ θ and high β at C3. D: ↗ α, ↘ θ and high β at C4. *Placebo testin*g protocol: Either prerecorded session or ↗ α at Oz.	First part: All participants successfully increased at Oz, with no effect on pain intensity. Second part: All five participants decreased frontal θ during training. α power increased in the central cortex in four patients during training. Four patients decreased frontal high β during training. The largest long-term changes were in the high β band of the insular cortex, the cingulate cortex and the dorsolateral prefrontal cortex. Placebo testing protocol: During the placebo prerecorded session, the brain activity was not different from baseline. Participants were successful increasing α power at Oz, but this had no effect on pain intensity.	These patients that achieved a clinically meaningful reduction in pain intensity were the ones that successfully increased α power and to some degree, decreased β.
Vučković et al. (2019)	↗ α, ↘ θ and high β between C2 and C4.	With respect to baseline power: 9/15 participants significantly increased α power. 7/15 significantly decreased θ power. −6/15 participants significantly decreased high β power.	Brain activity changes after NF were partially associated with pain improvements. Eight of the 12 participants that achieved pain improvements successfully increased α during NF. Three of the remaining four participants who achieved pain improvements with NF but did not increase α, did achieve a significant decrease in θ, high β or both.
Jensen et al. (2013a)	3 protocols: A: ↗ α and ↘ β at T3 and T4. B: ↗ SMR, ↘ θ and β at C3 and C4. C: ↗ SMR, ↘ θ and β at P3 and P4.	Pre- to post-treatment decrease in θ and increase in α, that were no longer significant at 3-month follow-up. No changes in β activity.	NA
Jensen et al. (2013b)	↗ α and ↘ high β at T3 and T4.	No significant pre- to post-session change in any of the five EEG bandwidths (δ, θ, α, β and γ).	There was no association between brain activity change with NF and pain changes.

(Continued)

TABLE 4 | Continued

Authors (year)	NF protocol	Effects in brain activity (pre- to post-treatment or during)	Association between brain activity change and pain improvements
Jacobs and Jensen (2015)	Tailored to each patient, but all received at some point a protocol involving ↗ α, low β, ↘ θ and high β. Several scalp locations used.	NA	NA
Jensen et al. (2016)	Before hypnosis: Increase θ (by ↗ 5–9 Hz and 8–11 Hz) at FP1 and F3. After hypnosis: ↗ low β, ↘ γ, high β and θ at Cz.	NA	NA
Jensen et al. (2018)	↗ θ at AFz.	There was no significant time effect in the NF group for any of the EEG bandwidths (δ, θ, α, β and γ).	NA
Prinsloo et al. (2019)	Normalize electrical activity in the Brodmann's areas 3, 4, 5, 13, 24, 32, and 33.	EEG changed toward EEG activity more representative of the normal population in all targeted Brodmann's areas but the 32.	Changes in the current source density in Brodmann's areas 24 and 33 accounted completely for the variance in pain changes with NF ($R^2 = 1$, $p = 0.012$).
Koberda et al. (2013)	Tailored protocols aimed at normalizing EEG activity.	The four participants evidenced changes toward a more normal brain activity pattern.	NA
Siniatchkin et al. (2000)	↗ and ↘ the amplitude of the SCPs at Cz.	Children with migraine were only able to decrease the amplitude of their SCPs; they were unable to increase cortical negativity. The control group of healthy children learned to both increase and decrease the amplitude of their SCPs.	No association between the change in the amplitude of the SCPs and the reduction of migraines.
Miltner et al. (1988)	↗ and ↘ the size of the N150-P260 complex at Cz.	Participants learned to increase and decrease the size of the N150-P260 complex. -Subjective pain intensity reports were slightly higher in the up-training condition compared to the down-training condition.	NA
DeCharms et al. (2005)	↗ and ↘ BOLD activity in the rACC.	The experimental healthy group learned to both increase and decrease BOLD activity in the rACC. The experimental group of patients with chronic pain learned to regulate BOLD activity in the rACC.	For the 6 patients with chronic pain that completed at least two training runs, there was a significant and strong association between the extent to which they were able to regulate BOLD activity in the rACC and pain intensity reductions ($r = 0.9$).
Guan et al. (2015)	↗ and ↘ BOLD activity in the rACC.	The experimental group was able to both increase and decrease BOLD activity in the rACC.	No association between the changes in BOLD activity and changes in pain ratings.
Emmert et al. (2014)	↘ BOLD activity in ACC. ↘ BOLD activity in lAIC.	Eight of the 14 participants were able to decrease the BOLD activity in the ACC. Nine of the 14 participants were able to decrease BOLD activity in the lAIC.	There were no differences in pain ratings between those who were able to decrease BOLD activity in lAIC and ACC and those who were not.
Rance et al. (2014a)	4 conditions: ↗ the BOLD activity in the rACC. ↗ the BOLD activity in the pInsL. ↘ the BOLD activity in the rACC. ↘ the BOLD activity in the pInsL.	Participants were able to increase BOLD activity in the pInsL and decrease BOLD activity in the rACC and pInsL.	NA
Rance et al. (2014b)	Increase the difference in activation levels between the rACC and pInsL. 2 conditions: [1] higher activation in rACC than in pInsL. [2] higher activation in pInsL than in rACC.	Participants were successful in achieving the training goals for the two conditions.	The achieved difference in activation between the rACC and the pInsL was not associated to changes in pain intensity ratings.

NA, Not assessed; NF, neurofeedback; EEG, electroencephalography; Hz, hertz; pir-HEG, passive infrared hemo-encephalography; SCPs, slow cortical potentials; ACC, anterior cingulate cortex; rACC, rostral anterior cingulate cortex; lAIC, left anterior insular cortex; pInsL, left posterior insula; BOLD, blood oxygen-level dependent.

eight individuals with tension-type headache compared to a waitlist control group ($n = 4$). The NF participants received 20 30-min sessions of a protocol aiming to increase α assessed from one or more (unreported) electrode sites. The treatment group reported a significant increase in the amount of time spent with a preponderance of α activity, but not in its overall amplitude. The NF group also reported statistically significant reductions in pain intensity and anxiety from pre- to post-treatment. The waitlist control group, on the other hand, did not evidence any significant changes in brain activity, pain intensity or anxiety from pre- to post-assessment.

Caro and colleagues conducted an uncontrolled study assessing the use of NF to reduce attention difficulties and

somatic symptoms in patients with fibromyalgia (Caro and Winter, 2011). Fifteen patients were treated with NF and compared with a historical control group comprised of 63 individuals receiving standard medical care. The NF group received 58 sessions on average (ranging from 40 to 98) aiming to increase SMR oscillation power, while inhibiting both θ and high β oscillations at the same time. The training electrode was placed over the center of the scalp (Cz in the international 10–20 system). The NF group reported significant mean reductions in global pain and fatigue severity (39 and 40%, respectively). The 63 control participants did not report any significant improvements in either outcome variable.

Another study reported on changes after a single session of NF in 18 individuals with CRPS-I participating in a 20-day multidisciplinary treatment program (Jensen et al., 2007). The treatment protocol used varied over the course of each 30-min session, and was tailored to each patient, depending on their reports of pain reduction (or not) as the session progressed. For example, if training at a specific site to increase the power of a specific bandwidth was associated with improvements, that training continued. Training usually began by reinforcing SMR activity at sites over temporal areas (T3 and T4 in the international 10–20 system) to "stabilize" brain activity. If the patient reported no improvement with this protocol, different electrode sites or training frequencies were used until (and if) the patient reported improvements. Participants reported an average pre- to post-session reduction of 2.3 points in pain intensity (on a 0–10 Numerical Rating Scale) of their primary pain. Half of the participants reported a pain intensity reduction that was clinically meaningful, that is, a reduction of 30% or more from pre- to post-session (Rowbotham, 2001).

A pilot study (Hasan et al., 2015) aimed to investigate the potential mechanisms underlying NF efficacy to treat central neuropathic pain in seven patients with chronic paraplegia. Four patients received 40 sessions, one received 20 and two received only three sessions. The first 10 min of the NF treatment aimed to increase α at occipital regions (Oz in the international 10-20 system) with a goal of increasing general relaxation. The remainder of the NF training session had a goal of pain reduction. In this second component of each training session, each patient received a combination of one of four different protocols (all in a 30- to 35-min period), depending on their response to each. Protocol A reinforced SMR and suppressed θ and high β assessed from the central area of the scalp (Cz in the international 10–20 system). Protocol B reinforced α and suppressed θ and high β from an electrode placed over the right parietal area (P4 in the international 10–20 system). Protocol C reinforced α and suppressed θ and high β from an electrode placed over the left central area (C3 in the international 10–20 system). Protocol D reinforced α and suppressed θ and high β at from an electrode placed over the right central area (C4 in the international 10–20 system). It is important to note that the α range targeted in this study was slightly higher than usual, that is, 9–12 Hz instead of the general 8–12 Hz, as lower α frequencies have been found to be associated with central neuropathic pain (Boord et al., 2008). Also, each participant received two "placebo" sessions at some point between sessions 10 and 20 (the specific sessions that were "placebo" sessions differed for each participant), with the goal of testing for placebo responses. One placebo protocol "fed back" pre-recorded data from a different NF session, and the other provided feedback aiming to increase α at the occipital area (Oz in the 10–20 system). Both placebo protocols were hypothesized to not have any impact on pain. Resting state EEG in both open eyes and closed eyes conditions and sLORETA imaging (a newer and more accurate LORETA) was recorded before and after treatment. In addition, the researchers assessed and recorded EEG activity before and during NF training. All participants received a different number of sessions of each protocol, and the sequence of protocols used also differed for each patient and changed depending on their initial response. The five patients that received at least 20 sessions reported statistically significant pre- to post-treatment reductions in pain intensity; four (80%) reported pain reductions that were clinically meaningful (>30%). The patients that achieved clinically meaningful reductions in pain intensity were the ones that successfully increased α power and, to some degree, decreased high β power. At one-month follow-up assessment the participants who reported reductions in pain still reported lower pain intensity, relative to baseline, although they also reported an increase in pain intensity of one to two points (on a 0–10 scale), relative to baseline. Additionally, regarding pre- to post-session effects, protocols C and D were associated with the greatest reductions in pain intensity, although three patients had strong muscle spasms with protocol C. Protocol B yielded a moderate reduction in pain intensity whereas protocol A did not decrease pain intensity for any of the patients. Also, in the two sessions used to test for placebo effects, participants successfully increased α power at the central occipital area (Oz in the international 10–20 system), but this had no impact in pain intensity. The largest long-term changes were in the high β band of the insular cortex, the cingulate cortex and the dorsolateral prefrontal cortex, assessed via sLORETA.

