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REVIEW ARTICLE

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Effects of neurofeedback in the management of chronic pain: A systematic review and meta-analysis of clinical trials

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Abstract

Background and Objective: Neurofeedback (NFB) 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 NFB 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) NFB in chronic pain patients were included. Only Randomized-controlled trials (RCT), non-randomized 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 NFB was reported by one high-quality RCT, five of six low-quality RCT or NRCT and 13 of 14 case-series. Pain reduction reported by studies ranged from 6% to 82%, with 10 studies reporting a clinically significant reduction in pain of >30%. The overall effect size was medium (cohen's d −0.76, 95% confidence interval −1.31 to −0.20). Studies were highly heterogeneous (Q [$df = 5$] = 18.46, $p = .002$, $I^2 = 73\%$). 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 safe and effective 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 NFB.

Significance: Neurofeedback is a novel neuromodulatory approach which can be used to reduce the severity of pain and pain-associated symptoms such as 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 randomized sham-controlled trials are needed in order to fully explore the potential of this therapy.

1 | INTRODUCTION

Chronic pain affects approximately 35%–50% of the UK population (Fayaz, Croft, Langford, Donaldson, & Jones, 2016). The costs of managing 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., 2009; Breivik, Collett, Ventafridda, Cohen, & Gallacher, 2006). Therefore, non-pharmacological therapies are being increasingly explored (Jensen, Day, & Miro, 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, Dussor, & Porreca, 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, Kim, Kim, & Chung, 2016; Sarnthein, Stern, Aufenberg, Rousson, & Jeanmonod, 2006). In general, chronic pain is associated with a relative decrease in alpha, increase in beta and increase in theta activity on electroencephalogram (EEG) recordings (Jensen, Sherlin, Hakimian, & Fregni, 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 EEG or Functional Magnetic Resonance Imaging (fMRI) signals (Bagdasaryan & Le Van Quyen, 2013) (Figure 1). NFB 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, Dias, & Cerqueira, 2019) for example. Many studies have been conducted recently

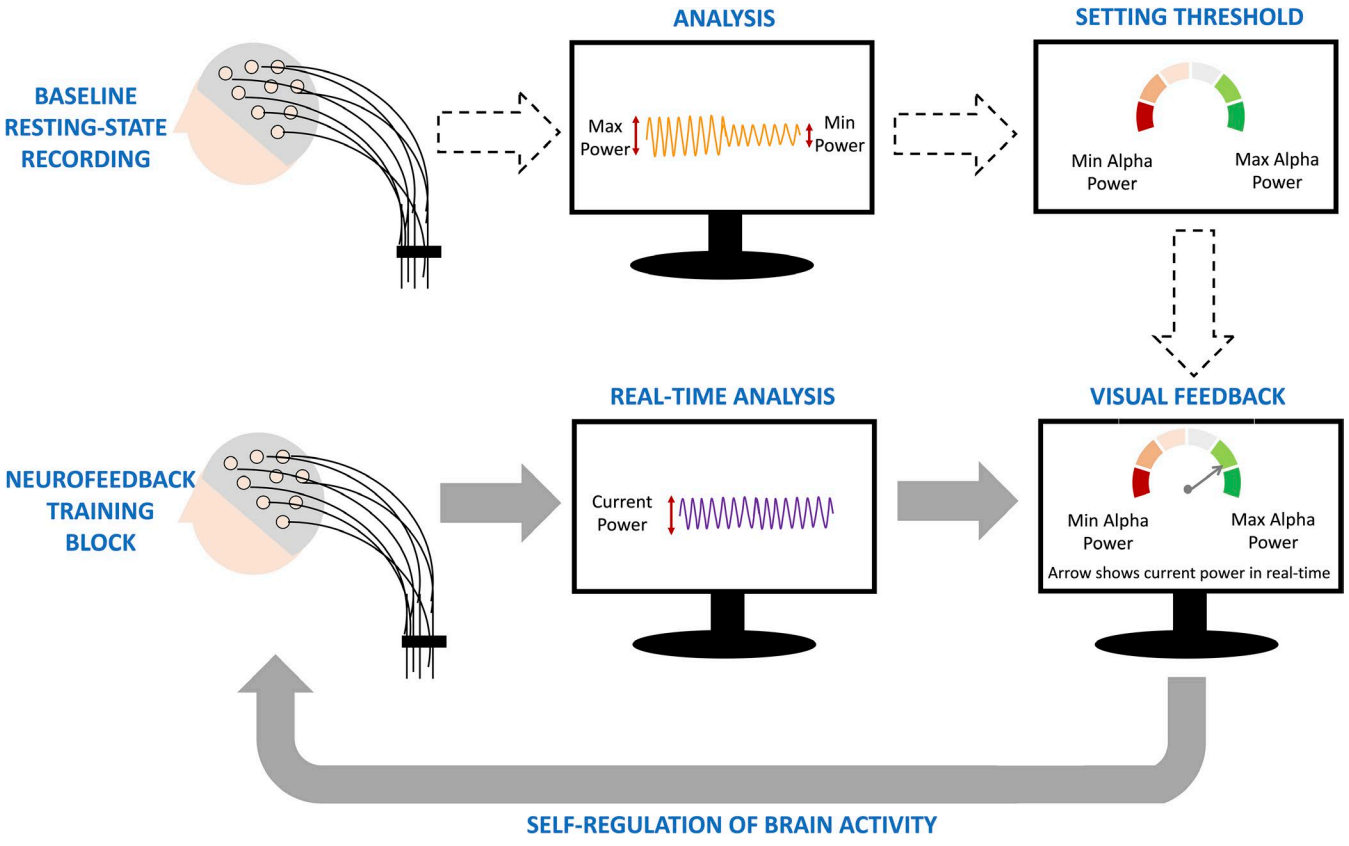

FIGURE 1 Schematic representation of neurofeedback training

in different pain syndromes such as fibromyalgia (Kayıran, Dursun, Dursun, Ermutlu, & Karamürsel, 2010), chemotherapy-induced neuropathy (Prinsloo et al., 2018) and central neuropathic pain (Vučković, Altaleb, Fraser, McGeady, & Purcell, 2019), however, no systematic reviews have been performed to synthesize the evidence available thus far regarding the efficacy of NFB 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, Carvalho, Prado, & Prado, 2019), and 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, Čeko, & Low, 2013; Reddan & Wager, 2019), it is essential to know whether NFB 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, noreviews have evaluated the effectiveness of NFB in the management of pain-associated symptoms in other chronic pain syndromes. This review aims to evaluate the efficacy and safety of NFB in alleviating pain and pain-associated symptoms in different chronic pain conditions.

