**EFFECTS OF NEUROFEEDBACK IN THE MANAGEMENT OF CHRONIC PAIN: A SYSTEMATIC REVIEW AND META-ANALYSIS OF CLINICAL TRIALS**

**Running Head:** Neurofeedback for Chronic Pain: Systematic Review

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**Significance:** Neurofeedback is a novel neuromodulatory approach which can be used to reduce the severity of pain and pain-associated symptoms such sleep disturbances, mood disturbances, fatigue and anxiety in a number of chronic pain conditions. It has a potential to provide integrative non-pharmacological management for chronic pain patients with pain refractory to pharmacological agents with high side-effect profiles. Further high-quality double-blinded randomised sham-controlled trials are needed in order to fully explore the potential of this therapy.

## 1. ABSTRACT

**Background and Objective:** Neurofeedback provides real-time feedback about neurophysiological signals to patients, thereby encouraging modulation of pain-associated brain activity. This review aims to evaluate the effectiveness and safety of neurofeedback in alleviating pain and pain-associated symptoms in chronic pain patients.

**Methods:** MEDLINE, PUBMED, Web of Science and PsycINFO databases were searched using the strategy: (“Neurofeedback” OR “EEG Biofeedback” OR “fMRI Biofeedback”) AND (“Pain” or “Chronic Pain”). Clinical trials reporting changes in pain following electroencephalogram (EEG) or functional magnetic resonance imaging (fMRI) neurofeedback in chronic pain patients were included. Only Randomised-controlled trials (RCT), non-randomised controlled trials (NRCT) and case series were included. Effect size was pooled for all RCTs in a meta-analysis.

**Results:** Twenty-one studies were included. Reduction in pain following neurofeedback was reported by one high-quality RCT, five of six NRCT or low-quality RCT and thirteen of fourteen case-series. Pain reduction reported by studies ranged from 6% to 82%, with ten studies reporting a clinically significant reduction in pain of >30%. The overall effect size was -0.76 (95% Confidence Interval -1.31 to -0.20). Studies were highly heterogenous [Q(df=5)=18.46, p<0.002, I2=73%]. Improvements in depression, anxiety, fatigue and sleep were also seen in some studies. Common side-effects included headache, nausea and drowsiness. These generally did not lead to withdrawal of therapy except in one study.

**Conclusions:** Neurofeedback is a novel therapy with promising but largely low-quality evidence supporting its use in chronic pain. Further high-quality trials comparing different protocols is warranted to determine the most efficacious way to deliver neurofeedback.

## 2. INTRODUCTION

Chronic pain affects approximately 35-50% of the UK population (Fayaz et al., 2016). The costs of chronic pain ($560-$630 billion in the US in 2010) are much greater than the costs associated with heart disease ($309 billion) and cancer ($243 billion) (Gaskin & Richard, 2012). Nevertheless, pain is inadequately controlled in 40-60% of chronic pain patients despite the numerous medications available (Breivik et al., 2006, 2009). Therefore, non-pharmacological therapies are being increasingly explored (Jensen et al., 2014).

Pain perception is a complex process, whereby the pain perceived by an individual is an integration of current information about the sensory stimulation and prior information from previous experiences which influence the emotions, attention and expectations of the individual about the pain (Ossipov et al., 2010). In order to target these higher-order processes, several studies have been performed to identify neurophysiological correlates of chronic pain (Boord et al., 2008; Dos Santos Pinheiro et al., 2016; Lim et al., 2016; Sarnthein et al., 2006). In general, chronic pain is associated with a relative decrease in alpha, increase in beta and increase in theta activity in electroencephalogram recordings (Jensen et al., 2009). These correlates of pain have been used to develop brain “training protocols” which help patients to increase or decrease their brain activity in the direction associated with pain-relief (Jensen et al., 2009).

Neurofeedback (NFB) is a novel technique which teaches individuals to self-regulate their brain activity by showing them real-time measurements of their electroencephalogram (EEG) or Functional Magnetic Resonance Imaging (fMRI) signals (Bagdasaryan & Le Van Quyen, 2013) [Figure 1]. Neurofeedback has been used to reduce the severity of many neuropsychiatric conditions such as Attention Deficit Hyperactivity Disorder (Van Doren et al., 2019), depression and anxiety (Schoenberg & David, 2014) and stroke rehabilitation (Carvalho et al., 2019) for example. Many studies have been conducted recently in different pain syndromes such as fibromyalgia (Kayıran et al., 2010), chemotherapy-induced neuropathy (Prinsloo et al., 2018) and central neuropathic pain (Vučković et al., 2019), however, no reviews have been performed to synthesise the evidence available thus far regarding the efficacy of neurofeedback in different chronic pain conditions.

