Is There Evidence for EEG-Neurofeedback Specificity in the Treatment of Internalizing Disorders? A Protocol for a Systematic Review and Meta-Analysis

Tyson Michael Perez¹, Paul Glue², Divya B Adhia³, Jerin Mathew⁴, and Dirk De Ridder⁵

¹ Departments of Surgical Sciences & Psychological Medicine, University of Otago, Dunedin, New Zealand
² Department of Psychological Medicine, University of Otago, Dunedin, New Zealand
³ Department of Surgical Sciences, University of Otago, Dunedin, New Zealand
⁴ School of Physiotherapy, University of Otago, Dunedin, New Zealand
⁵ Department of Surgical Sciences, University of Otago, Dunedin, New Zealand

Abstract

Background: Mental illnesses are increasing worldwide with the internalizing disorders (IDs; e.g., anxiety disorders, depressive disorders) being the most prevalent. Current first-line therapies (e.g., pharmacotherapy) offer high failure rates and substantial side effects. Electroencephalographic neurofeedback (EEG-NFB) has been shown to be an effective and safe treatment for these conditions; however, there remains much doubt regarding the existence of specificity (i.e., clinical effects specific to the modulation of the EEG variables of interest). This is a protocol for a quantitative review that will attempt to determine if there is evidence for EEG-NFB specificity in the treatment of IDs.

Methods: We will consider all published and unpublished randomized, double-blind (i.e., trainees and raters), sham/placebo-controlled (i.e., feedback contingent on a random signal, the activity from a different person’s brain, or an unrelated signal from the trainee’s own brain) trials involving humans with at least one ID diagnosis without exclusion by language, locality, ethnicity, age, or sex. Effect sizes will be calculated for individual studies and combined in a meta-analysis.

Discussion: This protocol outlines the research methodology for a quantitative review undertaken to assess for evidence of EEG-NFB specificity in the treatment of IDs.

Registration: This review was registered with the International Prospective Register of Systematic Reviews (PROSPERO; registration number: CRD42020159702).

Keywords: EEG; neurofeedback; internalizing disorders; emotional disorders; affective disorders

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*Address correspondence to: Tyson M Perez, Section of Neurosurgery, Department of Surgical Sciences, Dunedin School of Medicine, Dunedin Hospital, 201 Great King Street, Dunedin 9016, New Zealand. Email: tyson.perez@postgrad.otago.ac.nz

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Edited by:
Rex L. Cannon, PhD, SPESA Research Institute, Knoxville, Tennessee, USA

Reviewed by:
Randall Lyle, PhD, Mount Mercy University, Cedar Rapids, Iowa, USA
Estate M. Sokhadze, PhD, University of South Carolina, School of Medicine Greenville, Greenville, South Carolina, USA

Background and Rationale

Internalizing disorders (IDs; e.g., anxiety disorders, ANX; depressive disorders, DEP; posttraumatic stress disorder, PTSD; obsessive–compulsive disorder, OCD) are the most prevalent psychopathologies (Demyttenaere et al., 2004; Kessler et al., 2009; Kessler et al., 2007; Kessler et al., 2005; Wells et al., 2006) and can be broadly characterized by a proclivity to direct distress inwardly (Buchan, Sunderland, Carragher, Batterham, & Slade, 2014; Carragher, Krueger, Eaton, & Slade, 2015; Kotov et al., 2017; Krueger & Eaton, 2015; Rhee, Lahey, & Waldman, 2015). There are numerous shortcomings with traditional frontline ID treatments (i.e., pharmacotherapy and psychotherapy) including substantial long-term failure rates (Haller, Cohen Kadosh, Scerif, & Lau, 2015; James, James, Cowdrey, Soler, & Choke, 2015; Peters, Dunlop, & Downar, 2016; Pinter et al.,...
lack of access (Andrade et al., 2014; Bandelow & Michaelis, 2015; Haller et al., 2015; Möller et al., 2016; Schoenberg & David, 2014), and marked adverse side effects (Alvares, Quintana, Hickie, & Guastella, 2016; Haller et al., 2015; Möller et al., 2016; Pinter et al., 2019; Tiller, 2013). Moreover, a decades-long drought in the discovery of new agents has prompted pharmaceutical companies to abandon the neuropsychiatric space (Buzsáki & Watson, 2012), leading to appeals from around the world for innovative interventions (Haller et al., 2015; Kris, 2018; Lancet Global Mental Health Group et al., 2007; Pinter et al., 2019).