2 | 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, Liberati, Tetzlaff, & Altman, 2014).

2.1 | 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”).

2.2 | Inclusion and exclusion criteria

2.2.1 | Population

Clinical studies involving adults with chronic pain were included. Chronic pain was defined as pain lasting longer than 3 months in accordance with the International Classification of Disease guidelines (Treede et al., 2015). Non-clinical studies which used experimental pain models, whereby pain is induced through external stimulation in healthy individuals, were excluded.

2.2.2 | 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 biofeedback were also excluded.

2.2.3 | 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.

2.2.4 | 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.

2.3 | 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 finalized 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.

2.4 | 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 summarized as follows:

- Level I evidence: systematic review of RCT or n-of-1 trial.
- Level II evidence: well-designed RCTs.
- Level III evidence: non-RCTs (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:

- Randomization: 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 <80%.
- Data Collection: study did not treat the two groups equally in terms of additional tests, questionnaires and follow-up to assess clinical outcomes.

2.5 | Data extraction

Relevant information was extracted using a standardized 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, NFB intervention (NFB target i.e., frequencies rewarded/inhibited, brain regions/electrodes used, whether statistically significant change in signal was achieved, NFB 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 NFB, 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 NFB was statistically significant), follow-up period post-treatment and whether pain reduction was sustained at follow-up and adverse events.

2.6 | 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 in the plot.

Randomized controlled trials were combined in a meta-analysis. The effect size of the intervention was determined based on standardized weighted mean difference. Standardized 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 NFB. 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 I^2 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.

3 | RESULTS

3.1 | 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.

3.2 | 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; Kayıran et al., 2010; Kayiran, Dursun, Ermutlu, Dursun, & Karamursel, 2007), five in Central Neuropathic Pain in Paraplegic patients (Al-Taleb, Purcell,