Another study conducted by the same research team tested the use of self-administered NF to treat central neuropathic pain in 15 patients with chronic SCI (Vučković et al., 2019). Participants were offered up to four training sessions at the hospital before they had to self-administer the treatment at home. They were instructed to use NF on demand but at least once a week for two months, and to record pain intensity before and after each session. The NF session protocol consisted in reinforcing α power and suppressing θ and high β power as measured at a central site (specifically between C2 and C4 in the international 10–20 system). As in the previous study conducted by the same research team, the α range targeted was slightly higher than usual (i.e., 9–12 Hz). Each session lasted 30 to 35 min. In total, participants received or self-administered an average of 14 sessions, ranging from 3 to 48 sessions. Statistically significant pre- to post-session improvements in average pain intensity were found in 12 of the 15 participants, with eight participants achieving clinically meaningful reductions in each session on average. With respect to brain activity changes, each NF session was preceded by 2-min baseline EEG recording in the eyes-opened condition. Of the 15 participants, nine significantly increased α power with treatment, whereas seven and six participants significantly

decreased θ and high β power, respectively. These changes were partially associated with pain improvements. Specifically, eight of the 12 participants that achieved pain improvements successfully increased α during NF. Three of the remaining four participants who achieved pain improvements with NF but did not increase α, did achieve a significant decrease in θ, high β or both.

Another study tested the efficacy of three different NF protocols in 10 individuals with SCI and chronic pain (Jensen et al., 2013a). Each individual received 4 sessions of each of the following protocols in random order. Protocol A reinforced α and suppressed β activity measured from electrodes at the temporal sites frequently used in NF treatment for pain management (i.e., T3 and T4 in the international 10–20 system). Protocol B reinforced SMR activity and suppressed β and θ power assessed from electrodes at central sites (C3 and C4 in the international 10–20 system). Protocol C reinforced SMR activity and suppressed β and θ power at parietal sites (P3 and P4 in the international 10–20 system). There were similar pre- to post-session reductions in pain intensity for all three protocols. However, statistically significant pre- to post-treatment (i.e., after the 12 sessions) reductions were not found in average pain intensity. In addition, there were not statistically significant pre- to post-treatment improvements in fatigue, sleep quality and pain interference. The investigators also assessed and reported resting EEG in eyes closed condition at pretreatment, post-treatment and 3-month follow-up. In line with the protocols, there were both an increase of α power and a decrease in θ power from pre- to post-treatment. These changes in α and θ power were not sustained and were no longer different from baseline levels at the 3-month follow-up. β power did not change significantly over time, despite the fact that all three protocols aimed to decrease it.

Another study (Jensen et al., 2013b) assessed the effects of a single 20-min session of four different interventions [NF, hypnosis, concentration-meditation and transcranial Direct Current Stimulation (tDCS)] on pain intensity in thirty patients with SCI and chronic pain, compared to a tDCS sham procedure. Each intervention session took place in a different day. The NF session protocol consisted in reinforcing α and suppressing high β power measured at right and left temporal sites (T3 and T4 in the international 10–20 system). In addition, resting state EEG was recorded for 10 min in eyes closed before and after each of the five procedures. Neither pain intensity nor EEG activity in any of the five bandwidths (i.e., δ, θ, α, β, and γ) changed significantly after a single session of NF. Also, the associations between changes in EEG power at the different bandwidths and changes in pain intensity were not significant.

Jacobs and Jensen (Jacobs and Jensen, 2015) published a case series reporting the use of NF as a treatment for four individuals with a variety of chronic pain problems. The first patient was a 19-year-old girl with abdominal pain. She received 41 NF sessions. The second patient was a 56-year-old woman with migraine headaches who received 32 sessions. The third patient was a 14-year-old young man with chronic testicular pain who received 22 NF sessions, and the fourth patient was a 47-year-old man with severe gastrointestinal pain who received 26 sessions of NF treatment. The treatment protocols were tailored for each patient based on standard practice recommendations for addressing the presenting problems of the patients. Given the common practice of rewarding increases in α and low β power for chronic pain management, all the patients received training that involved these components for at least some of the sessions. Specifically, at some point, they all received a protocol that involved rewarding increases in α and low β power and decreases in θ and high β power. A number of electrode positions were used as training sites, with the goal of identifying the sites and protocols that would be most effective for each patient. All four patients achieved clinically meaningful reductions in pain intensity or pain frequency at some point during treatment, although one of the patients reported that his pain intensity returned to baseline levels by the end of the treatment.

Two pilot studies were conducted to explore the possibility that NF might be used for enhancing the effect of hypnosis for chronic pain management in individuals with multiple sclerosis. In the first of these (Jensen et al., 2016), participants were randomly allocated to receive five sessions of self-hypnosis (one face-to-face session and four prerecorded sessions), preceded by either four 30-min sessions of NF ($n = 10$) or four 20-min sessions of relaxation training, which served as a control group ($n = 9$). After each session, all the individuals received one self-hypnosis session. The NF protocol aimed to increase θ power by reinforcing slow wave power (5–9 and 8–11 Hz) at frontal sites (FP1 and F3 in the international 10–20 system), based on evidence suggesting that higher levels of θ power are associated with greater response to hypnosis (Jensen et al., 2015). These investigators had a concern that an excess of θ power might result in negative effects, given the association between θ activity and having a diagnosis of attention deficit disorder (Arns et al., 2013). To address this possibility, after each hypnosis session, the participants received 10 additional minutes of a NF protocol aiming to reverse any enhanced θ with a protocol reinforcing low β while inhibiting γ, high β, and θ at a central site (Cz in the international 10–20 system). The participants who received the hypnosis treatment preceded by either the NF or relaxation treatment reported statistically significant reductions in average pain intensity, pain interference and fatigue severity. In the group receiving NF treatment, participants reported larger decreases in average pain intensity from pre- to post-treatment and from pretreatment to 1-month follow up, compared to the participants receiving the relaxation treatment. No differences between the NF and relaxation groups were found regarding improvements in pain interference or fatigue severity.

In the second study (Jensen et al., 2018), individuals with multiple sclerosis and either chronic pain, chronic fatigue or both pain and fatigue, were randomly allocated to receive five sessions of self-hypnosis (one face-to-face session and four prerecorded sessions), preceded by either six 30-min sessions of NF ($n = 12$), six 30-min sessions of mindfulness meditation (MM; $n = 10$) or no intervention ($n = 10$). After this, all participants received one face-to-face hypnosis session, and then four prerecorded hypnosis sessions (recorded by the same clinicians who provided the single face-to-face hypnosis session), targeting pain reduction, fatigue reduction, or both, depending on the presenting problem(s) of the participants. The NF group received in addition four sessions of NF immediately before the recorded

hypnosis treatment sessions, and the MM group received an additional four sessions of MM immediately before the recorded hypnosis treatment sessions. Therefore, the NF and MM groups received 11 sessions in total (six NF or MM sessions alone, one face-to-face hypnosis session, and then four "combined" NF with hypnosis or MM with hypnosis sessions), and the control group received five sessions in total (the single face-to-face hypnosis session and four pre-recorded hypnosis sessions. The NF protocol reinforced an increase in θ power at the frontal midline region of the scalp (AFz in the international 10–20 system). Participants in all three conditions reported statistically significant reductions in pain intensity from pretreatment to 1-month follow-up, which were the highest for the NF group. Both the NF and MM groups reported similar significant pain intensity reductions with six sessions of each treatment alone. At 1-month follow-up, the NF group had maintained the gains made during treatment, whereas the pain intensity ratings in the MM group returned to baseline levels. Fatigue severity ratings improved similarly for the three groups, with a small decrease from baseline to before the hypnotic treatment and an additional decrease after the hypnotic treatment. Nevertheless, fatigue severity increased slightly from post-treatment to follow-up. With respect to the secondary outcomes (sleep disturbance, pain interference and depression), only the NF group reported significant improvements from pretreatment to 1-month follow-up. EEG data were recorded for both the NF and MM groups at baseline, after the first six sessions (pre-hypnosis) and at the last NF or MM session (post-treatment). Although there were some differences in the mean amplitudes of the five EEG bandwidths from baseline to pre-hypnosis or from pre-hypnosis to post-treatment, there was no significant time effect for neither the NF nor the MM groups.