Neurofeedback has also been used in the management of other symptoms such as anxiety and mood disturbances (Markiewicz, 2017), insomnia (Lima et al., 2019), fatigue (Luctkar-Flude & Groll, 2015). However, very few studies have looked at improvements in these symptoms in the context of pain. As these factors play a major role in an individual’s experience of pain (Bushnell et al., 2013; Reddan et al., 2019), it is essential to know whether neurofeedback can act as an integrative therapy targeting multiple psychosocial aspects of pain. Only one such review has been performed where improvements in pain-associated symptoms (Hetkamp et al., 2019) have been studied in cancer patients. However, no reviews have evaluated the effectiveness of neurofeedback in the management of pain-associated symptoms in other chronic pain syndromes. This review aims to evaluate the efficacy and safety of neurofeedback in alleviating pain and pain-associated symptoms in different chronic pain conditions.

**[Figure 1]**

## 4. LITERATURE SEARCH METHODS

This systematic review and meta-analysis was conducted as per the guidelines outlined by Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement (Moher et al., 2014).

**4.1 Search Strategy**

Relevant studies were identified by conducting a search of current literature using four databases: MEDLINE, PUBMED, PsycINFO and Web of Science. The search strategy used for a comprehensive search was as follows: (“Neurofeedback” OR “EEG Biofeedback” OR “fMRI Biofeedback”) AND (“Pain” or “Chronic Pain”).

**4.2 Inclusion and Exclusion Criteria**

**Population**

Clinical studies involving adults with chronic pain were included. Chronic pain was defined as pain lasting longer than three months in accordance with the International Classification of Disease guidelines (Treede et al., 2015). Non-clinical studies which use experimental pain models, whereby pain is induced through external stimulation in healthy individuals, were excluded.

**Intervention**

Neurofeedback was defined as any EEG or fMRI-based feedback training where the patients are actively participating in the modulation of their neurophysiological signals, therefore, are being trained to increase voluntary control over their brain activity. As a result, studies which used a passive form of feedback, where photic or electromagnetic stimulations were used to alter the neurophysiological signals without active input from the patients, were excluded. Studies which provided only Electromyogram (EMG) biofeedback were also excluded.

**Study Design**

Only primary research studies were included. This comprised randomized controlled trials (RCT), non-randomized controlled trials and case-series. Reviews, case-reports and editorial reports were excluded.

**Outcomes**

Studies had to report changes in pain in order to be included in this review. Studies could also include other measures such as fatigue, sleep and cognition in addition to pain.

**4.3 Selection Process**

All studies identified using the specified search strategy from the four databases were first screened using the title and the abstract. Abstracts were included or excluded based on the criteria defined above. Only publications written in English were included. Abstracts which met the criteria were then rescreened using the full-text article. These were assessed for their methodological quality and reporting of outcomes prior to final inclusion in the review. The finalised studies were then critically appraised. All screening, grading and data extraction were undertaken by two independent reviewers, KP and HS, and a third reviewer, MS, was involved in cases of disagreement.

**4.4 Quality Assessment**

All the studies included in this review were graded using the Oxford Centre for Evidence-Based Medicine (OCEBM) 2011 Level of Evidence Tool (Howick et al., 2011). The initial level of evidence was assigned depending on the type of study.

The grading system is summarised as follows:

* Level I Evidence: Systematic Review of RCT or n-of-1 Trial
* Level II Evidence: Well-designed Randomized Controlled Trials
* Level III Evidence: Non-randomised Controlled Trials (RCT with a risk of bias due to flaws in randomization, blinding, confounders, attrition and data collection method were graded down to Level III)
* Level IV Evidence: Case-series
* Level V Evidence: Mechanism-based reasoning

Risk of bias was assessed in the following domains and studies were considered to be at high risk of bias and graded down if:

* Randomisation: Study did not report any appropriate method for randomisation of participants
* Blinding: Study protocol was not double-blinded
* Confounders: Study reported baseline characteristics of the two arms to be different for variables which could affect the outcome of patients
* Attrition : Study had a follow-up rate of less than 80%
* Data Collection: Study did not treat the two groups equally in terms of additional tests, questionnaires and follow-up to assess clinical outcomes

**4.5 Data Extraction**

Relevant information was extracted using a standardised data collection form. Details of each study were then summarized in a table which has been included in this review. The following data was extracted: patient population/sample size, control group/sample size, neurofeedback intervention (neurofeedback target i.e. frequencies rewarded/inhibited, brain regions/electrodes used, whether statistically significant change in signal was achieved, neurofeedback system, form of feedback stimulus, duration of session, number of sessions, duration of training), details about control group, concomitant therapy such as pharmacotherapy, physical therapy or psychotherapy provided alongside neurofeedback, outcome measures used, mean pain ratings pre and post treatment in intervention and control group with standard deviations, % reduction in pain ratings from baseline, results (outcomes were divided into two depending on whether change in outcome measure after neurofeedback was statistically significant), follow-up period post-treatment and whether pain reduction was sustained at follow-up and adverse events.