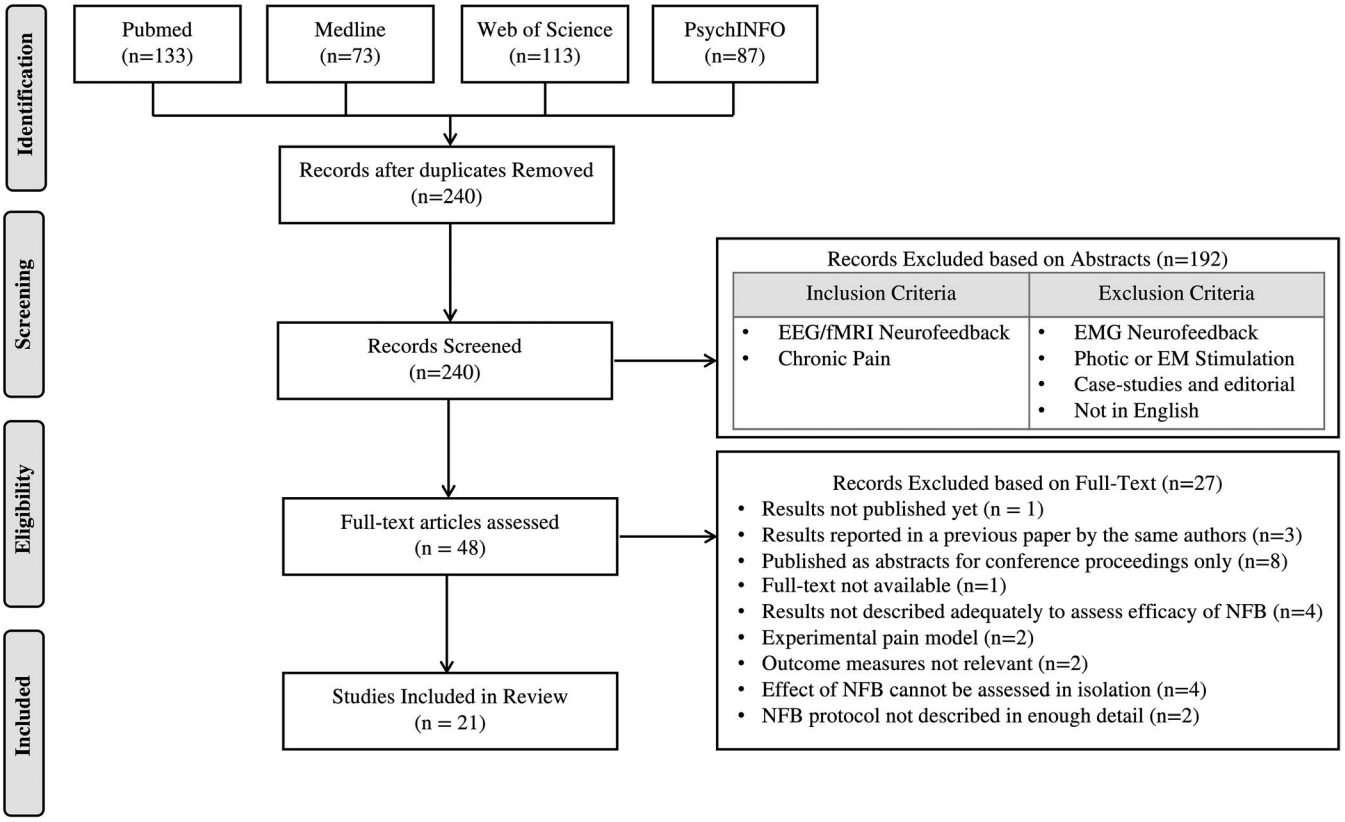

FIGURE 2 PRISMA flow chart for the literature search

Fraser, Petric-Gray, & Vuckovic, 2019; Hassan, Fraser, Conway, Allan, & Vuckovic, 2015; Jensen, Gertz, et al., 2013; Jensen, Sherlin, et al., 2013; Vučković et al., 2019), two in Traumatic Brain Injury (Elbogen et al., 2019; Hershaw, Hill-Pearson, Arango, Souvignier, & Pazdan, 2020), one in Chemotherapy-Induced Peripheral Neuropathy (Prinsloo et al., 2018), one in Primary Headache (Farahani et al., 2014), one in Complex Regional Pain Syndrome Type I (Jensen, Grierson, Tracy-Smith, Bacigalupi, & Othmer, 2007), one in Post-Herpetic Neuralgia (Guan et al., 2015) and one in chronic lower back pain (Mayaud et al., 2019). Five studies had a cohort with a mixture of chronic pain conditions (DeCharms et al., 2005; Ibric & Dragomirescu, 2009; Koberda, 2015a, 2015b; Koberda, Koberda, Bienkiewicz, Moses, & Koberda, 2013). Sample size ranged from 3 to 41 patients. In total, 491 patients were followed-up across the 21 studies included.

3.3 | Risk of bias

In this review, one study was of Level II Evidence, six studies were of Level III Evidence and 14 studies were of Level IV Evidence. Most NFB 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 RCT (Guan et al., 2015). The remaining six controlled trials were either non-randomized or had methodological weaknesses, and hence were graded down as Level III evidence.

Table 2 summarizes the results of critical appraisal of the controlled trials included in this review. There were three key sources of bias– lack of randomization, 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, 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

TABLE 1 Summary of neurofeedback protocols and results of studies included in this review

Study	OCEBM level	Experimental group Patients Sample size (withdrawals) Age (years) Sex (% Male)	Control group Patients Sample size (withdrawals) Age (years) Sex (% male) Control procedure	Concomitant therapy (psychoactive treatment/ physical therapy/ psychotherapy) % of cohort Change in dose	NFB target Electrode Achievement of target change in power	Neurofeedback protocol Stimulus Length of NFB No of sessions Duration	Outcome measure	% pain reduction from baseline	Significant improvement	NO significant improvement	Side effects	Follow-up period pos-treatment Effect of NFB sustained? Yes/No	Pattern of results for pain reduction (+positive, 0mixed, −negative results)
EEG neurofeedback													
Prinsloo et al. (2018)	III	Chemotherapy-induced peripheral neuropathy $n = 35$ (5) 62 ± 10 years 13% Male	Chemotherapy-induced peripheral neuropathy $n = 36$ (4) 63 ± 11 years (No intervention—on waiting list for NFB)	Psychoactive treatment (21%) (No change in dose during NFB treatment)	⬆ α (8–12 Hz) ⬇ β (13–45 Hz) Frontal Achieved	Power NFB Audio + visual 45 min 20 sessions 10 weeks	BPI PQAS MDASI SF–36 BFI PSQI	45%	Pain severity Pain interference Numbness Fatigue Cancer-related symptom severity Physical functioning Quality of life	Sleep	—	4 months Yes	+
Jensen, Sherlin, et al. (2013)	III	Central neuropathic pain syndrome $n = 30$ 49 years	Central neuropathic pain syndrome $n = 30$ 49 years (Sham tDCS)	None reported	⬆ α (8–12 Hz) ⬇ β_2 (18–30 Hz) Electrodes: T3/T4 Not achieved	Power NFB Audio + visual 1 session 20 min	NRS	Not significant	—	Pain	—	—	−
Kayiran et al. (2010)	III	Fibromyalgia $n = 20$ (2) 32 ± 6 years	Fibromyalgia $n = 20$ (2) 32 ± 7 years (Escitalopram 10 mg per day)	None taking psychoactive treatment (0%)	⬆ SMR (12–15 Hz) ⬇ θ (4–7 Hz) ⬇ θ:SMR Electrode: C4 Achieved	Power NFB Visual 10 x 3 min 20 sessions 4 weeks	VAS Pain VAS Fatigue FIQ SF–36 HAS/BAS HDS/BDS	82%	Pain Fatigue Depression Anxiety Social functioning Physical functioning	—	—	5 months Yes	+
Caro and Winter (2011)	III	Fibromyalgia $n = 15$ 67 ± 12 years 7% Male	Fibromyalgia $n = 63$ 51 ± 14 years 21% Male (Medical care)	None reported	⬆ SMR (12–15 Hz) ⬇ θ (4–8 Hz) ⬇ β_2 (22–30 Hz) Electrode: Cz Not reported	Power NFB 40 + sessions	NRS	39%	Pain Tenderness Fatigue	Psychological distress Stiffness	—	—	+
Farahani et al. (2014)	III	Primary headache $n = 15$ 38 ± 7 years 53% Male	Primary headache $n = 15$ 37 ± 9 years 53% Male (No treatment)	None taking psychoactive treatment (0%)	⬆ SMR (12–15 Hz) ⬇ θ (4–8 Hz) ⬇ β_2 (21–30 Hz) Electrodes: T3/T4 Not reported	Power NFB Visual 30 min 15 sessions 5 weeks	Blanchard headache diary (BHD) Headache questionnaire (ICD-III)	19%	Pain intensity Pain frequency Pain duration	—	—	—	+

(Continues)

TABLE 1 (Continued)