Surface Z-Score NF and LORETA Z-Score NF

Prinsloo and colleagues conducted an exploratory study to assess the use of LORETA Z-score NF (i.e., with a goal toward normalizing brain activity) to treat pain in patients with head and neck cancer undergoing radiation therapy (Prinsloo et al., 2019). In this study, pain intensity and resting eyes-open EEG activity was measured at three time points: baseline (i.e., before starting radiation therapy), after starting radiation therapy and when and if patients reported a pain intensity score of 4 or higher, and after the NF treatment. Pain intensity was also assessed and reported before and after NF sessions 1 and 3. Fourteen patients received one to six 20-min sessions of LORETA Z-score NF targeting a normalization of the activity in the Brodmann's areas number three, four, five, 13, 24, 32, and 33, in real time. As reported by the investigators, 14 patients received one or more sessions, 12 received at least three sessions and five received six NF sessions. Significant pre- to post-session reductions in pain intensity was reported by 93% of the participants at either session one (n=9), with an average mean reduction of 2.1 points (SD = 1.54; on a 0–10 NRS scale) or session three ($n = 8$), with an average reduction of 1.13 points (SD = 0.35; it was not clear based on the data presented by the investigators how many of these participants reported significant pain reductions in both sessions). With respect to brain activity changes, there was a change toward normality in the current source density of all targeted brain areas but one (i.e., Brodmann's area 32). Interestingly, regression analysis found that changes in the current source density in Brodmann's area 24 accounted for ∼92% of pain variance, and current source density in Brodmann's area 33 accounted for the rest. Specifically, lower levels of current source density in Brodmann's area 24 and higher levels of current source density in Brodmann's area 33 were significant predictors of pain intensity.

Another case series (Koberda et al., 2013) reported the use of both 19-channel Surface Z-score and 19-channel LORETA Z-score NF to decrease pain in four patients with different pain problems. The first patient had neuropathic pain and received 65 sessions. At the initial assessment, his qEEG showed an excess of β activity at temporal locations whereas LORETA imaging showed an excess in θ and β activity at the left insular cortex. The second patient had chronic pain associated with depression and received 25 sessions. Her initial qEEG showed an excess of δ and β power in frontal and central areas, and the LORETA imaging showed "dysregulation" in the anterior cingulate cortex. The third patient had both postherpetic neuropathy and sensory motor polyneuropathy, and received 45 sessions. His qEEG showed an excess of δ power in frontal areas, and the LORETA imaging showed "dysregulation" in the left insular cortex. The fourth and final patient had trigeminal neuralgia and received 10 sessions of NF. Her qEEG showed an excess of δ and θ power in fronto-temporal areas and an excess of β in frontal areas, whereas the LORETA imaging showed "dysregulation" in the left insular cortex. The investigators did not specify the number of sessions that each patient received of each treatment approach (i.e., surface Z-score or LORETA Z-score NF). Compared with the pre-treatment pain levels, all the patients reported substantial reductions in pain intensity, ranging from 50% reduction to complete remission. With respect to brain activity changes, and whether assessed with qEEG or LORETA, all patients evidenced changes in the direction of more normal brain activity patterns over the course of treatment.

ERP-Based NF

Two studies used ERP-based NF to modulate pain: one was a clinical study whereas the other was an experimental study with laboratory induced pain.

Clinical Pain Study

The first study (Siniatchkin et al., 2000) was a controlled trial that examined the efficacy of Slow Cortical Potentials NF in a small sample ($n = 10$) of children with migraine without aura. Participants in this study were compared with two control groups: a wait-list control group of children with migraines ($n = 10$) and a control group of healthy children who also received the NF treatment ($n = 10$). This latter control group was used to compare the ability to self-regulate slow cortical potentials in children with migraine compared to healthy children. The NF protocol was conducted with brain activity measures from the central region of the scalp (Cz in the international 10–20 system) and consisted in two different tasks that were trained during the same session: each task was to either increase or decrease the amplitude of the SCPs. Additionally, EEG was recorded at frontal

and central sites (Fz and Cz in the international 10–20 system). Children in the treatment group and in the healthy control group were able to control the amplitude of their SCPs after the 10 sessions. However, the group of children with migraine was only able to decrease cortical negativity (i.e., decrease the amplitude of their SCPs). After 10 sessions, the treatment group showed significant reductions in the number of days with migraine per month; effects that were not found in the wait-list control group. There was no association between the extent of decrease in the amplitude of the SCPs with NF and the reduction in the number of days with migraine.

Laboratory Induced Pain Study

The second study aimed to test whether it was possible to modify pain intensity via increasing the ability to alter the N150-P260 complex evoked by aversive stimulation (Miltner et al., 1988). In this study, 10 otherwise healthy male individuals underwent a single 120-min experimental session. First, the individual's pain threshold and the amount of noxious stimulation required for the participant to experience a pain intensity at 20% above his or her pain threshold were measured. Then, the baseline ERPs and subjective pain intensity in response to the simulation with an intensity of 20% above the threshold were measured. The last part of the session was devoted to the NF training in the form of two different tasks when presented with the same noxious stimulation used at baseline (i.e., 20% above threshold): one in which the subjects were reinforced for increasing the size of the N150-P260 complex and one in which they were reinforced for decreasing the size of this complex. Both tasks were randomly presented during the session. EEG was recorded at central areas of the scalp (i.e., Cz according the international 10–20 system), where the NF intervention was conducted. With respect to brain activity, the subjects were able to learn to alter the size of the N150-P260 complex consistent with the training. Also, pain intensity reports were different in the up-training and down-training conditions; when presented with identical noxious stimuli, those in the up-training condition reported slightly higher pain intensity reports than those in the down-training condition. Despite the differences in pain intensity reports between both conditions, however, the decrease after the whole session in pain intensity ratings was not statistically significant.

Evidence Regarding the Effects of fMRI-Based NF

To date, five studies have evaluated the efficacy of rt-fMRI NF to modulate pain: two were clinical studies whereas the other three were experimental studies with laboratory induced pain.

Clinical Pain Studies

DeCharms and colleagues tested whether it was possible for individuals to learn to control brain activation in the rostral anterior cingulate cortex (rACC) in a single session of rt-fMRI NF (DeCharms et al., 2005). This study used seven groups. Of these, two were experimental groups that received the rt-fMRI NF and five were control groups. The first experimental group, which was comprised of eight healthy individuals, was compared to four healthy control groups (three of them had eight individuals and one had four individuals) that underwent similar procedures but without valid feedback from rACC (i.e., training using sham rt-fMRI data belonging to another subject recorded session, or training using rt-fMRI data from a brain area other than the rACC). These four control groups were used to determine if the effects of the rt-fMRI NF were due to the ability to modulate the activation in the rACC rather than due to non-specific (i.e., placebo) effects. The second experimental group, which was comprised of eight patients with chronic pain, was compared to a control group of four patients with chronic pain that were trained with autonomic biofeedback. The rt-fMRI NF protocol consisted of training runs (i.e., a specific training period within a training session) in which participants were asked to both increase and decrease BOLD activity in the region of interest within the rACC, hypothesized to be an important area underlying the experience of pain. Each training run lasted 13 min and was comprised by five 60-second increase cycles and five 60-s decrease cycles. A thermal noxious stimulus was presented for 30 s to the healthy participants only in each cycle. All the healthy subjects went through a localizer scan, three training runs and a posttest scan, whereas, patients with chronic pain also had the localizer and posttest scan but could choose the number of training runs they were willing to do. Thus, four patients had three training runs, two patients had two training runs and two patients had one training run. After each training run, all study participants were asked to report pain intensity.

The experimental healthy group learned to modulate the BOLD activity in the rACC, whereas the control groups did not. The experimental healthy group learned to both increase and decrease BOLD activity in the rACC, affecting pain perception differently. That is, noxious stimuli presented when subjects were trying to increase BOLD activity in the rACC were rated as significantly more painful than when subjects were trying to do the opposite; that is, to decrease BOLD activity in the rACC activation. The control over pain intensity achieved by the healthy experimental group (who trained with valid feedback from rACC) was significantly larger than for any of the four healthy control groups (who underwent similar training but without valid feedback from rACC). With respect to the experimental group of patients with chronic pain, they reported a 44% pre- to post-session decrease in pain intensity. There was a strong association between the level of control over the BOLD activity in the rACC achieved by the patients with chronic pain after rt-fMRI NF and the change in pain ratings ($r = 0.9$, $p < 0.01$). Also, the pain intensity reductions in this group were three times greater than those reported by participants who received the autonomic biofeedback intervention.

A more recent study evaluated the effects of a single session of rt-fMRI NF to teach voluntary control over activation in the rACC (Guan et al., 2015). The participants in this study had postherpetic neuralgia, and were randomly allocated to either an experimental group, which received real information from the rACC, or to a control group, which received sham information from a different brain region (i.e., the posterior cingulate cortex). In this experiment, both the experimental ($n = 8$) and the control ($n = 6$) groups were reinforced at different times for increasing and decreasing activation in the respective regions of interest.

The experimental group was able to both up- and down-regulate BOLD activity in the rACC significantly better than the control group, suggesting that rACC activity may be more amendable to control than activity in the posterior cingulate cortex. Moreover, the experimental group achieved significantly greater changes in pain intensity compared to the control group. In the up-regulation condition, pain intensity ratings increased 1.8 and 0.1 (on a 0–10 scale) for the experimental and control groups, respectively. In the down-regulation condition, pain intensity ratings decreased 1.5 for the experimental group and 0.5 in the control group. However, the associations between changes in BOLD activity and changes in pain intensity for either the up- and down-regulation conditions were not statistically significant.

Laboratory Induced Pain Studies

Emmert et al. (2014) assessed the use of a single session of rt-fMRI NF in healthy individuals targeting two different regions hypothesized to be associated with the processing of pain information: the ACC and the left anterior insular cortex (lAIC). Both groups were first asked to participate in a localizer task with noxious heat stimulation to establish the specific pain-sensitive target region in the AIC or ACC for each participant. Next the NF training was conducted, during which participants received feedback to decrease the BOLD activity during pain stimulation in the brain area identified during the localizer task for that participant. Over half of the participants in each group were able to successfully decrease BOLD activity in either the ACC or lAIC. Both the lAIC ($n = 14$) and ACC ($n = 14$) groups significantly reduced pain ratings in the feedback task compared to the localizer task. Moreover, there was no significant difference in the reduction of pain intensity between the lAIC and the ACC groups, nor there was a significant difference in pain ratings between those who successfully decreased BOLD activity and those who did not.