**4.6 Data Synthesis**

The key parameters of all studies were presented and described in the form of a bubble plot. Studies were shown as individual bubbles with the % reduction in pain ratings on y-axis and number of training sessions on the x-axis. The size of the bubble was determined by the sample size and the colour determined by the target feedback signals. Studies reporting insufficient information regarding these parameters were not included.

Randomised controlled trials were combined in a meta-analysis. The effect size of the intervention was determined based on standardised weighted mean difference. Standardised weighted mean difference, Cohen’s *d*, between intervention and control group was calculated for the continuous data on post-treatment pain ratings which was measured using a number of different measurement scales. The studies were weighted by the inverse variance such that studies with smaller variance and likely larger sample size were given more weight. The meta-analysis was performed in Review Manager 5.3 using Random Effects models and the results were presented as a forest plot.

A negative effect size suggested that pain ratings were lower in the intervention compared to control group, therefore, favouring the conclusion of pain reduction following neurofeedback. An overall combined effect size with 95% confidence interval was calculated. The magnitude of the overall combined effect size, as given by Cohen’s d, was interpreted as follows: 0.20-0.49 small, 0.50-0.79 medium and >0.80 large (Lachenbruch & Cohen, 1989). Statistical heterogeneity was tested using the I2 statistics which estimates the percentage of variation in the effect sizes which can be attributed to unique differences in true population effect size between the studies in addition to sampling error. Possible publication bias would be determined using funnel plots and Eggers’ test.

## 5. RESULTS

**5.1 Study Selection**

Figure 2 summarizes the number of studies screened at each stage of the selection process. A total of 240 studies were identified from searching the databases. From these, 192 were excluded and 48 included based on the title and abstract. A further 27 articles were excluded based on full text for the reasons detailed in Figure 2. Finally, the remaining 21 studies were included in this review and critically appraised.

**[Figure 2]**

**5.2 Study Characteristics**

The details of all the included studies have been provided in Table 1. Several chronic pain conditions have been investigated with four studies in Fibromyalgia (Caro & Winter, 2011; Goldway et al., 2019; Kayiran et al., 2007; Kayıran et al., 2010), 5 in Central Neuropathic Pain in Paraplegic patients (Al-Taleb et al., 2019; Hassan et al., 2015; Jensen, Gertz, et al., 2013; Jensen, Sherlin, et al., 2013; Vučković et al., 2019), 2 in Traumatic Brain Injury (Elbogen et al., 2019; Hershaw et al., 2020), 1 in Chemotherapy-Induced Peripheral Neuropathy (Prinsloo et al., 2018), 1 in Primary Headache (Farahani et al., 2014), 1 in Complex Regional Pain Syndrome Type I (Jensen et al., 2007), 1 in Post-Herpetic Neuralgia (Guan et al., 2015) and 1 in chronic lower back pain (Mayaud et al., 2019). 5 studies had a cohort with a mixture of chronic pain conditions (DeCharms et al., 2005; Ibric & Dragomirescu, 2009; Koberda, 2015b, 2015a; Koberda et al., 2013). Sample size ranged from 3 to 41 patients. In total, 491 patients were followed-up across the 21 studies included.

**[Table 1]**

**5.3 Risk of Bias**

In this review, 1 study was of Level II Evidence, 6 studies were of Level III Evidence and 14 studies were of Level IV Evidence. Most neurofeedback studies were case-series, precisely 14, with only the intervention group and no control group. The other seven studies had a control group; however, only one of these was a high-quality Level II randomised controlled trial (Guan et al., 2015). The remaining six controlled trials were either non-randomised or had methodological weaknesses, and hence were graded down as Level III evidence.