Study	OCEBM level	Experimental group Patients sample size (withdrawals) Age (years) Sex (% Male)	Control group Patients Sample size (withdrawals) Age (years) Sex (% male) Control procedure	Concomitant therapy (psychoactive treatment/ physical therapy/ psychotherapy) % of cohort Change in dose	NFB target Electrode Achievement of target change in power	Neurofeedback protocol Stimulus Length of NFB No of sessions Duration	Outcome measure	% pain reduction from baseline	Significant improvement	NO significant improvement	Side effects	Follow-up period pos-treatment Effect of NFB sustained? Yes/No	Pattern of results for pain reduction (+positive, 0mixed, −negative results)
Elbogen et al. (2019)	IV	Traumatic brain injury $n = 41$ (5) 39 ± 10 years 85% male	None	Psychoactive treatment (31%) Psychotherapy (5%) Both (25%) (Change in dose not reported)	⬆ α (8–13 Hz) Electrodes: FP1 Not reported	Power NFB (Home-based NFB therapy) Audio 10 min Avg 33 sessions 3 months	NRS PCL−5 PHQ−9 Suicidal ideations PROMIS for Sleep, Pain interference, anger	16%	Pain intensity Pain interference Depression PTSD Anger Sleep Suicidal ideation	—	Headset discomfort Drowsiness Irritability Headaches Dizziness Vibration Muscle twitching	—	+
Jensen et al. (2007)	IV	Complex regional pain syndrome Type-I (CRPS-I) $n = 18$ 10% male	None	Psychoactive treatment Physical therapy Eclectic psychotherapy (100%)	Range of frequencies using combinations of 2–13 Hz and 14–30 Hz Electrodes: P3/P4, FP1/FP2, T3/T4, FPO2/FPA2, Cz/Fz, F7/F8, F3/F4 Not reported	Power NFB Audio + visual + tactile 30 min 1 session 1 week	NRS	42%	Pain Muscle spasm Muscle tension Well-being	Deep ache Skin sensitivity	—	—	+
Vučković et al. (2019)	IV	Central neuropathic pain syndrome $n = 20$ (5) 51 ± 14 years 80% male	None	Psychoactive treatment (most) (No change in dose during NFB treatment)	⬆ α (8–12 Hz) ⬇ θ (4–8 Hz) ⬇ β_2 (20–30 Hz) Electrodes: C4 Achieved	Power NFB (home-based NFB therapy) Visual 6 × 5 min 3–48 sessions 6–18 weeks	VNS BPI NPSI	33%	Pain	—	Occasional Headache Hypersensitivity in the soles of the feet	—	+
Al-Taleb et al. (2019)	IV	Central neuropathic pain syndrome $n = 20$ (8) 51 ± 14 years 85% male	None	Psychoactive treatment (most) (No change in dose during NFB treatment)	⬆ α (8–12 Hz) ⬇ θ (4–8 Hz) ⬇ β_2 (20–30 Hz) Electrode: C4 Achieved	Power NFB (home-based NFB therapy) Visual 6 × 5 min 8–40 session 8 weeks	BPI NPSI QUESQ	33%	Pain —	—	Occasional headache Hypersensitivity in feet	—	+
Mayaud et al. (2019)	IV	Chronic low back pain $n = 16$ (3) avg 37 years 0% male	None	Psychoactive treatment Physical therapy Psychotherapy (100%)	⬆ α (8–12 Hz) Achieved	Power NFB visual 6 × 5 min 20 sessions	VAS HDS HAS Dallas	—	Pain Anxiety Depression	—	—	6 months Yes	+

(Continues)

TABLE 1 (Continued)

Study	OCEBM level	Experimental group Patients Sample size (withdrawals) Age (years) Sex (% Male)	Control group Patients Sample size (withdrawals) Age (years) Sex (% male) Control procedure	Concomitant therapy (psychoactive treatment/ physical therapy/ psychotherapy) % of cohort Change in dose	NFB target Electrode Achievement of target change in power	Neurofeedback protocol Stimulus Length of NFB No of sessions Duration	Outcome measure	% pain reduction from baseline	Significant improvement	NO significant improvement	Side effects	Follow-up period pos-treatment Effect of NFB sustained? Yes/No	Pattern of results for pain reduction (+positive, 0mixed, −negative results)
Jensen, Sherlin, et al. (2013)	IV	Central neuropathic pain syndrome $n = 13$ (3) 46 ± 13 years 70% male	None	None reported	3 protocols P1: ⬆ α/⬇β_1 (T3–T4) P2: ⬆ 10–15 Hz/ ⬇β_1-θ (C3–A1 and C4–A2) P3: ⬆ 10–15 Hz/⬇β_1-θ (P3-A1 and P4-A2) Achieved (for alpha and theta only)	Power NFB 12 sessions (4 sessions of each of the 3 protocols)	NRS PROMIS MOSS FSS	12%	Worst pain intensity Degree of pain unpleasantness	Average pain intensity Pain interference Sleep quality Fatigue	—	3 month Yes	0
Ibric and Dragomirescu (2009)	IV	Chronic pain $n = 10$ 49 ± 16 years	None	Psychoactive treatment Physical therapy Psychotherapy (100%)	⬆ SMR (12–15 Hz) ⬇ θ (4–7 Hz) ⬇ β_2 (22–30 Hz) Electrodes: C3/Cz, C4/Cz, C3/C4, F3/F4 Not reported	Power NFB Audio + visual 15–145 sessions	—	—	Pain Headache Depression Anxiety Sleep Gait Tremor Spasticity Cognition Quality of life	—	—	—	+
Hassan et al. (2015)	IV	Central neuropathic pain syndrome $n = 7$ (2) 50 ± 4 years 86% male	None	Psychoactive treatment (No change in dose during NFB treatment) (100%)	Protocols P1: ⬆ SMR/⬇β_2-θ (Cz) P2: ⬆ α/⬇ β_2-θ (P4) P3: ⬆ α/⬇ β_2-θ (C3) P4: ⬆ α/⬇ β_2-θ (C4) Achieved (beta only)	Power NFB Audio + visual 8 × 5 min 40 sessions 1–3/week	BPI VNS	30%	Pain Pleasant warmth replacing unpleasant sensations	—	Spasm (uncontrolled movements of lower limbs)	1 month Yes	+
Kayiran et al. (2007)	IV	Fibromyalgia $n = 3$ 32 ± 1 years 100% male	None	None taking psychoactive treatment (0%)	⬆ SMR (12–15 Hz) ⬇ θ (4–7 Hz) ⬆ SMR:θ Ratio Electrodes: C4 No statistics	Power NFB Visual 30 min 10 session 3 weeks	VAS HDS HAS BDS BAS SF-36	55%	Pain Fatigue Depression Anxiety Physical functioning Social functioning Role limitations General mental health	—	—	—	+