The final two studies were conducted by a single research team and used similar procedures. Both studies included 10 healthy individuals. The investigators conducted an anatomical scan, a baseline run, and 24 training runs over four consecutive days. Each of the training runs was comprised of six regulation phases (where the individuals received electrical noxious stimulation along with rt-fMRI NF training) and six non-regulation phases (where participants engaged in mental arithmetic tasks).

The first study (Rance et al., 2014a) aimed to evaluate the effect of separately increasing and decreasing the BOLD activity in the rACC and left posterior insula (pInsL) on pain intensity. The study had four conditions: increase BOLD activity in rACC, decrease BOLD activity in rACC, increase BOLD activity in pInsL and decrease BOLD activity in pInsL. Three of the conditions (all except the condition that aimed to increase activity in the rACC) resulted in brain activity changes in the intended directions. However, none of the four conditions resulted in significant changes in pain intensity ratings.

In the second study, the investigators (Rance et al., 2014b) aimed to assess the effect of disrupting a part of the pain processing network by training participants to increase the *difference* in activation levels between two brain regions: the rACC and pInsL. Participants received rt-fMRI NF training with the goal to achieve two states: one where the activation of the rACC was higher than the activation of the pInsL, and a second state where the activation of the pInsL was higher than the activation of the rACC. Although the participants were successful in achieving the training goals, pain intensity ratings did not change significantly from the first to the last training trial.

Risk of Bias

The details of the quality ratings according to the Quality Assessment Tool for Quantitative Studies are presented in **Table 5**. It is noteworthy that none of the studies received a "strong" rating for the components of selection bias and confounders. All but two of the studies were rated as either "strong" or "moderate" in study design. Most ($k = 17$, 71%) of the studies were rated as weak in the blinding component, and just one study (4%) was double-blinded (i.e., it received a "strong" rating for the blinding component). Seventeen studies (71%) used reliable and valid measures to assess outcomes and 14 studies (58%) were rated as "strong" with respect to withdrawals and drop-outs.

DISCUSSION

In this review we summarized the available evidence regarding the efficacy of NF as a treatment for pain and its effects on pain-related brain activity. To our knowledge, this is the first review to systematically summarize the use and effects of NF as an intervention for any type of pain and pain-related outcomes.

NF Protocols Studied

The first aim of this review was to describe the different types of NF and NF protocols that have been used in pain research and how NF has been used for pain management. Most of the 24 studies that were included and reviewed were EEG-based and focused mostly on adults with migraines or headache and other chronic pain conditions, such as fibromyalgia or cancer-related pain. Of the five types of NF that we identified and described, brain oscillation power-based NF was evaluated the most often.

Within each type of NF studied, the specific protocols used varied from study to study. Although some NF protocols shared some features, no two studies used the exact same protocol. To the extent that several high-quality clinical trials are needed to draw conclusions regarding the efficacy of a clinical intervention, the lack of consistency in the NF protocols studied means that the field has not advanced enough to be able to draw strong conclusions regarding the efficacy of specific NF protocols for pain management.

Efficacy of NF

The second aim of the study was to summarize the evidence regarding NF and different NF protocols for modulating pain and improving pain-related outcomes. As a whole, and given the generally positive results in the studies reviewed, the findings indicate that NF procedures have the potential for reducing pain and improving other outcomes in individuals with chronic pain. Most of the studies reviewed found significant pre- to post-treatment improvements in pain intensity and/or pain

TABLE 5 | Quality ratings for the included studies.

Authors, year	Selection bias	Study design	Confounders	Blinding	Data collection methods	Withdrawals and drop-outs
Caro and Winter (2011)	3	2	N/A	3	2	3
DeCharms et al. (2005)	2	2	3	3	1	1
Emmert et al. (2014)	3	1	2	3	1	1
Farahani et al. (2014)	2	1	2	3	1	1
Guan et al. (2015)	3	1	2	1	1	1
Hasan et al. (2015)	3	2	N/A	3	1	2
Jacobs and Jensen (2015)	3	3	N/A	N/A	3	N/A
Jensen et al. (2018)	2	1	2	3	1	1
Jensen et al. (2013a)	3	2	N/A	3	1	1
Jensen et al. (2016)	3	1	3	3	1	1
Jensen et al. (2007)	3	2	N/A	3	2	1
Jensen et al. (2013b)	2	2	N/A	2	1	1
Kayiran et al. (2010)	3	1	3	2	1	1
Koberda et al. (2013)	3	3	N/A	N/A	3	N/A
Mathew et al. (1987)	3	1	3	3	2	2
Miltner et al. (1988)	2	2	N/A	3	1	1
Prinsloo et al. (2019)	3	2	N/A	3	1	2
Prinsloo et al. (2018)	2	1	2	3	1	2
Rance et al. (2014a)	3	2	2	3	1	1
Rance et al. (2014b)	3	2	2	3	1	1
Siniatchkin et al. (2000)	3	1	2	2	1	3
Stokes and Lappin (2010)	3	2	N/A	3	3	1
Vučković et al. (2019)	3	2	N/A	N/A	1	2
Walker (2011)	3	2	N/A	3	3	3

Strong (1) Moderate (2) Weak (3); confounders and blinding components were not assessed for studies without control group or for case-series; withdrawals/drop-outs component was not assessed for case-series.

frequency, with some of these improvements being maintained at follow-up (when follow-up was evaluated). Also, most of these studies found significant improvements in other pain-related variables such as fatigue, sleep problems/sleep quality, anxiety, depression, and pain-related interference. NF was also found to enhance the effects of hypnosis for chronic pain management and to reduce the perception of experimentally induced pain in healthy individuals.

However, and as alluded to previously, the high level of protocol heterogeneity and the heterogeneity in the characteristics of the samples studied do not allow us to draw conclusions regarding the efficacy of NF types and specific NF protocols. That said, there were some patterns in the study findings that could be used for hypothesis generation for future research. For example, the brain oscillation power-based NF protocols often included some combination of protocols that increased α and SMR power, and decreased β and θ power. Another commonly used protocol was to tailor NF treatment to each individual participant based on their baseline qEEG assessment, with a goal of bringing their qEEG in line with normative values. Most of these studies found positive results for the NF interventions evaluated. These preliminary findings raise the possibility that the beneficial effects of NF may be due to (1) NF's effects on the power of one or more specific bandwidths or (2) NF's ability to normalize bandwidth power across the spectrum. The need for more research in this area is discussed in more detail in the next section.

The Mechanisms That Underlie NF Treatment

As mentioned previously, in the context of pain treatment, NF aims to change brain activity that is thought to underlie or influence the experience of pain (Ibric and Dragomirescu, 2009). The third aim of the current review was to determine the level of evidence regarding the effect of NF training on targeted brain activity, and the associations of these with improvements in pain outcomes. Unfortunately, almost a third of the studies included in the review did not assess changes in brain activity. Moreover, those studies that did include some measure of brain activity studied different domains of brain activity. For example, some studies evaluated whether there were any brain activity changes *during* a training session or training sessions, whereas others evaluated pre- to post-treatment changes in resting state activity.

An important question that remains unanswered is how exactly NF works to reduce pain intensity. Although a given NF protocol usually seeks to alter brain activity in a specific way, as noted previously, researchers do not always include a manipulation check to determine if (and how much) brain

activity changed as intended. Moreover, when such checks are performed, the findings indicate that even if the treatment protocol was effective for reducing pain, it was not always effective for changing brain activity as originally intended (Rogala et al., 2016; Omejc et al., 2018). In fact, in many studies the changes in pain intensity or frequency occurred irrespective of whether the targeted brain activity modulation occurred (Siniatchkin et al., 2000; Jensen et al., 2013b; Emmert et al., 2014; Rance et al., 2014b; Guan et al., 2015). It remains possible that much, if not all, of the beneficial effects of many NF protocols are due to their non-specific effects (e.g., effects on patient outcome expectancies, or effects on mechanisms that may be shared across different NF protocols, such as perceived self-efficacy), as argued by Thibault and colleagues (Thibault et al., 2017).

Mechanism research is needed to address the specificity of NF treatment. For example, participants in a clinical trial could be randomly assigned to one of three conditions: (1) a condition targeting an increase in a specific bandwidth power; (2) a condition that seeks to normalize power across all bandwidths, based on the results of a pre-treatment qEEG assessment; or (3) a control condition (e.g., sham EEG or a protocol that seeks to decrease α power). qEEG could be assessed before and after treatment sessions, during one or more of the treatment sessions and before and after treatment. A finding that participants in one or the other of the experimental conditions report larger improvements in pain than participants in the control condition could be used as evidence for the potential specificity of NF's effects. Even more importantly, additional evidence for treatment specificity could come from mediation analyses to determine the extent to which pre- to post-treatment changes in the power of one or more bandwidths or the ability of an individual to alter bandwidth power during a treatment session mediates the beneficial effects of the experimental conditions relative to the control condition. One example of such a mediation analyses performed in the context of an exploratory study was recently published by Prinsloo and colleagues (Prinsloo et al., 2019). They found that changes in the current source density in two of the targeted Brodmann's areas (the ventral and the dorsal parts of the ACC) completely mediated the reduction in pain intensity achieved with LORETA Z-score NF in patients with cancer undergoing radiation therapy (Prinsloo et al., 2019). This finding provides preliminary support for the specific effects of the NF protocol examined, and points to the activity in the ACC as a potential mechanism for NF interventions that should be examined in future NF studies.