Table 2 summarises the results of critical appraisal of the controlled trials included in this review. There were three key sources of bias– lack of randomisation, high attrition rate and lack of appropriate blinding. Factors commonly reported to lead to attrition included co-existing illnesses (Al-Taleb et al., 2019; Jensen, Gertz, et al., 2013), transportation (Hassan et al., 2015; Mayaud et al., 2019; Prinsloo et al., 2018), perceived ineffectiveness of treatment (Hassan et al., 2015; Jensen, Gertz, et al., 2013), personal issues (Prinsloo et al., 2018), death due to factors not associated with the intervention (Prinsloo et al., 2018) and moving residence (Al-Taleb et al., 2019; Jensen, Gertz, et al., 2013; Prinsloo et al., 2018; Vučković et al., 2019).

More importantly, lack of blinding was the source of bias in five studies (Caro & Winter, 2011; Farahani et al., 2014; Jensen, Sherlin, et al., 2013; Kayıran et al., 2010; Prinsloo et al., 2018). In the study conducted by Farahani et al. (2014 and Prinsloo et al. (2018), the control group received no treatment or intervention. Jensen, Sherlin, Askew, et al. (2013) provided sham transcranial direct current stimulation to the control group. In the study by Kayiran et al. (2007), the control group received Escitalopram 10 mg per day whereas in the study by Caro & Winter (2011) they received the standard medical care. Whilst these control groups enabled comparison of neurofeedback to standard medical care and other interventions, the form of intervention used in these control groups meant that blinding could not be performed appropriately as the patients would be aware of the treatment they were receiving. This could lead to differences in pain scores reported by the patients as this might depend on the belief of the patient in the intervention. Only two studies (Goldway et al., 2019; Guan et al., 2015) implemented sham neurofeedback in the control group which was an appropriate control as the patients would truly not be aware whether they were receiving real-time neurofeedback or not. Of these two, one study (Goldway et al., 2019) had to be downgraded despite proper randomisation and blinding due to high attrition rates.

Amongst the two studies providing sham neurofeedback to the control group, there were differences in terms of what constituted the sham treatment. In the fMRI neurofeedback study by Guan et al. (2015) sham neurofeedback involved provision of feedback based on signals from a brain region different to the intervention group. Selection of a particular brain region to provide sham neurofeedback raises the potential issue of selecting a region which might be an unknown component of the pain matrix, therefore, not guaranteeing that such sham feedback will not affect pain perception. An alternative way in which sham neurofeedback has been delivered is through provision of signals from a different patient (Goldway et al., 2019). This can be thought of as a more valid sham treatment as the patient is not truly receiving feedback about their own control over the EEG oscillations and the visual/auditory stimulus that they are presented is independent on their brain oscillations. However, this might increase the attrition rate as it can lead to frustration and lack of perceived control amongst participants.

**[Table 2]**

**5.4 Results of Studies**

**5.4.1 Neurofeedback Interventions**

Overall, the neurofeedback studies can be divided into EEG and fMRI driven neurofeedback. EEG neurofeedback was more widely investigated, precisely by 18 studies, whereas fMRI neurofeedback was investigated by only three studies.

EEG Neurofeedback involved feedback of real-time EEG recordings of the patient. EEG oscillations investigated in these studies are conventionally categorized based on their frequency into theta (4-7 Hz), alpha (8-12 Hz), low beta or beta1 (15-20 Hz) and high beta or beta2 (22-30 Hz). Another oscillation which is widely investigated is sensorimotor rhythm (SMR). SMR refers to oscillations in the 12-15 Hz range which appear in a spindle-like pattern over the sensorimotor cortex during idling of the motor cortex (Collura & Siever, 2009; Timmers, 2013). Motor execution or motor imagery which causes to activation of the motor cortex leads to a decrease in measured SMR (Timmers, 2013).

Within EEG neurofeedback, the frequencies which were rewarded and inhibited varied. 2 studies increased alpha alone (Elbogen et al., 2019; Mayaud et al., 2019), 2 studies increased alpha and decreased beta (Jensen, Sherlin, et al., 2013; Prinsloo et al., 2018), 4 studies increased alpha, decreased beta and decreased theta (Al-Taleb et al., 2019; Hassan et al., 2015; Jensen, Gertz, et al., 2013; Vučković et al., 2019), 2 studies increased SMR and decreased theta (Kayiran et al., 2007; Kayıran et al., 2010), 3 studies increased SMR, decreased theta and decreased beta (Caro & Winter, 2011; Farahani et al., 2014; Ibric & Dragomirescu, 2009) and 1 study increased alpha and SMR and decreased beta and theta (Hassan et al., 2015). The scalp regions used to provide neurofeedback varied widely between studies. Electrodes used by the studies in this review include C3, C4, Cz, T3, T4, FP1, P3 and P4 [Figure 3].