(Continues)

TABLE 1 (Continued)

Study	OCEBM level	Experimental group Patients Sample size (withdrawals) Age (years) Sex (% Male)	Control group Patients Sample size (withdrawals) Age (years) Sex (% male) Control procedure	Concomitant therapy (psychoactive treatment/ physical therapy/ psychotherapy) % of cohort Change in dose	NFB target Electrode Achievement of target change in power	Neurofeedback protocol Stimulus Length of NFB No of sessions Duration	Outcome measure	% pain reduction from baseline	Significant improvement	NO significant improvement	Side effects	Follow-up period post-treatment Effect of NFB sustained? Yes/No	Pattern of results for pain reduction (+positive, 0mixed, −negative results)
Hershaw et al. (2020)	IV	Traumatic brain injury (TBI) $n = 38$ (11) 33 ± 8 years 85% Male	None	None taking psychoactive treatment (0%)	Normalize Z-Score for alpha, beta and theta Not reported	Z-Score Visual 10–30 min 15–20 session 6 weeks	PCL-M PHQ−9 NSI MOSS CPG MIDAS SWLS SEsX	6%	Depression Migraine Pain disability Post-concussive somatic symptoms Affect dysregulation Cognitive dysfunction	Pain Intensity PTSD Score Sleep	Nausea Increasing headache	3 months Yes	0
Koberda (2015a)	IV	Chronic Pain $n = 10$	None	Psychoactive treatment (100%)	Normalize Z-Score Not reported	Z-Score NFB 10–25 sessions	—	—	Pain Headache Depression Anxiety Memory	—	—	—	+
Koberda (2015b)	IV	Chronic Pain $n = 6$	None	Psychoactive treatment (100%)	Normalize Z-Score Not reported	Z-Score NFB 10–65 sessions	—	—	Pain Depression Headaches	—	—	—	+
Koberda et al. (2013)	IV	Chronic pain $n = 4$	None	Psychoactive treatment (100%)	Normalize Z-Score Not reported	Z-Score NFB 10–45 sessions	—	—	Pain Depression Memory	—	—	—	+
fMRI neurofeedback													
Guan et al. (2015)	II	Post-herpetic neuralgia $n = 8$ (0) 59 ± 2 years 63% male	Post-herpetic neuralgia $n = 8$ (2) 61.33 ± 3.43 years 50% male (NFB from PCC)	None reported	Up-regulate rACC BOLD Down-regulate rACC BOLD Electrode: Pz Achieved	fMRI NFB Visual 5 × 60 s 1 session 1 week	NRS	64%	Pain decreased on down-regulation Pain increased on up-regulation	—	—	—	+
Goldway et al. (2019)	III	Fibromyalgia $n = 31$ (6) 36 ± 12 years 4% male	Fibromyalgia $n = 12$ (3) 35.9 ± 10.6 years 22% male (EEG from another patient)	Psychoactive treatment (No change in dose during NFB treatment)	Decrease Amyg-EFP Achieved	Amyg-EFP NFB Audio + visual 10 sessions 5 weeks	VAS FIQ STAI-T BDI PSIQ McGill	7%	Pain REM latency Sleep quality Affect improved between pre and post-therapy	Affect did not improve post-therapy and follow-up	—	~16 months Yes	+

(Continues)

TABLE 1 (Continued)

Study	OCEBM level	Experimental group Patients sample size (withdrawals) Age (years) Sex (% Male)	Control group Patients Sample size (withdrawals) Age (years) Sex (% male) Control procedure	Concomitant therapy (psychoactive treatment/ physical therapy/ psychotherapy) % of cohort Change in dose	NFB target Electrode Achievement of target change in power	Neurofeedback protocol Stimulus Length of NFB No of sessions Duration	Outcome measure	% pain reduction from baseline	Significant improvement	NO significant improvement	Side effects	Follow-up period post-treatment Effect of NFB sustained? Yes/No	Pattern of results for pain reduction (+positive, 0mixed, −negative results)
DeCharms et al. (2005)	IV	Chronic pain $n = 8$ avg 37 years	None	None reported	Up-regulate rACC BOLD Down-regulate rACC BOLD Achieved	fMRI NFB Visual 6 × 60 s 1 session	McGill VAS	44%	Pain	—	—	—	+

Note: Frequencies: theta (4–7 Hz), alpha (8–12 Hz), low beta or β_1 (15–20 Hz), high beta or β_2 (22–30 Hz) and sensorimotor rhythm (12–15 Hz) over sensorimotor cortex.