With aberrations in the brain's electrical activity well recognized in IDs (Alhaj, Wisniewski, & McAllister-Williams, 2010; Buzsáki & Watson, 2012; Iosifescu, 2011; Jokić-Begić & Begić, 2003; Pizzagalli et al., 2002; Wahbeh & Oken, 2013), electroencephalographic neurofeedback (EEG-NFB) has been touted as a possible solution. EEG-NFB is a noninvasive form of biofeedback that teaches the brain to modify its function via a closed-loop brain–computer interface, whereby an exogenous sensory stimulus (e.g., audible tone) is fed back to the participant in real time following some predetermined electrical activity recorded from the scalp (Arns et al., 2017; Collura, 2013; Marzbani, Marateb, & Mansourian, 2016; Orndorff-Plunkett, Singh, Aragón, & Pineda, 2017; Sitaram et al., 2016). EEG-NFB is widely believed to work predominantly through operant conditioning, a type of associative learning whereby the probability of some given electrical behavior is modified via a temporally associated reinforcing stimulus (Alkoby, Abu-Rmileh, Shriki, & Toddor, 2018; Enriquez-Geppert, Huster, & Herrmann, 2017; Orndorff-Plunkett et al., 2017). Although the use of EEG-NFB for IDs in routine clinical psychiatric practice has yet to receive widespread support (Arns et al., 2017; Begemann, Florisse, van Lutterveld, Kooyman, & Sommer, 2016; Omejc, Rojc, Battaglini, & Marusic, 2019), there is substantial evidence that EEG-NFB is efficacious (e.g., Askovic et al., 2019; Bell, Moss, & Kallmeyer, 2019; Cheon et al., 2017; Chiba et al., 2019; Hou et al., 2021; Noohi, Miraghaie, Arabi, & Nooripour, 2017; Orndorff-Plunkett et al., 2017; Panisch & Hai, 2018; Reiter, Andersen, & Carlsson, 2016; Ros et al., 2017; Schoenberg & David, 2014; Tolin, Davies, Moskow, & Hofmann, 2020; van der Kolk et al., 2016; Wang et al., 2019).

That said, skeptics claim that EEG-NFB’s effects stem entirely from nonspecific factors (e.g., expectations, demand characteristics, context) based on multiple randomized, sham/placebo-controlled trials of attention-deficit/hyperactivity disorder (ADHD) showing comparable clinical improvements in both experimental and control groups (Ghaziri & Thibault, 2019; Neurofeedback Collaborative Group et al., 2020; Schönenberg et al., 2017a, 2017b; Thibault, Lifshitz, & Raz, 2016; Thibault, Veissière, Olson, & Raz, 2018). Among other criticisms, EEG-NFB proponents point out that evidence of EEG-learning (i.e., improvement in the targeted electrophysiological variable) in the active groups and a lack thereof in the controls, considered by many a prerequisite for the evaluation EEG-NFB’s specificity (Arns, Heinrich, & Strehl, 2014; Holtmann, Sonuga-Barke, Cortese, & Brandeis, 2014; Kerson & Collaborative Neurofeedback Group, 2013; Sherlin et al., 2011; Szewczyk, Ratomska, & Jaśkiewicz, 2018; Witte, Kober, & Wood, 2018; Zuberer, Brandeis, & Drechsler, 2015), was conspicuously absent in the trials presented as evidence for wholly nonspecific effects (Pigott, Cannon, & Trullinger, 2018; Trullinger, Novian, Russell-Chapin, & Pradhan, 2019).

Objectives

The aim of our review is to comprehensively evaluate all relevant and available ID-focused randomized, double-blind, sham/placebo-controlled trials for evidence of EEG-NFB specificity via clinical outcome measures.