**[Figure 3]**

In contrast to EEG neurofeedback, fMRI Neurofeedback detected activation of particular brain areas by analysing Blood-oxygen level-dependent (BOLD) signals from the area of interest. This information was fed back to the patient in order to decrease or increase the BOLD signal (Hawkinson et al., 2012). For example, fMRI neurofeedback was used to decrease the activation of areas associated with pain perception such as anterior cingulate cortex (Guan et al., 2015). This form of neurofeedback suffers from a lag of 5-8 sec inherent in the BOLD response relative to the neural activity that produced it, in contrast to the near-instantaneous estimation of power form EEG recordings (Hawkinson et al., 2012).

There is a large heterogeneity in the neurofeedback systems, approaches and protocols used in the included EEG and fMRI studies. Most studies provided feedback in a visual or auditory format. The number of neurofeedback sessions conducted by the included studies ranged from 1 to 145 with most studies offering 20-40 sessions. Most studies provided 30-45 min of neurofeedback per session broken down into sub-sessions. The frequency of training session varied from 1 per week to 5 per week. None of the studies report the possibility of patients self-exercising at home without feedback signal at home following training, therefore the chances of such practice increasing effectiveness of the practice session cannot be determined.

**5.4.2 Efficacy of Neurofeedback in Chronic Pain Management**

**EEG Neurofeedback**

Fourteen studies provided neurofeedback to change oscillatory power. There were no Level II studies on Power EEG Neurofeedback, 5 level III studies (Caro & Winter, 2011; Farahani et al., 2014; Jensen, Sherlin, et al., 2013; Kayıran et al., 2010; Prinsloo et al., 2018) and 9 Level IV studies (Al-Taleb et al., 2019; Elbogen et al., 2019; Hassan et al., 2015; Ibric & Dragomirescu, 2009; Jensen et al., 2007; Jensen, Gertz, et al., 2013; Kayiran et al., 2007; Mayaud et al., 2019; Vučković et al., 2019). All studies reported a significant reduction in pain after neurofeedback therapy except one Level III study (Jensen, Sherlin, et al., 2013). This study only provided one single session of neurofeedback which lasted 20 min. The reduction in pain ratings reported by the studies were in the range of 6% to 82% from baseline. Ten studies reported a reduction in pain of >30% which is considered to be clinically significant (Dworkin et al., 2005). One of the studies which strikingly stands out is by Kayıran et al., (2010) which demonstrated a reduction in pain ratings of 82% over the course of neurofeedback therapy. This was the only study with the protocol combining an increase in SMR and a decrease in theta. In addition, this study provided training sessions five times per week which is the most frequent administration of neurofeedback amongst all the included neurofeedback studies in this review.

Additionally, these improvements in symptoms were sustained for longer periods of time in all seven studies which followed-up patients beyond treatment period (Goldway et al., 2019; Hassan et al., 2015; Hershaw et al., 2020; Jensen, Gertz, et al., 2013; Kayıran et al., 2010; Mayaud et al., 2019; Prinsloo et al., 2018). Most of these studies followed the patients for around 3-6 months (Table 1), but one study followed the patients for as long as approximately 16 months. This long-term effect of neurofeedback suggests that any improvement in symptom is more likely to be due to the therapeutic effect rather than placebo.

Four Level IV studies (Hershaw et al., 2020; Koberda, 2015a, 2015b; Koberda et al., 2013) have been reported using Z-Score Neurofeedback. All studies report a reduction in pain. However, these improvements seen in case studies have not been subsequently investigated by any controlled trials.

**fMRI Neurofeedback**

Only three studies investigating fMRI neurofeedback were included – one Level II (Guan et al., 2015), one Level III study (Goldway et al., 2019) and one Level IV study(DeCharms et al., 2005). The only Level II study was compromised by a small sample size (Guan et al., 2015). All studies reported a reduction in pain ratings, although one of the studies reported that pain reduction occurred at follow-up rather than immediately post-therapy.

**5.5 Synthesis of Results**

Figure 4 shows the result of the meta-analysis presented as a forest plot of the six randomised controlled trials included in this review. Using the random effects model, the overall effect of neurofeedback in chronic pain patients was statistically significant (*d*=-0.76, 95% CI [-1.31, -0.20]). This represents a medium effect size according to the criteria of interpretation of Cohen’s *d* (Lachenbruch & Cohen, 1989). The meta-analysis revealed a high heterogeneity value [Q (df = 5) = 18.46, p<0.002] corresponding to a high value for I2 of 73%. A funnel plot was not created due to the small number of studies included in the meta-analysis.