Abbreviations: BAS, Beck Anxiety Scale; BDS, Beck Depression Scale; BFI, Big Five Inventory; BPI, Brief Pain Inventory; CGI, Clinician-rated Global Impression Score; CPG, Chronic Pain Grade questionnaire; FIQ, Fibromyalgia Impact Questionnaire; FSS, Fatigue Severity Scale; HAS, Hamilton Anxiety Scale; HDS, Hamilton Depression Scale; MDASI, MD Anderson Symptom Inventory; MIDAS, Migraine Disability Assessment Scale; MOSS, 6-Item Medical Outcome Study Sleep Scale; NPSI, Neuropathic Pain Symptom Inventory; NRS, Numerical Rating Scale; NSI, Neurobehavioral Symptom Inventory; PCL-5, PTSD Checklist for DSM-5; PGI, Patient-rated Global Impression Sale; PHQ-9, Patient Health Questionnaire-9; PQAS, Pain Quality Assessment Scale; PROMIS, Patient Reported Outcomes Measurement Information System; PSIQ, Professional Self Identity Questionnaire; PSQI, Pittsburgh Sleep Quality Index; QUESQ, Questionnaire Semantique De Quebec; SCL, 90-R—Symptom Checklist 90 R Questionnaire; SEsX, Self-Efficacy for Symptom Management Scale (SEsX); SF-36, 36-Item Short Form Survey; STAI, State-Trait Anxiety Inventory; SWLS, Satisfaction with Life Scale; VAS, Visual Analogue Scale.

in the study by Caro and Winter (2011) they received the standard medical care. Whilst these control groups enabled comparison of NFB 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 these might depend on the belief of the patient in the intervention. Only two studies (Goldway et al., 2019; Guan et al., 2015) implemented sham NFB in the control group which was an appropriate control as the patients would truly not be aware whether they were receiving real-time NFB or not. Of these two, one study (Goldway et al., 2019) had to be downgraded despite proper randomization and blinding due to high attrition rates.

Amongst the two studies providing sham NFB to the control group, there were differences in terms of what constituted the sham treatment. In the fMRI NFB study by Guan et al. (2015) sham NFB 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 NFB 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 NFB 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 of their brain oscillations. However, this might increase the attrition rate as it can lead to frustration and lack of perceived control amongst participants.

3.4 | Results of studies

3.4.1 | NFB interventions

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

EEG NFB involved feedback of real-time EEG recordings of the patient. EEG oscillations investigated in these studies were conventionally categorized based on their frequency into theta (4–7 Hz), alpha (8–12 Hz), low beta or beta$_1$ (15–20 Hz) and high beta or beta$_2$ (22–30 Hz). Another oscillation which was widely investigated was 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 -activation of the motor cortex leads to a decrease in measured SMR (Timmers, 2013).

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

In contrast to EEG NFB, fMRI NFB 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 NFB was used to decrease the activation of areas associated with pain perception such as anterior cingulate cortex (Guan et al., 2015). This form of NFB suffers from a lag of 5–8 s 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 was a large heterogeneity in the NFB 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 NFB 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 NFB per session broken down into 5 min sub-sessions. The frequency of training session varied from 1 per week to 5 per week. None of the studies reported the possibility of patients self-exercising at home without feedback signal, therefore the chances of such practice increasing performance at the next training session cannot be determined.

3.4.2 | Efficacy of NFB in chronic pain management

EEG NFB

Fourteen studies provided NFB to change oscillatory power. There were no Level II studies on Power EEG NFB, 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, Gertz, et al., 2013; Jensen et al., 2007; Kayiran et al., 2007; Mayaud et al., 2019; Vučković et al., 2019). All studies reported a significant reduction in pain after NFB therapy except one Level III study (Jensen, Sherlin, et al., 2013). This study only provided one single session of NFB 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 NFB 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 NFB amongst all the included NFB 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 the 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 NFB 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 NFB. All these studies report a reduction in pain. However, these improvements seen in case studies have not been subsequently investigated by any controlled trials.

fMRI NFB

Only three studies investigating fMRI NFB were included—one Level II (Guan et al., 2015), one Level III (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.

3.5 | Synthesis of results

Figure 4 shows the result of the meta-analysis presented as a forest plot of the six RCTs included in this review.

TABLE 2 Risk of bias in the controlled trials included in this review

Study	Randomization	Blinding	Confounders	Attrition	Data collection	Level of evidence
Guan et al. (2015)	Low	Low	Low	Low	Low	II
Goldway et al. (2019)	Low	Low	Low	High	Low	III
Jensen, Sherlin, et al. (2013)	Low	High	Low	Low	Low	III
Farahani et al. (2014)	Low	High	Low	Low	Low	III
Prinsloo et al. (2018)	Low	High	Low	Low	Low	III
Kayiran et al. (2010)	Low	High	Low	Low	Low	III
Caro et al. (2011)	High	High	Low	Low	Low	III

Using the random effects model, the overall effect of NFB in chronic pain patients was statistically significant ($d = -0.76$, 95% CI [−1.31, −0.20]). This represents a medium to high effect size according to the criteria of interpretation of Cohen's d (Lachenbruch & Cohen, 1989). The meta-analysis revealed a high degree of heterogeneity [$Q(df = 5) = 18.46$, $p = .002$] corresponding to a high value for I^2 of 73%. Publication bias was not assessed due to the small number of studies included in the meta-analysis.

3.6 | Additional analysis

3.6.1 | 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 NFB studies.

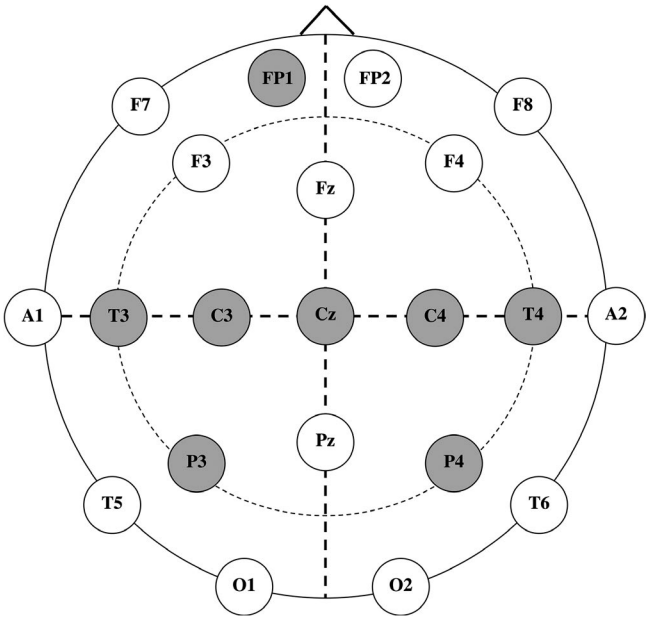

FIGURE 3 Locations of electrodes (blue circles) used to provide neurofeedback

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 NFB 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.