Eligibility Criteria

We will consider all EEG-NFB published and unpublished trials involving humans with at least one ID diagnosis per the Diagnostic and Statistical Manual of Mental Disorders (DSM; American Psychiatric Association, 2013) or the International Classification of Diseases (ICD; World Health Organization, 2018) with no exclusion by language, locality, ethnicity, age, or sex. To minimize bias and control for nonspecific effects, all trials must be randomized, double-blind (trainees and raters), and sham/placebo-controlled (i.e., feedback contingent on a random signal, the activity from a different person’s brain, or an unrelated signal from the trainee’s own brain).

Information Sources

Studies eligible for review will be identified in a literature search from earliest dates within multiple databases including Scopus, PubMed, Ovid MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), Embase, Allied and Complementary Medicine (AMED), PsycInfo, and PsycoExtra. The electronic database searches will be supplemented by searching for trial protocols.
through the World Health Organization's International Clinical Trials Registry Platform (ICTRP), ClinicalTrials.gov, and the Australia New Zealand Clinical Trials Registry (ANZCTR). Additionally, citation lists of relevant articles and previous systematic reviews will be hand-searched for trials meeting our criteria but not located by the electronic database searches.

**Search Strategy**
The search strategies were peer reviewed by the University's Health Sciences Librarian with expertise in systematic review searching but not otherwise associated with the project. Literature search strategies were developed using medical subject heading (MeSH) and text words related to internalizing disorders and neurofeedback. When possible, limits imposed included participant type (i.e., human) and study design (e.g., randomized controlled trial, controlled clinical trial). As an example, our search strategy for Ovid MEDLINE will use exploded subject headings linked by Boolean operators (i.e., OR, AND) as follows: exp depression/ OR exp anxiety/ OR exp fear/ OR exp anxiety disorders/ OR exp mood disorders/ OR exp neurotic disorders/ OR exp "Trauma and Stressor Related Disorders" OR exp anorexia/ OR "Feeding and Eating Disorders"/ AND exp Biofeedback, Psychology/ with limits Humans and Randomized Controlled Trial. A detailed account of the search strategies for the various databases can be found in Supplement 1.

**Data Management, Selection Process, and Data Collection Process**
A single reviewer will collate the list of possible studies for inclusion and export them to EndNote (version X9) where duplicates will be removed. Two independent reviewers (TP & JM) will screen titles and abstracts for eligibility. Each reviewer will independently assess full reports of trials that appear to meet the inclusion criteria, or where there is any uncertainty. We will seek additional information from study authors, via a maximum of three email requests, where necessary to resolve questions regarding eligibility. Disagreements will be resolved in discussion between TP and JM, otherwise a third team member (DA) will become involved to make the final decision. Reasons for excluding trials will be recorded. The independent reviewers will not be blinded to the journal titles, trial authors, or institutions. Data will be extracted by independent reviewers (TP & JM) via a table generated in Word (Microsoft 365). A synthesis of the findings will be generated.

**Data Items**
The data items extracted will include (a) first author and publication/completion year, (b) primary condition(s) under study, (c) participant demographics (e.g., ages, sexes, etc.), (d) sham/placebo type, (e) EEG-NFB protocol (e.g., targets, reward rate, number/frequency/duration of sessions), (f) clinical outcome measure, and (g) evidence of targeted EEG-learning.

**Outcomes and Prioritization**
Our primary outcome of interest is between-group mean difference in change/final scores collected from clinician ratings or self/parent/teacher reports. In the event of a combination of the latter, the order of preference is self > parent > teacher. In the case of multiple rating scales for a given condition, the scale querying the most central aspects of the condition under study will be selected. In the case of multiple values for a single scale (i.e., total vs. subscale scores), total scores will be used. In the case of multiple posttreatment data collection time points, values obtained furthest from treatment termination will be given preference as it is believed that long-term outcomes may help to clarify the issue of specificity (Van Doren et al., 2019). To date, standard EEG-NFB protocols have not been established for the treatment of IDs (Banerjee & Argáez, 2017); therefore, no protocols will be excluded.