**[Figure 4]**

**5.6 Additional Analysis**

**5.6.1 Factors influencing Pain Reduction**

Figure 5 shows the bubble plot demonstrating the impact of target signal, number of training sessions and sample size on the % reduction in pain ratings from baseline reported by different neurofeedback studies.

Neurofeedback studies which increased SMR and decreased theta (light green bubbles) were very effective in reducing pain as both studies reported a >50% reduction in pain. However, decreasing beta in addition to these two frequencies (dark green bubbles) reduced the effectiveness of the training. Increasing the number of training sessions increased pain reduction for both of these protocols.

Neurofeedback studies which increased alpha and decreased beta or increased alpha, decreased beta and decreased theta were moderately effective. Effectiveness increased with increasing number of training sessions. Increasing alpha in isolation was less effective, however only one study investigated this protocol.

Results of fMRI neurofeedback studies were highly variable and did not show any obvious trends. However, these results might have been due to the small sample size and the small number of training sessions in these studies.

**[Figure 5]**

**5.6.2 Correlation between Change in Neurophysiological Signal and Reduction in Pain**

Figure 6 shows a schematic representation of the success of different neurofeedback studies in changing the neurophysiological signal and reducing the pain perceived by the patients. Only 10 out of the 21 studies reported changes in neurophysiological signals following neurofeedback and were shown in this figure. This includes 10 out of 19 studies reporting a reduction in pain and one out of the two studies reporting no reduction in pain. Figure 6 shows that all the studies which reported a reduction in the pain also reported a statistically significant change in neurophysiological signals following neurofeedback in the desired direction. One study which did not report a reduction in pain did not have any significant change in neurophysiological signals either.

**[Figure 6]**

**5.6.3 Concomitant use of other therapies**

The use of psychoactive pharmacotherapy has been reported inconsistently between studies. Five studies did not report anything on this subject (Caro & Winter, 2011; DeCharms et al., 2005; Guan et al., 2015; Jensen, Gertz, et al., 2013; Jensen, Sherlin, et al., 2013). Out of 16 studies which did report, four studies specifically excluded patients on pharmacotherapy (Farahani et al., 2014; Hershaw et al., 2020; Kayiran et al., 2007; Kayıran et al., 2010), five studies did not allow a change in dose of these drugs during the neurofeedback training period (Al-Taleb et al., 2019; Goldway et al., 2019; Hassan et al., 2015; Prinsloo et al., 2018; Vučković et al., 2019) and seven studies provided no information on changes in dose during neurofeedback training. No information is available on whether these doses were changed in the 3 months prior to start of neurofeedback training.

Physical therapy was provided alongside neurofeedback by three studies. (Ibric & Dragomirescu, 2009; Jensen et al., 2007; Mayaud et al., 2019). Psychotherapy such as talking therapy, psychosocial therapy or cognitive behavioural therapy was offered alongside neurofeedback by four studies (Elbogen et al., 2019; Ibric & Dragomirescu, 2009; Jensen et al., 2007; Mayaud et al., 2019). Due to lack of adequate reporting of changes in these concomitant therapy during neurofeedback training, it is difficult to determine whether these additional therapies had an impact of pain reduction reported by the study cohorts.

**5.6.4 Benefit of Neurofeedback in Pain-associated Symptom Management**

Pain-associated symptoms had been investigated in 16 out of 21 studies included. 8 out of 8 studies investigating depression (Elbogen et al., 2019; Ibric & Dragomirescu, 2009; Kayiran et al., 2007; Kayıran et al., 2010; Koberda, 2015a, 2015b; Koberda et al., 2013; Mayaud et al., 2019), 5 out of 5 studies investigating anxiety (Ibric & Dragomirescu, 2009; Kayiran et al., 2007; Kayıran et al., 2010; Koberda, 2015b; Mayaud et al., 2019), 4 out of 5 studies investigating fatigue (Caro & Winter, 2011; Jensen, Gertz, et al., 2013; Kayiran et al., 2007; Kayıran et al., 2010; Prinsloo et al., 2018) and 4 out of 6 studies investigating sleep (Elbogen et al., 2019; Goldway et al., 2019; Hershaw et al., 2020; Ibric & Dragomirescu, 2009; Jensen, Gertz, et al., 2013; Prinsloo et al., 2018) in chronic pain patients reported an improvement in these symptoms after neurofeedback. Other condition-specific symptoms have also been reported to improve post-therapy. These have been summarised in Table 1.