Study Quality

The fourth and final aim of this review was to assess the quality of the studies included. The results of the quality analysis were mixed. On one hand, all but two of the studies were rated as either "strong" or "moderate" with respect to study design. It is important to note that "strong" study quality is a rating assigned to RCTs or controlled clinical trials, whereas the "moderate" study quality is a rating assigned to studies with a pre-post design, with either just one cohort or with a control group, or case-control studies. It is also important to note that only three studies included in the review were RCTs. Also, more than half of the studies used reliable and valid measures to assess outcomes and were rated as "strong" with respect to withdrawals and drop-outs. On the other hand, most of the studies reviewed had relatively small sample sizes and were pilot studies.

In order to maximize the quality of future clinical trials in this area, so that future systematic reviews could draw more definitive conclusions regarding the efficacy of NF for pain management, researchers should ponder several important study quality considerations. First, future studies would benefit from more robust experimental designs and a more homogeneous and clearer reporting of the protocols and outcomes of the study. In order to achieve this, consensus recommendations on the reporting and experimental design of clinical and cognitive-behavioral neurofeedback studies was recently published (Ros et al., 2020). These recommendations could serve as a framework for the design, conduct, and reporting NF studies.

Second, it is necessary for future studies to estimate sample sizes a priori, ensuring they are adequate for the planned statistical analyses. To be on the safe side, given that pilot studies often over-estimate effect sizes, researchers should seriously consider exceeding the estimated sample size. This would also help to ensure that the samples are large enough to allow for drop-outs or potential missing data.

Third, less than a third of the studies included in this review conducted follow-up assessments. This issue does not allow us to determine if the gains in the studies that did find a reduction in pain intensity or pain frequency at posttreatment were maintained for any period of time after treatment. For NF to be recommended, future studies should consistently report NF effects after treatment and in successive follow-ups.

Fourth, with rare exceptions, most of the studies included in this review used adult samples. As chronic pain is also highly prevalent in children and adolescents (Huguet and Miró, 2008), it would be essential to include these segments of the population in future studies in order to ascertain NF's efficacy in youths.

Fifth, most of the studies did not report several confounding factors, such as medication intake and duration of the problem. Thus, we were not able to take into account the moderating effect of these factors in the effects of NF on pain.

Finally, detailed information about the studies was often lacking. For example, the interventions were often not described in enough detail to allow for replicability. Moreover, detail was sometimes lacking in the description of the outcomes (e.g., reporting decrease or increase percentages only, rather than specific baseline and post-treatment numbers in addition to percentages). In addition to the fact that some studies did not report brain activity information, those which did reported a large variety of variables; it appears that there are no standards yet for reporting basic brain activity information. All of these limitations prevented us from encapsulating and drawing firm conclusions on the efficacy of NF to modulate pain.

Future Studies

In order to improve on the quality and utility of clinical trials, future studies should seek to identify the protocols that work best for each pain condition, the number of sessions needed to see improvements, the brain mechanisms involved, and how long

the improvements are maintained after treatment (Van Boxtel and Gruzelier, 2014), both in youths and adults. However, it is possible that determining fixed protocols for each condition might not be the best path, and instead, tailored protocols for each individual might be better to improve the efficacy of NF studies (Rogala et al., 2016). Also, and in light of some researchers questioning the benefits of NF over and above placebo (Thibault et al., 2017), future studies should consider including a placebo condition. In our review, only three studies controlled for possible placebo effects; for example, by targeting a brain region or a frequency band assumed to be unrelated to pain processing.

Limitations

There are a number of limitations to this review that should be acknowledged. Because we sought to summarize the evidence of NF used to modulate any type of pain, inclusion criteria were broad. As a result, the included studies were highly heterogeneous, so that we were not able to conduct a meta-analysis. Another limitation is that our data search was limited to studies published in either English or Spanish. It is possible that we overlooked some additional relevant contributions to the field published in journals written in additional languages.

Summary and Conclusions

This review provides positive preliminary evidence of NF as a potential treatment for chronic pain. However, higher quality studies using similar procedures and outcome measures are still needed to: (1) determine the extent to which promising preliminary studies replicate in order to determine if NF is effective, (2) elucidate the mechanisms of NF treatments on pain, and (3) determine the best NF approach(es) for individuals with chronic pain.

AUTHOR CONTRIBUTIONS

RR conceptualized the study, created the research strategy, selected the studies, and extracted the data. RV contributed to the previous tasks and independently selected the studies. JM and MJ supervised all the steps of the process. All authors participated in the interpretation of the data, drafted the work and revised it critically for important intellectual content, and provided approval for publication of the content.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

4.3 Study III

A neurofeedback-based intervention to reduce pain intensity and improve function in adolescents with chronic back pain: study protocol for a single-blind controlled randomized pilot feasibility trial.

A neurofeedback-based intervention to reduce pain intensity and improve function in adolescents with chronic back pain: study protocol for a single-blind controlled randomized pilot feasibility trial

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Abstract

Background

Chronic back pain is a common condition in adolescents. Treatment recommendations for this population are based on suboptimal-quality or indirect evidence, usually derived from studies including a variety of chronic pain problems. As the brain is crucial in the processing of pain information, neurofeedback, an intervention that has been found to improve pain and pain-related outcomes in adults, might be a potentially beneficial treatment for adolescents with chronic back pain.

Aims

This protocol describes a single-blind sham-controlled randomized pilot trial designed to test the effects on pain intensity and pain-related outcomes, as well as the feasibility, safety and acceptability, of two neurofeedback protocols that have been found to be effective to manage chronic pain when used with adults.

Method

Adolescents aged 11-18 years with chronic back pain will be recruited and randomized to either two active neurofeedback treatment conditions or a sham neurofeedback condition. Outcome measures include pain intensity, pain interference, physical function, psychological function, feasibility, safety and acceptability measures.

Results

This study will investigate the effects of neurofeedback in pain and pain-related outcomes in a sample of adolescents with chronic back pain.

Conclusions

The results of this pilot study will inform and determine the viability of a future fully powered randomized controlled trial.

Key words: Neurofeedback; chronic back pain; electroencephalogram; adolescents.

INTRODUCTION

Chronic back pain is a common problem among adolescents [1], and can negatively impact adolescents' physical, psychological, social, and school function [1–6]. Moreover, chronic pain in children and adolescents is associated with a high societal impact and economic burden [7].

The prevalence of back pain and chronic back pain in youths is high, although the specific rates can vary as a function of the definition used, the study population, and the study design [8,9]. For example, an overview of 27 systematic reviews on back pain in children and adolescents found a monthly prevalence rate ranging from 18% to 24%, with prevalence rates of chronic back pain ranging from 5% to 12% [10]. Moreover, the prevalence and impact of chronic back pain appears to be

increasing in adolescents. For example, Huguet and Miró [11] found a prevalence of 4% in youths aged 8 to 16 years living in Catalonia, while a recent study conducted in the same area with a similar sample showed a prevalence of 16% [1]. In addition, two recent studies using data from the Health Behavior in School-Aged Children study also reported a significant 3% increase in the prevalence of chronic back pain among adolescents aged 11 to 15 years from 2001 to 2014 [9]. This rate of increase was found to be 4% considering four additional years, from 2001 to 2018 [8]. In addition to the significant steady increase in prevalence of chronic back pain, research has shown that chronic back pain during adolescence tends to worsen over time [12]. Moreover, low back pain during childhood and adolescence are predictors of back pain in adulthood [13].

Recently, Frosch and colleagues [14] produced an evidence-based guideline for the treatment of chronic non-specific back pain in children and adolescents. This guideline recommended physical therapy (i.e., physical activity) and psychotherapy (i.e., cognitive behavioral therapy) to treat non-specific pediatric back pain, while intensive interdisciplinary treatment programs were recommended for those children or adolescents with chronic non-specific back pain when unimodal interventions were not effective. In addition, this same study advised against pharmacological interventions or invasive treatments and

advocated for education and physical activity to prevent back pain in children and adolescents. Despite how important this study was, as the first to attempt to summarize the available evidence for treatment options for chronic non-specific back pain in children and adolescents, the aforementioned recommendations were based on suboptimal-quality evidence or indirect evidence (e.g., some recommendations were based on studies that included a wide range of chronic pain conditions). Therefore, additional high-quality research on treatment's efficacy for children and adolescents with back pain and chronic non-specific back pain is warranted.

The brain plays a key role in the onset and maintenance of pain, and can be viewed as the final common pathway to the experience of pain [15]. Consistent with this idea, structural, functional and neurophysiological abnormalities have been identified in the brains of individuals with chronic pain [16–18]. Similarly, EEG patterns in individuals with chronic pain differ from those without chronic pain [19]. For example, one study found that children and adolescents aged 10 to 18 with chronic musculoskeletal pain showed increased resting global delta and beta power compared with healthy controls [20]. As these abnormalities may be reversible with treatment [18,21], it stands to reason to study treatments that target brain activity directly, such as neurofeedback (NF).

NF is a non-invasive treatment that aims to change brain activity in ways that may lead to improved health and comfort. It can help the patient change their brain activity by providing real-time information about brain activity, usually via visual and/or auditory feedback. NF can be performed either by using brain activity measured by EEG, functional Magnetic Resonance Imaging (fMRI) or both [22], although EEG-based NF is the method that has been used and studied the most [23]. Normally, the goal of NF treatment is to increase brain activity that is hypothesized to be associated with reduced pain processing and increased relaxation, and to decrease brain activity that is hypothesized to be associated with the processing of nociceptive information [24].