3.6.2 | Correlation between change in neurophysiological signal and reduction in pain

Figure 6 shows a schematic representation of the success of different NFB 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 NFB 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 NFB in the desired direction. One study which did not report a reduction in pain did not have any significant change in neurophysiological signals either.

3.6.3 | Concomitant use of other therapies

The use of psychoactive pharmacotherapy has been reported inconsistently between studies. Five studies did not report anything

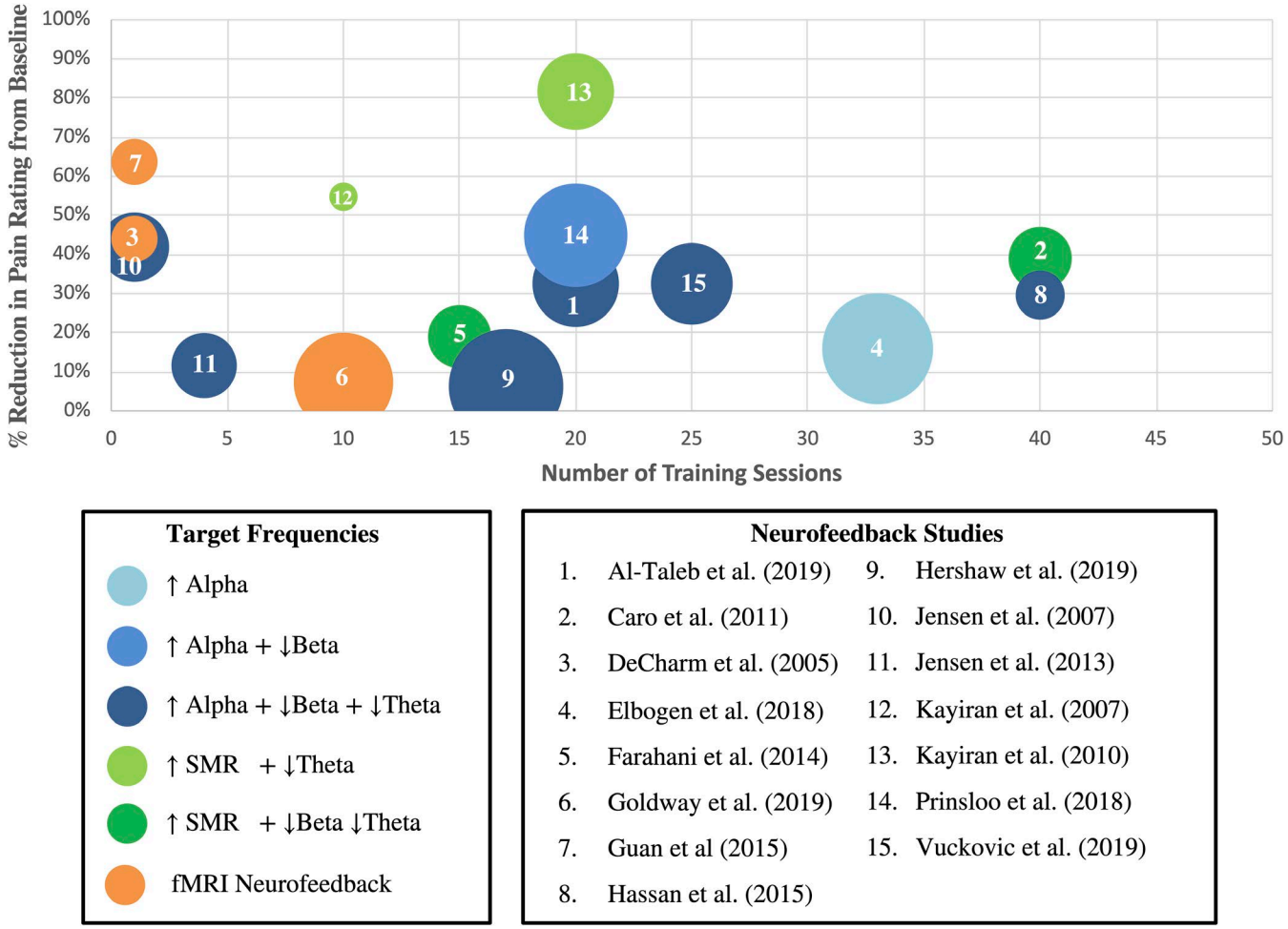

FIGURE 4 Bubble plot showing impact of different neurofeedback training parameters on pain reduction following neurofeedback therapy

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; Kayıran et al., 2010; Kayiran et al., 2007), five studies did not allow a change in dose of these drugs during the NFB 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 NFB training. No information is available on whether these doses were changed in the 3 months prior to start of NFB training.

Physical therapy was provided alongside NFB 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 NFB 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 NFB training, it is difficult to determine whether these additional therapies had an impact of pain reduction reported by the study cohorts.

3.6.4 | Benefit of NFB in pain-associated symptom management

Pain-associated symptoms had been investigated in 16 out of 21 studies included. Eight out of eight studies investigating depression (Elbogen et al., 2019; Ibric & Dragomirescu, 2009; Kayıran et al., 2010; Kayiran et al., 2007; Koberda, 2015a, 2015b; Koberda et al., 2013; Mayaud et al., 2019), five out of five studies investigating anxiety (Ibric & Dragomirescu, 2009; Kayıran et al., 2010; Kayiran et al., 2007; Koberda, 2015b; Mayaud et al., 2019), four out of five studies investigating fatigue (Caro & Winter, 2011; Jensen, Gertz, et al., 2013; Kayıran et al., 2010; Kayiran et al., 2007; Prinsloo et al., 2018) and four out of six 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 NFB. Other condition-specific symptoms have also been reported to improve post-therapy. These have been summarized in Table 1.