**5.6.5 Side Effects reported in Neurofeedback Studies**

Adverse events have been reported by five studies included in this review. Studies involving paraplegic patients with central neuropathic pain reported occasional headaches and hypersensitivity in the soles of the feet due to some recovery of proprioception which was managed by reducing the frequency of training session (Al-Taleb et al., 2019; Vučković et al., 2019). Another study looking at paraplegic patients with central neuropathic pain reported spasms and uncontrolled movements of the lower limb in those patients with incomplete paraplegia (Hassan et al., 2015; Vučković et al., 2019). However, none of these side effects led to the withdrawal of patients from the study. In contrast, in a study looking at patients with Traumatic Brain Injury, increased nausea and increasing intensity of pre-existing headache led to withdrawal of five patients from the study (Hershaw et al., 2020). This was the only study which reported termination of therapy due to side effects. Other studies in a similar group of patients with traumatic brain injury (Elbogen et al., 2019) reported symptoms of drowsiness, irritability, headaches, dizziness, vibration and muscle twitching.

## 6. DISCUSSION

Neurofeedback is a novel approach towards pain management through training patients to develop voluntary control over their brain activity. The application of neurofeedback has been studied increasingly in patients with a variety of conditions over the last decade. However, there has been no review of the efficacy of neurofeedback in the management of chronic pain to date. This is the first review to synthesize the evidence regarding the efficacy of neurofeedback in improving both pain and pain-associated symptoms across a range of chronic pain conditions. Here, we have elaborated on the different neurofeedback protocols investigated by the studies so far and highlighted potential issues pertaining to the design of neurofeedback studies.

The results of the meta-analysis show that neurofeedback has a medium effect size overall in chronic pain population. However, most of the studies conducted to date are of Level IV evidence (14 studies) with relatively few Level II (1 studies) and III studies (6 studies). The only Level II study performed did report an improvement in pain, however, this study is limited by its small sample size (Guan et al., 2015). Furthermore, it uses fMRI neurofeedback which is less common and there are no Level II studies for EEG neurofeedback which is a more feasible form of therapy. Out of the six Level III studies, five reported improvement in pain (Caro & Winter, 2011; Farahani et al., 2014; Goldway et al., 2019; Kayıran et al., 2010; Prinsloo et al., 2018). One of the two Level III studies which did not report improvement in pain only provided one single session of neurofeedback which lasted 20 min, therefore, the full benefit of neurofeedback which occurs through operant learning over a series of sessions may not have been achieved (Jensen, Sherlin, et al., 2013). Out of the 14 Level IV studies, 13 reported improvement in pain with the remaining one study reporting an improvement in pain disability but not pain intensity (Hershaw et al., 2020). Overall, 19 out of the 21 studies included in this review have reported a significant improvement in pain. Seven studies which followed-up patients beyond treatment found that the improvement in symptoms was sustained several months later.

This review revealed that one of the key methodological limitations in the neurofeedback studies conducted thus far has been the lack of an appropriate control. Only two studies used sham neurofeedback as their control (Goldway et al., 2019; Guan et al., 2015) with a majority of controlled trials using standard medical therapy or no therapy as controls. This makes blinding of patients impossible resulting in differential reporting of symptom improvement between groups. Nevertheless, our confidence in these findings is increased by the fact that in the ten studies which reported their analysis of changes in neurophysiological signal following neurofeedback, the changes in pain ratings were supported by significant changes in neurophysiological signals. Hence, it can be inferred that the reduction in pain reported is more likely to be due to changes in neurophysiological signals rather than solely due to any placebo effect. Such conclusions are still susceptible to outcome reporting bias as 11 out of 21 studies in this review did not report changes in EEG or fMRI signal post neurofeedback and publication bias as studies which did not find a reduction in pain are also less likely to be published.

The percentage reduction in pain reported by the studies varied widely and no single protocol has emerged to become widely accepted as the most effective way to deliver neurofeedback. Several factors could explain such heterogeneity in pain reduction. For instance, studies with more training session reported higher reduction in pain. This is expected since practice likely increases the ability of individuals to modulate their brain oscillations, therefore, increasing the effectiveness of the therapy (Bagdasaryan & Le Van Quyen, 2013). Studies which targeted SMR and theta frequencies reported more pain reduction than other studies, although this cannot be determined with certainty due to the limited number studies targeting each combination of frequencies. Other factors which could have affected the efficacy of treatment would be region of the scalp from where the feedback signal was provided, forms of feedback signal provided and frequency of training sessions. Heterogeneity between studies in several of these variables at once makes it difficult to compare results of two studies to determine which protocol is most efficacious. Nevertheless, pain reduction following neurofeedback was seen in a variety of chronic pain conditions ranging from fibromyalgia to neuropathic pain to primary headache and it is difficult to assess whether it is more effective for particular chronic pain condition than the other due to differences in other aspects of protocol between studies investigating the same chronic pain population.