Several studies have evaluated the use of NF as a treatment for different types of chronic pain. Three systematic reviews and one meta-analysis summarized the data on the use of NF for chronic pain and all concluded that NF is a promising treatment option that improves pain and pain-related outcomes [25–27]. Regarding brain oscillation power-based NF, interventions often included a combination of protocols that increased alpha and sensorimotor rhythm (SMR) power and decreased beta and theta power [27]. Although no protocol has been found to be the most effective, studies that targeted SMR and theta power seemed to achieve a greater pain reduction, especially at the right central of the

scalp [26]. However, these reviews also underlined the need for higher quality studies with more robust designs to establish NF as a widely used treatment option [25–27].

Only three studies have evaluated the effects of NF as a treatment option for chronic low back pain to date. The first was a pilot study testing 20 60-minute sessions of EEG alpha-synchrony NF training in a sample of 16 multi-resistant individuals with chronic low back pain (i.e., individuals who have not responded to other interventions); these investigators found that NF treatment was associated with a non-significant reduction in the severity of outcomes, including pain intensity, anxiety, depression, and disability. Of these, reductions in the severity of anxiety and disability continued for up to 12 months, although this reduction was still not statistically significant, relative to baseline levels [28]. A second study evaluated the effects of six different treatment conditions in a sample of 97 individuals with chronic low back pain: (1) alpha wave NF, (2) CBT, (3) physical therapy, (4) alpha wave NF and CBT (NF-CBT), (5) alpha wave NF and physical therapy (NF-PT), and (6) no treatment controls. The NF condition consisted of three 10-minute sessions per day at home; the CBT condition consisted of eight 50-minute sessions; the physical therapy condition consisted of eight 50-minute sessions and daily home-exercises. Pre- to post-treatment effects were calculated

separately for early chronic pain cases (less than one year from diagnosis) and late chronic pain cases (more than one year from diagnosis). The individuals in NF alone group evidenced a pre- to post-treatment increase in resting state alpha bandwidth power, but no reduction in pain. However, the alpha wave NF-CBT group, the alpha wave NF-PT group, the PT group and the CBT group evidenced a pre- to post-treatment reduction in low back pain intensity in early chronic pain cases. With respect to the late chronic pain cases, only the NF-CBT group and the NF-PT group evidenced pre- to post-treatment reductions in low back pain intensity, with lower effect sizes than evidenced by the early chronic cases [29]. The most recent study was a double-blind randomized placebo-controlled pilot assessing the use of 12 30-minute sessions of infraslow (i.e., 0.0 to 0.1 Hz) NF in 60 individuals with chronic low back pain allocated to four different treatment conditions: (1) up-training infraslow wave activity in the pregenual anterior cingulate cortex (pgACC), (2) down-training infraslow wave activity in both the dorsal anterior cingulate cortex (dACC) and the somatosensory cortex (SSC), (3) simultaneously up-training infraslow wave activity in the pgACC and down-training infraslow wave activity in the dACC and SCC, and (4) placebo NF (i.e., targeting areas unrelated to pain experience). All treatment groups reported reductions in pain severity and related

disability, but the condition up-training infraslow wave activity in the pgACC achieved a higher proportion of participants with clinically meaningful reductions in pain severity and related disability than all the other groups [30].

These three studies assessing the use of NF as a treatment for chronic back pain have been conducted with adult samples. However, NF has the potential to yield even better and longer-lasting results in children and adolescents, as plasticity is higher and brain activity is more malleable in children than in adults [31,32]. As no study to date has assessed the use of NF as a treatment for adolescents with chronic back pain, a pilot study testing the effects, feasibility, safety, acceptability and satisfaction of some of the NF protocols suggested to be more effective [26,27] is warranted.

Given these considerations, the primary aim of this study is to estimate the effects of the two different and viable NF protocols that have been found to be more effective when used with adults on pain intensity in adolescents with chronic back pain. The secondary objectives are to: (1) estimate the effects of two NF protocols on secondary outcomes, (2) determine if there are measurable changes in resting state EEG activity after treatment, and (3) to evaluate the feasibility, safety, and acceptability of NF as a treatment for adolescents with chronic back pain.

METHOD

Design

This protocol describes a single-blind sham-controlled randomized pilot trial. It was written according following the Standard Protocol Items: Recommendations for interventional Trials (SPIRIT) checklist [33] and will follow the Consolidated Standards of Reporting Trials (CONSORT) guidelines [34]. A researcher will randomly assign selected participants using a randomization software to receive one of the two active interventions or the sham intervention. Participants will be blinded to whether they are allocated to one of the two active interventions or to the sham intervention.

Recruitment strategy

Convenience sampling method will be used to recruit participants from Salou, a municipality of the province of Tarragona in Catalonia, Spain. Adolescents who meet inclusion criteria attending the Primary Care Center of Salou will be invited to participate in the study. Secondary and high schools will be contacted and asked to advertise the study to adolescents, providing an email of the principal investigator to any interested student for screening and possible study participation.

Participants

Adolescents aged 11 to 18 with chronic back pain will be eligible to participate. In this study, chronic back pain will be defined as a pain in any region of the back that has lasted for at least 3 months, that was present at least 50% of the time during the 3-month period, and with an average pain intensity of >=4 on an 11-point NRS.

Sample size

This pilot study aims to determine the feasibility of fully powered RCT. Therefore, sample size calculation will not be performed. Based on common procedures for pilot studies [35], a sample of 45 participants (15/group) was deemed enough to achieve the feasibility objective and estimate treatment effects.

Procedure and design

Once potential participants will be screened for eligibility, a researcher will call their parents or legal guardian to describe the study and to invite the adolescent to participate. If the parents or guardians given their consent, both the parents or legal guardians and their son or daughter will be invited to come to the Primary Care Centre to meet with the principal investigator and address any questions they may have about the study and to sign an informed consent. Youths under 14 years of age will require their parents' or legal guardian's consent to participate,

whereas youths aged 15 years or older will provide their own consent. Once the informed consent is signed, and if possible, pretreatment assessment will take place that same day. If not, the pretreatment assessment will be scheduled another day depending on the participants' availability.

Hardware equipment

The electroencephalogram and NF treatment will be obtained and delivered using the ActiCAP slim headset (Brain Products GmbH, Gilching, Germany), the amplifier BrainMaster Discovery 24 (Brainmaster Technologies, Inc, Ohio, USA), a laptop HP OMEN 15 (Intel Core i7-7700HQ CPU @ 2.8 GHZ) and a secondary screen HP OMEN 25 (Hewlett-Packard Inc, California, USA).

Variables and measures

Information on the demographic characteristics will be collected from each participant at pre-treatment whereas the information on the electroencephalography and outcome variables will be collected at pre-treatment, post-treatment, and 3-month follow-up. In addition, participants will also respond to questions about *safety, acceptability and satisfaction.*

Demographic characteristics

Participants will be asked to provide information about their sex, age, and school grade.

Outcome measures

Pain-related characteristics

The frequency of back pain will be assessed using a 5-point Likert scale (1 = "Every day," 2 = "More than once a week," 3 = "Once a week," 4 = "Once or twice times per month," 5 = "Once in the last 3 months") [1]. Also, participants will be asked to report the average back pain intensity in the last 7 days, using a 0-10 Numerical Rating Scale (NRS-11), where 0 = "No pain" and 10 = "Very much pain." This scale has been used extensively and has shown to provide reliable and valid scores when used with children aged 6 years and older [36]. Following the latest recommendations from the International Association for the Study of Pain, chronic back pain will be defined as a pain in any region of the back that has lasted for at least 3 months and that was present at least once a week during this 3-month period [37].

Pain-related interference

Pain interference will be assessed using the Spanish version of the 8-item Pediatric Patient-Reported Outcomes Measurement Information System (PROMIS) Pain Interference scale v2.0 (PROMIS-PI [38]). This questionnaire asks respondents to rate how often pain has interfered

with 8 activities during the last 7 days using a 5-point Likert scale (1= "Never," 2= "Almost never," 3= "Sometimes," 4= "Often," and 5= "Almost always"). Pain interference scores will be obtained by summing the participants' ratings for each item and transforming the summed scores to T-scores. The PROMIS-PI has been shown to provide valid and reliable data of pain interference in children and adolescents [39], including samples of adolescents with chronic back pain [1].

Physical function

Participants will be asked to respond to measures assessing sleep disturbance, mobility, and fatigue. Sleep disturbance will be assessed with the Spanish version of the 5-item PROMIS pediatric Sleep Disturbance short form V1.0 [40]. The PROMIS Sleep Disturbance scale (PROMIS-SD) assess a variety of sleep quality indicators, and ask respondents to indicate the frequency with which they experienced each sleep problem indicator during the last 7 days using a 5-point Likert scale (1 = "Never," 2 = "Almost never," 3 = "Sometimes," 4 = "Often," and 5 = "Almost always"). Responses to each item are summed and transformed to T-Scores. This scale has been shown to provide valid and reliable information about sleep disturbance when used with young individuals [41,42], including samples of adolescents with chronic pain [1].

Mobility will be assessed using the Spanish version of the mobility subscale of the PROMIS Pediatric-25 Profile Form v2.0 [39]. The mobility scale is comprised of 4 items, and asks respondents to indicate how able they were to perform 4 activities during the last 7 days using a 5-point Likert scale (1 = "Not able to do," 2 = "With a lot of trouble," 3 = "With some trouble," 4 = "With a little trouble," and 5 = "With no trouble"). Responses to each item are summed and transformed to T-Scores. Research supports the reliability and validity of the measure when used with adolescents [39] including samples of adolescents with chronic pain [1].