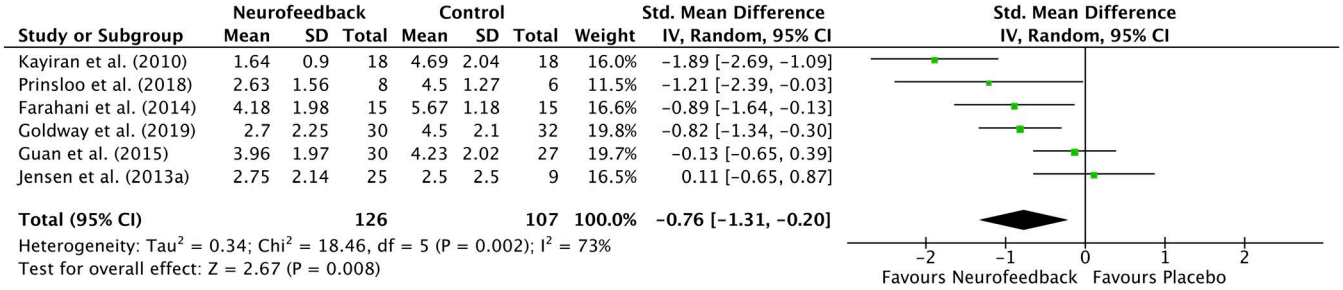

FIGURE 5 Forest plot representing meta-analysis of effect size reported by different neurofeedback studies in chronic pain patients

3.6.5 | Side effects reported in NFB 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.

4 | DISCUSSION

Neurofeedback is a novel approach towards pain management through training patients to develop voluntary control over their brain activity. The application of NFB 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 NFB in the management of chronic pain to date. This is the first systematic review to synthesize the evidence regarding the efficacy of NFB in improving both pain and pain-associated symptoms across a range of chronic pain conditions. Here, we have elaborated on the different NFB protocols investigated by the studies so far and highlighted potential issues pertaining to the design of NFB studies.

The results of the meta-analysis show that NFB has a medium to high effect size overall in the chronic pain

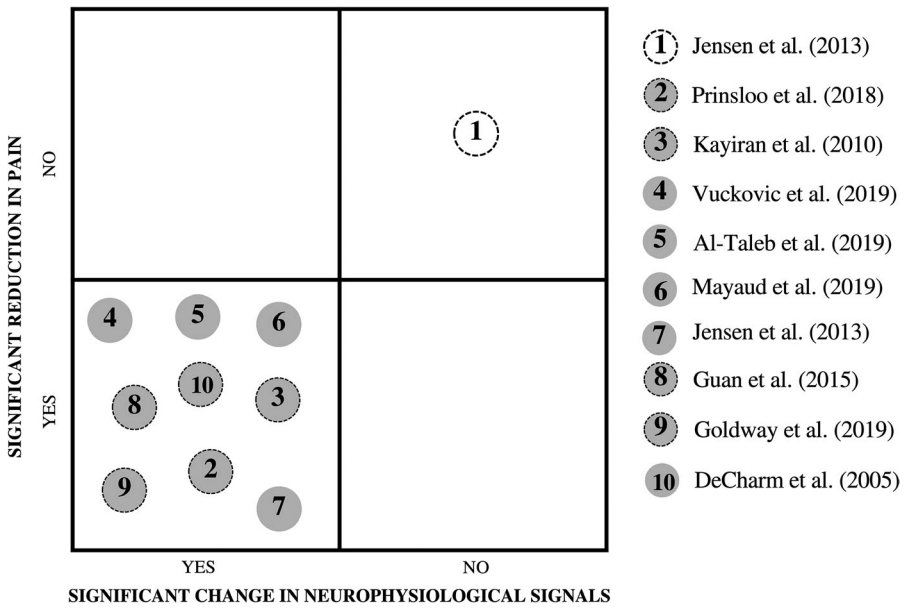

FIGURE 6 Summary of Changes in pain ratings and neurophysiological signals reported by the neurofeedback studies. (Circles with dotted borders represent controlled studies of Level II and III)

population. However, most of the studies conducted to date are of Level IV evidence (14 studies) with relatively few Level II (one study) and III studies (six studies). The only Level II study performed did report an improvement in pain, however, this study was limited by its small sample size (Guan et al., 2015). Furthermore, it uses fMRI NFB which is less common and there are no Level II studies for EEG NFB 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 NFB which lasted 20 min, therefore, the full benefit of NFB 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 NFB studies conducted thus far has been the lack of an appropriate control. Only two studies used sham NFB 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 10 studies which reported their analysis of changes in neurophysiological signal following NFB, 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 NFB 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 NFB. Several factors could explain such heterogeneity in pain reduction. For instance, studies with more training session reported a greater 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 bethe region of the scalp from where the feedback signal was provided, the form of feedback signal provided and the 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 NFB 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 NFB in reducing pain appears to be present in several studies with heterogenous methods irrespective of NFB 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. The spatial specificity of frequency change might not be 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 NFB 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 NFB 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 NFB. It is well-known that the prevalence of depression, anxiety and sleep (Bonvanie, Oldehinkel, Rosmalen, & Janssens, 2016; Feingold, Brill, Goor-Aryeh, Delayahu, & Lev-Ran, 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, NFB 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 NFB. 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 NFB training without any adverse events.

Whilst NFB 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 NFB treatment to become more widely adopted. NFB 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 NFB 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 NFB interventions, with its full potential yet to be explored.

5 | CONCLUSIONS

Neurofeedback is anovel 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 NFB therapy. The studies reviewed involved a variety of NFB 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 NFB control. Future studies should aim to publish data on changes in neurophysiological signals as well as pain ratings before and after training 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 NFB studies.

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None.

CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

KP and HS conducted the literature search, screening and data extraction. MS acted as the third reviewer in cases of disagreement. KP conducted the meta-analysis of the data in RevMan and wrote the manuscript. All authors were involved in the analysis and interpretation of the data and revising the manuscript for important intellectual content.

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