The positive impact of neurofeedback in reducing pain appears to be present in several studies with heterogenous methods irrespective of neurofeedback protocol chosen. This could be due to a few reasons. One possible explanation for this might be that electrode locations or frequency targeted are not important and spatial specificity of frequency change is not as important determinant of successful pain reduction as previously thought. Alternatively, it might suggest that providing feedback from a given electrode may not necessarily result in frequency change specific to that electrode, meaning that participants may be increasing the target frequency over all electrodes to perform well in neurofeedback even if feedback is only contingent on change in one of those electrodes. Therefore, it might be the case that increasing control over one’s brain activity in general could reduce pain regardless of the parameters being controlled. This raises some fundamental questions relating to the mechanism underlying neurofeedback training which need to be answered by future studies.

Several studies in this review have reported improvement in pain-associated symptoms, such as depression, anxiety, fatigue, sleep, etc following neurofeedback. It is well-known that the prevalence of depression, anxiety and sleep (Bonvanie et al., 2016; Feingold et al., 2017; Zis et al., 2017) is considerably high in the chronic pain populations and these factors often have a detrimental effect on the ongoing pain of patients. Therefore, neurofeedback can potentially provide a holistic approach to the management of chronic pain patients as the ability of the therapy to simultaneously manage these co-existing conditions may lead to better overall well-being of individuals. -

The findings of this review are consistent with the findings of previous review (Luctkar-Flude & Groll, 2015) with regards to the safety of neurofeedback. The side effects reported have been relatively mild and have been reported to often self-resolve over the course of the training. Out of all the studies included in this review, there has been a withdrawal of patients due to side effects in only one of the studies (Hershaw et al., 2020). Nonetheless, the majority of patients in most of the studies have been able to complete neurofeedback training without any adverse events.

Whilst neurofeedback has shown promising results in improving pain and pain-associated symptoms in the studies so far, our review points to the need for higher quality evidence in order for neurofeedback treatment to become more widely adopted. Neurofeedback can be used to provide pain management to patients in their home environment on a regular basis at much lower costs as and when required. This has already been demonstrated by three Level IV studies included in this review which used home-based EEG neurofeedback therapy using head-sets to alleviate central neuropathic pain (Al-Taleb et al., 2019; Elbogen et al., 2019; Vučković et al., 2019). Such non-invasive therapy can benefit a large number of patients with pain refractory to pharmacological therapy. These patients have been estimated to form 40-60% of the chronic pain population (Breivik et al., 2006, 2009). Numerous approaches are available to deliver such neurofeedback interventions, with its full potential yet to be explored.

## 7. CONCLUSIONS

Neurofeedback is an emerging novel non-pharmacological therapy for the management of patients with chronic pain. Our review reports that there is nascent but mostly low-quality evidence for a reduction in pain, additional improvement in pain-associated symptoms and relatively few side effects following neurofeedback therapy. The studies reviewed involved a variety of neurofeedback systems, approaches and protocols. These have not yet been fully investigated in order to determine the most efficacious way to deliver this therapy. The only high-quality RCT (Guan et al., 2015) conducted was limited by a small sample size. There is a need for more robust well-designed RCTs which address the methodological limitations of current studies and include a larger sample size, double-blinded protocol and appropriate sham neurofeedback control. Future studies should aim to publish data on changes in neurophysiological signals as well as pain ratings before and after training in order to enable determination of whether true “EEG learning” has actually occurred. Despite these limitations, the results of current studies are very promising and warrant further research in this field in order to fully explore the potential of this therapy. This review provides information on studies to date in order to assist the development of robust protocols for future neurofeedback studies.

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**Legends**

**Figure 1. Schematic Representation of Neurofeedback Training**

**Figure 2. PRISMA Flow Chart for the Literature Search**

**Figure 3. Locations of Electrodes (blue circles) used to provide neurofeedback**

**Figure 4. Bubble plot showing impact of different neurofeedback training parameters on pain reduction following neurofeedback therapy**

**Figure 5. Forest Plot representing meta-analysis of effect size reported by different neurofeedback studies in chronic pain patients.**

**Figure 6. Summary of Changes in Pain Ratings and Neurophysiological Signals reported by the Neurofeedback Studies. (Circles with dotted borders represent controlled studies of Level II and III)**

**Table 1. Summary of Neurofeedback Protocols and Results of studies included in this review**

**Table 2. Risk of bias in the controlled trials included in this review**