Fatigue will be assessed with the Silhouettes Fatigue Scale (SFS; [43]). The SFS depicts six human silhouettes who appear to have increasing levels of fatigue from left to right, and respondents are asked to select the figure that best represents their average level of fatigue. In this study, participants will have to identify the figure that best represents their average fatigue level during the last 7 days. Standardized instructions will be the following: "*These silhouettes show how much a person can be fatigued. The first silhouette shows no fatigue. The silhouettes show more and more fatigue up to the sixth silhouette that shows severe fatigue. Please, indicate the silhouette that shows how much fatigued you have been during the previous week*." The SFS has shown to provide reliable

and valid data when used with different samples, including individuals with chronic pain [43], English-speaking individuals with physical disabilities and chronic pain [44], and Turkish-speaking individuals with multiple sclerosis [45].

Psychological function

Participants will be asked to respond to measures of anxiety, depression, and cognitive function. Anxiety and depression will be assessed using the Spanish versions of the anxiety and depression subscales of the PROMIS Pediatric-25 Profile Form v2.0 [38]. Each subscale is comprised of 4 items asking to rate the frequency with which they experience 4 anxiety and 4 depressive symptoms in the last seven days using a 5-point Likert scale (1 ="Never," 2 ="Almost never," 3 ="Sometimes," 4 ="Often," and 5 ="Almost always"). Responses to both the anxiety subscale and the depression subscale will be summed and transformed to T-scores. The Pediatric-25 Profile Form scales have been shown to be able to report reliable and valid scores of anxiety and depressive symptoms [40], including samples of Spanish-speaking adolescents with chronic pain [6].

Cognitive function will be assessed with the Spanish version of the 7-item PROMIS pediatric cognitive function short form v1.0 (PROMIS-CF [39,46])**.** With this scale, respondents are asked to indicate how often

they had experienced problems with 7 different cognitive function domains during the last 4 weeks using a 5-point Likert scale (1 = “All the time,” 2 = “Most of the time,” 3 = “Some of the time,” 4 = “A little of the time,” and 5 = “None of the time”). Responses to each item will be summed and transformed to T-scores. Research supports the reliability and validity of the scores of the pediatric form of the PROMIS-CF [39], including samples of Spanish-speaking adolescents with chronic pain [1].

Feasibility, safety, acceptability, and satisfaction

Feasibility will be assessed by measuring adherence (i.e., percentage of the number of sessions that participants will attend of the total number of sessions) and dropout rates (i.e., percentage of participants who will drop out in each group of the total number of participants in each enrolled in each group).

Safety will be measured by asking participants to respond at each visit to the following question: “Have you experienced any adverse effect that you feel was related to the treatment?” Adverse effects will be described as any harmful symptoms reasonably resulting from the treatment.

Acceptability and satisfaction will be measured at post- treatment and at the 3-month follow-up assessment, by asking respondents to rate, (1) "How acceptable was the treatment?" and (2) "How satisfied are you

with the treatment?" on numerical rating scales ranging from 0 (i.e., not acceptable/satisfied at all) to 10 (i.e., extremely acceptable/as satisfied as anyone could be).

EEG recording and analysis

Before the recordings, each participant will be seated in a comfortable position, and their forehead and earlobes will be prepped with Nuprep (Weaver and Company, Aurora, CO). Next, each participant's head circumference will be measured to choose the most appropriate cap size. Then, the electrode cap with pre-measured sites following the 10/20 system will be fit to each participant's head. Each electrode site will be filled with SuperVisc High-Viscosity Electrolyte-Gel (EasyCap GmbH, Herrsching, Germany) and a blunt-tip syringe will be used to gently abrade the skin and move the hair until the impedance values for each active electrode are below 5 *kΩ*. To minimize artifacts in the EEG recording, participants will be asked to follow the following instructions once the recording starts: to remain still, to blink as little as possible, to avoid any facial movements, eye movements, head and neck movements, clenching their teeth and swallowing. EEG data will be digitally recorded using the BrainAvatar 4.6.4 software and 19 Ag/AgCl electrodes (FP1, FP2, F3, F4, Fz, F7, F8, C3, C4, Cz, T3, T4, T5, T6, P3, P4, Pz, O1, and O2) referenced to the left mastoid and with the ground in FPz. The signals will

be recorded using DC and a bandpass filter of 0.3-60 Hz, at a 256 Hz sampling rate.

Resting-state EEG will be recorded for 10 min (eyes open condition), while the participant will be instructed to look at a spot on the wall. During each recording, a researcher will monitor the EEG recording and ensure the participant remains awake.

Raw EEG data from each participant will then be exported into the OpenVibe software (Open Platform for Virtual Brain Environments), to be inspected and plotted using manual artifact-rejection. All artifacts (e.g., eye blinks, eye movements, body movements and teeth clenching) will be removed from the stream of EEG, and the first two minutes of artifact free data will be used for analysis. Fast-Fourier Transformation will be used to compute the power spectral density for relative power bands delta (δ 1–3.5 Hz), theta (θ 4–7 Hz), alpha (α 8–12 Hz), SMR (12-15 Hz), beta1 (β1 15–20 Hz), high beta (high β 21-30 Hz), using a 2-second (500 sample) epoch length and an overlapping window advancement factor of 32 samples.

Intervention

For the NF training and the sham-NF condition, the EEG will be recorded from an electrode placed over the right central area (C4). The reference electrode will be placed at the left mastoid and the ground

electrode will be placed at FPz. Bandwidth amplitude values will be transformed into visual feedback. Specifically, participants will be asked to choose a movie from an available selection, as previous studies have suggested bigger learning effects occur when the reinforcer is more relevant for the participant [47]. A dimmer will be overlapped on the screen used to give feedback to the participant. The movie will be played with a clear screen when the subject is meeting the protocol criteria, whereas it will turn opaque when the participant's bandwidth activity moves away from the protocol's criteria.

Participants will be seated in front of the computer screen that will display the selected movie, informed about the feedback system and asked to follow the continuous feedback process by trying to make the screen clear as the movie is played. They will be encouraged to be as relaxed as possible and to focus on the movie. The treatment session will be composed of four 10-min training periods, with a minute to rest between them. The two active treatments and the sham-NF group will all consist in 10 45-min sessions conducted twice a week. Protocol A will aim to increase SMR activity (12-15 Hz) and decrease θ activity (4-7 Hz) from an electrode placed over the right central area (C4). Protocol B will aim to increase α activity (8–12 Hz) and decrease θ activity and high β activity (21-30 Hz) from an electrode placed over the right central area (C4). The

conditions for the sham NF group will be identical to those in the active group except for the origin of the feedback displayed to participants. Specifically, pre-recorded sessions with healthy individuals will be used to display the feedback. Thus, it will be a pre-recorded session that will drive the reinforcement, irrespective of the participants actual EEG.

Data analyses

For descriptive purposes, we will compute means and standard deviations for continuous variables, and number and percentages for categorical variables at baseline for the whole sample and for each study arm. Then, continuous variables will be compared between the three intervention groups using an ANOVA and categorical variables will be compared using a chi-square test.

To address the primary aim, that is, to estimate the effects of two NF protocols on pain intensity in adolescents with chronic back pain, we will conduct a series of mixed ANOVAs, with group allocation as the between group factor and time as the within-subject factor. We will estimate the effect size for the overall group effect, and also perform a univariate t-tests to estimate the effect sizes related to differences in pain intensity between each time point and between each treatment condition. The primary variable of interest will be the effect sizes of the representing difference in pain intensity between the two active

treatment conditions and the sham condition. In addition, we will compute the percent of change in pain intensity associated with each treatment condition, in order to identify the percentage of participants achieving clinically meaningful reductions in pain intensity (in this study defined by a reduction of 30% or more; [48]).

To address the aim of estimating the effects of two NF protocols on secondary outcomes, that is, the rest of clinical measures and resting EEG activity, we will also conduct a series of mixed ANOVAs, with group allocation as the between group factor and time as the within-subject factor. As we have planned for the primary outcome variable, we will also conduct a series of univariate t-tests to estimate the differences in each outcome between each time point and between each treatment condition for the secondary outcomes.

Finally, to address the last aim – that is, to understand the feasibility, safety, and acceptability of the NF protocols – we will compute descriptive statistics for the measures of each feasibility domain, consistent with recommendations for feasibility studies [49]. Our *a priori* criteria to conclude that a fully-powered clinical trial to test one or both of the protocols is feasible are: (1) protocol will achieve an adherence of =>80% and a dropout rate of =<20%. The criteria to conclude that that the interventions are safe will be a lack of adverse events bothersome

enough to cause participants to seek medical treatment. Last, our criteria to conclude that one or both of the interventions are acceptable will be the achievement of ≥ than 7 in the acceptability and satisfaction questions. Although the study is not powered to detect statistically significant effects and will focus on the estimate of effect sizes, we will report significant effect if they emerge, using a *P* value of < .05. Statistical analyses will be conducted using STATA 14 (Stata Corp., TX, USA).

Ethical approval

The study will be conducted in agreement with the principles of the Helsinki Declaration and the guidelines of Good Clinical Practice. Informed consent will be obtained from participants and/or participants parents prior to the study enrolment. The study protocol was submitted to the Clinical Research Ethics Committee (CEIC) of the Primary Care Research Institute (IDIAP) Jordi Gol, and is pending to be approved.

DISCUSSION

This study will estimate the effect sizes associated with two different NF protocols for reducing pain intensity and producing improvements in a number of secondary outcomes in a sample of adolescents with chronic back pain. To the best of our knowledge, this is the first study that will assess the effects of two NF protocols that have

previously been useful to decrease chronic pain in adults in a sample of adolescents with chronic back pain, using a sham-NF control group. The results of this study will provide preliminary information in regard to the efficacy, feasibility, safety, acceptability and satisfaction of NF as a treatment to improve function in adolescents with chronic back pain. The findings will then be used to inform the design of a fully powered and definitive clinical trial to evaluate the effects of NF in adolescents with chronic back pain.