**Risk of Bias in Individual Studies**
Two independent reviewers (TMP & JM) will assess the risk of bias using the Cochrane Risk of Bias tool version 2 (RoB 2) which covers five domains (domain 1: risk of bias arising from the randomization process; domain 2: risk of bias due to deviations from the intended interventions; domain 3: risk of bias due to missing outcome data; domain 4: risk of bias in measurement of the outcome; domain 5: risk of bias in the selection of the reported result) as well an overall risk of bias. A judgment as to the possible risk of bias (i.e., low, some concerns, or high) on each of the domains will be made from the report. If there is insufficient detail reported in the study, the original study investigators will be contacted for more information. These judgements will be made based on the criteria for judging the risk of bias (Higgins et al., 2020). Disagreements will be resolved in discussion between TMP and JM, otherwise a third team member (DA) will become involved to make the final decision.

**Synthesis**
If enough studies are available, a meta-analysis will be performed utilizing inverse variance and random effects modelling to generate an overall
standardized mean difference (95% CI). Effect sizes (95% CI) will be calculated and displayed in a forest plot using RevMan (version 5.4.1). In cases of missing data, we will attempt to contact the trial authors to obtain the missing data. Statistical heterogeneity will be tested using the Chi² test (significance level: 0.1) and I² statistic (0% to 40%; might not be important; 30% to 60%; may represent moderate heterogeneity; 50% to 90%; may represent substantial heterogeneity; 75% to 100%; considerable heterogeneity). If high levels of heterogeneity among the trials exist (I² ≥ 50% or p < 0.1), important characteristics of the included studies (e.g., overall level of bias) will be analyzed via meta-regression or sensitivity analysis to try to explain the source of heterogeneity.

Meta-bias(es)
The potential for publication and small sample biases will be explored by funnel plots and Egger’s test if ≥ 10 studies are available.

Confidence in Cumulative Evidence
The quality of the cumulative evidence will be assessed using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE). Quality will be adjudicated as high (there is a lot of confidence that the true effect lies close to that of the estimated effect), moderate (the true effect is probably close to the estimated effect), low (the true effect might be markedly different from the estimated effect), or very low (the true effect is likely to be substantially different from the estimated effect).

Discussion
Neuropsychiatric disorders are among the most common causes of morbidity and mortality (Kessler et al., 2009) with rates markedly increasing worldwide in recent years (Duffy, Twenge, & Joiner, 2019; Haidt & Allen, 2020; Keyes, Gary, O’Malley, Hamilton, & Schulenberg, 2019; Pfeifer & Allen, 2020; Twenge, Cooper, Joiner, Duffy, & Binu, 2019). Among them, the IDs, which are characterized by distress experienced inwardly (Buchan et al., 2014; Cosgrove et al., 2011), are the most prevalent. Recently, a government inquiry here in New Zealand has shed light on the shortcomings of traditional frontline treatments (e.g., pharmacotherapy) and called for wider implementation of nonpharmaceutical approaches in treatment of mental health problems (Kris, 2018). Moreover, scientists around the world are calling for research into “novel interventions that may be based on altering plasticity or returning circuitry rather than neurotransmitter pharmacology” (Insel & Wang, 2010). EEG-NFB appears to be a safe, noninvasive, and efficacious that can be used as an adjunct or stand-alone treatment; however, there are questions regarding the nature of those effects. Specifically, there is much controversy surrounding the existence of specific effects. We hope that our review helps bring some clarity to this debate.

Author Declarations
This systematic review is part of a PhD thesis supported by the Department of Surgical Sciences, University of Otago, Dunedin, New Zealand. The department had no role in the design, implementation, analyses, interpretation, or dissemination of the results. All data generated or analyzed during this study are included in this published article and its supplementary information files. The authors declare that they have no competing interests. TMP is the guarantor and drafter of the manuscript. All authors contributed to the development of the selection criteria, the risk of bias assessment strategy and data extraction criteria. TMP developed and implemented the search strategy. PG provided expertise on mental health disorders. JM assisted with the article selections. All authors read, provided feedback, and approved the final manuscript.

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