Conclusions

We expect that the results of this study will shed light into the potential of NF as a treatment for adolescents with chronic back pain. In addition, if the improvements in the study outcomes are similar to those found by previous studies with adult samples, we expect that this will pave the way for further research into the use of NF not only as a treatment for adolescents with chronic back pain, but also for other chronic pain conditions in youths.

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5. Discussion

This dissertation has focused on the potential use of neurofeedback as a treatment for adolescents with chronic back pain.

5.1 Trends of chronic back pain in adolescents

The first objective was "to study the prevalence of chronic back pain in adolescents and examine its trend over time". This aim was pursued by conducting a secondary analysis of data from 650,851 adolescents from 33 countries or regions, retrieved from four consecutive waves (2001/02, 2005/06, 2009/10 and 2013/14) of the HBSC study. The key findings of this study were that the prevalence of chronic back pain was higher (1) in each successive wave over time, (2) in girls compared to boys, and (3) in older adolescents compared to younger ones. In addition to this, we also found that the increase in the prevalence of chronic back pain over time was significantly higher in older girls compared to younger girls, and in older boys compared to younger boys. In short, the prevalence of chronic back pain in adolescents increased a 3.3% from 2001/02 to 2013/14, and this increase ranged between 1% in 11-year-old boys and 7% in 15-year-old girls. The results of Study I contributed to confirm the hypothesis that the prevalence of chronic pain in children and adolescents

has increased over the last decades (Calvo-Muñoz et al., 2013; King et al., 2011; Potrebny et al., 2017).

Before we conducted Study I, only two studies based on Finnish samples had examined the trends in the prevalence of back pain among adolescents over time. Our findings were similar to those reported by Hakala and colleagues (2002), that also found an increase in the prevalence of low back pain from 1991 to 2001. However, they were different from those reported by Ståhl and colleagues (2014), that observed no changes in the prevalence of low back pain over a longer period of time, specifically from 1991 to 2011. Since we conducted Study I, a couple studies have also used HBSC data to examine the prevalence of chronic back pain in adolescents over time. The first one expanded our study with the inclusion of the next HBSC survey wave available (i.e., 2017/18), and found an additional 0.5% increase in the prevalence of chronic back pain in adolescents from 2013/14 to 2017/18 (Roman-Juan et al., 2022). The second study examined the prevalence of chronic back pain in Danish adolescents from 1991/92 to 2017/18, using a more restrictive definition of chronic back pain (i.e., daily or several days a week during the last 6 months). Despite the use of this different definition, this study also found that the prevalence of chronic back pain had significantly increased from 8.9% in 1991/92 to 11.7% in 2018.

These additional studies support the validity of our findings, showing that the prevalence of chronic back pain in adolescents has increased over the last two decades, and should warrant increased efforts in terms of prevention and treatment for this condition and population. Research has shown that a substantial percentage of adolescents with chronic back pain might continue to experience chronic pain into adulthood (Hestbaek et al., 2006; Stevens & Zempsky, 2021). Therefore, the increasing prevalence of chronic back pain in adolescents might in turn increase the number of adults that will have chronic back pain. And this is no trivial matter, as at the moment low back pain is already the leading cause of years lived with disability when analyzed globally, with the subsequent impact this has on health and social systems (Wu et al., 2020).

5.2 Neurofeedback for adolescents with chronic back pain

The second objective was "to learn about the current state of knowledge regarding the use of neurofeedback as a treatment for chronic pain". The findings from Study II indicate that neurofeedback has the potential to decrease pain and improve pain-related outcomes in adults with chronic pain. Most of the studies included in the review found significant pre- to post-treatment reductions in pain intensity and/or

frequency (i.e., number of migraines), with some of these improvements being sustained at follow-up. Likewise, most of the studies found significant improvements in pain-related outcomes, such psychological symptoms, fatigue, and pain-related interference. However, the high degree of heterogeneity in several aspects of the included studies did not allow to draw strong conclusions regarding the efficacy and mechanisms of neurofeedback for chronic pain. We now address some of these issues, as they were carefully considered to devise Study III.

First, several types of neurofeedback were used in the reviewed studies, most of them EEG-based. The type of neurofeedback that was used the most was brain oscillation power-based neurofeedback. However, within each type of neurofeedback, several protocols were used to the extent that no two studies evaluated the exact same protocol (i.e., different frequencies targeted, different electrode locations, different number of sessions). Second, the samples of the included studies were very heterogenous. The most common condition was migraines, although several other pain problems were evaluated. Except for one study, samples were comprised by adults. Third, the purpose for which neurofeedback was used was not always the same. Although most studies evaluated neurofeedback as a treatment for clinical pain, two used it to enhance the effect of hypnosis and four studies were experimental, with

laboratory induced pain. Fourth, several studies did not assess brain activity, and those that did used different domains of brain activity. Finally, the quality of the included studies was mixed. Most of the studies were pilots with small sample sizes, lacking adequate control conditions, and proper follow-up assessments.

Next, we elaborate on how we addressed these limitations and considerations to devise a methodologically sound trial in Study III. It is important to note that despite it is our intention to conduct a fully powered randomized controlled trial (RCT), we prepared a protocol for a pilot feasibility trial, as this type of study plays a key role in improving the quality of a definitive RCT by allowing to test preliminary effects, identify potential improvements and address the feasibility of the intervention (Eldridge et al., 2016).

The type of neurofeedback that we opted for is the brain oscillation power-based neurofeedback, as it is the one that has been studied the most, showing positive findings. The neurofeedback protocols to be used were chosen based on the findings from Study II (Roy et al., 2020) and the subsequent meta-analyses on the effects of neurofeedback for chronic pain (Hesam-Shariati et al., 2022; Patel et al., 2020). Protocol A, aiming to increase SMR activity (12-15 Hz) and decrease θ activity (4-7 Hz) from an electrode placed over the right central area (C4), was chosen

because it was the one that has achieved the highest reduction in pain intensity. Protocol B, aiming to increase α activity (8–12 Hz) and decrease θ activity and high β activity (21-30 Hz), was chosen because it was the most commonly assessed as a treatment for chronic pain.

In regard to the sample, the intervention has been developed to be used with adolescents aged 11 to 18 with chronic back pain. We believe it is important to note that this is the first study using neurofeedback as a treatment for this population, and the second to use neurofeedback as a treatment for chronic pain in youths. Neurofeedback might be able to yield even better and longer-lasting results in this population, as plasticity is higher and brain activity is more malleable in children than in adults (Erpelding et al., 2016; Freitas et al., 2011).

On another note, we also plan to include the changes in brain activity (i.e., resting state EEG) as an outcome. This is crucial for two reasons. First, because studies assessing the EEG pattern of youths with chronic pain are scarce (Ocay et al., 2022). In fact, to our knowledge no prior study has studied the EEG of adolescents with chronic back pain. Conducting studies on this subject is important, as it is very likely that EEG patterns of adolescents with chronic pain differ from those found in adults. And second, as neurofeedback intends to alter brain activity, it is paramount to include a brain activity outcome (i.e., resting state EEG pre-

and post-treatment) to assess if the treatment achieved the desired effects, that is to say, brain activity changes (Rogala et al., 2016).

Last, we took several steps to ensure a study as methodologically robust as possible. First, participants are to be randomized into the two active conditions or the control group. In addition to this, participants will be blinded in regard to whether they are assigned to an active treatment condition or the control condition. Second, the control condition will consist of a sham neurofeedback intervention. This is particularly important, because some studies have suggested that neurofeedback effects are due to non-specific effects (i.e., placebo effect; Thibault et al., 2018). In addition, and to ensure the improvements in pain intensity and pain-related outcomes endured, we have planned a 3-month follow-up assessment.

To our knowledge, the study described in the protocol will be the first one to assess the effects of two neurofeedback protocols, that have been previously used, and found efficacious (Al-Taleb et al., 2019; Kayıran et al., 2010; Vučković et al., 2019), to decrease chronic pain in adults, in a sample of adolescents with chronic back pain. If positive, the results of this pilot will warrant a fully powered RCT testing the efficacy of neurofeedback as a treatment for chronic back pain in adolescents.

Similarly, it might also encourage additional research into neurofeedback as a potential treatment for other pain problems in adolescents.

The interest in neurofeedback for chronic pain management has been growing, as shown by the increase in the number of publications on the subject. Since we performed the systematic review in Study II (July 2020), two meta-analyses (Hesam-Shariati et al., 2022; Patel et al., 2020) have also assessed the evidence of neurofeedback as a treatment for chronic pain, reaching similar conclusions to ours. Noteworthy, three studies have been conducted using neurofeedback as a treatment for chronic low back pain in adults (Adhia et al., 2023; Mayaud et al., 2019; Shimizu et al., 2022). All three studies reported generally positive results using different neurofeedback approaches. However, it was the study conducted by Adhia and colleagues (2023), using infraslow neurofeedback (i.e., 0.0 to 0.1 Hz), that achieved the greatest reductions in pain severity and related disability. More details about these three studies are reported in Study III.

6. Conclusions

The main conclusions of this dissertation are the following:

1. The prevalence of chronic back pain in adolescents has significantly increased over the last two decades, especially in older girls. In light of this, additional resources and efforts to improve the management of chronic back pain in this population are warranted.

2. Despite the fact that higher research quality is needed, neurofeedback has the potential to decrease pain and improve function in individuals with chronic pain.

3. The results of the pilot feasibility trial study will provide preliminary data on the effects of neurofeedback as a treatment for adolescents with chronic back pain, that if positive, might warrant a fully powered RCT and further research into the effects of neurofeedback for other pain problems in children and adolescents.

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