Effectiveness of neurofeedback therapy for anxiety and stress in adults living with a chronic illness: a systematic review protocol

Farriss Blaskovits[1] · Jane Tyerman[1] · Marian Luctkar-Flude[2,3]

[1]Trent/Fleming School of Nursing, Trent University, Peterborough, Canada, [2]School of Nursing, Queen's University, Kingston, Canada, and [3]Queen's Collaboration for Health Care Quality: a Joanna Briggs Institute Center of Excellence, Kingston, Canada

Review question/objective: The objective of this review is to systematically examine the effectiveness of neurofeedback therapy for managing anxiety and stress in adults living with a chronic illness.

The specific objectives are to identify which neurofeedback systems and/or protocols demonstrate effectiveness and determine the level of supporting evidence.

The review question is as follows: What is the effectiveness of neurofeedback therapy for managing anxiety and stress in an adult population aged 18 years of age or older living with a chronic illness?

Keywords Anxiety; EEG biofeedback; mood disorder; neurofeedback; neurotherapy; stress

Background

Chronic illness is a substantial global burden, with the World Health Organization (WHO) reporting that 38 million of 56 million deaths worldwide in 2012 were due to non-communicable, or chronic, illness.[1] Furthermore, chronic illness in the Canadian population is estimated to increase by 4.7% from 2010 to 2030.[2]

Chronic illness has numerous definitions, but commonalities include a lengthy time course, progressive severity and decreased overall functioning causing impaired quality of life.[1,3] The WHO focuses on medically based chronic illnesses;[4] however, mental illness, drug abuse and chronic pain can be included given their long persistence and drain on sufferers.[2,5,6]

Anxiety, stress and distress associated with chronic medical conditions have been well documented.[7,8] Anxiety is the subjective psychological experience of environmental stressors which is marked by continued excessive worry, sleep abnormalities, difficulty concentrating, emotional lability, fatigue and restlessness.[9,10] Stress/distress is the psychological and hormonal response to environmental pressures.[10,11]

Although separate definitions of anxiety and stress/distress are presented, these terms are often used interchangeably due to their inherent connection with each other.

Chronic anxiety and stress can increase catecholamine release, decrease growth hormones, and aberrantly activate immune and inflammatory cascades.[12] As such, stress and anxiety can directly influence illness progression and can lead to irritable bowel syndrome exacerbations and increased cardiovascular risk.[7] Increased frequency of general anxiety disorder has also been found in people with asthma, cancer and chronic pain.[7] This comorbidity of anxiety with chronic illness can cause increased morbidity, mortality and decreased quality of life.[13] Traditional treatment for anxiety includes psychological treatments such as cognitive therapy, cognitive behavioral therapy, exposure therapy and self-help groups, as well as pharmacological modalities such as benzodiazepines and antidepressants.[14] Neurofeedback may reduce or eliminate the use of these medications.

Anxiety and stress also have direct neurobiological consequences. Stress hormones have been linked to neuronal remodeling, excitotoxic damage and neuroanatomical changes to the hippocampus and basolateral amygdala.[15] Alpha electroencephalography (EEG) recordings have revealed right frontal lateralization in anxious aroused patients as

compared to healthy control populations.[16] Such brain-specific alternations hint at the usefulness of a therapy such as neurofeedback in regulating anxiety. Neurofeedback is a novel complementary and alternative medicine therapy that is being used mainly by psychologists to treat a number of psychological conditions, including anxiety, depression, post-traumatic stress disorder (PTSD) and attention deficit hyperactivity disorder (ADHD).[17] As this is not a mainstream medical therapy, it is unclear whether individuals with anxiety and stress secondary to a chronic illness will also benefit from this therapy.

Alpha EEG biofeedback, neurotherapy or neurofeedback is a non-invasive drug-free technique. Brain activity is monitored by recording electrodes placed at designated locations on the scalp. Waveforms are then fed back to the patient through computer generated auditory or visual stimuli.[18] When waveforms balance within a healthy threshold, the system provides positive reinforcement such as a pleasant tone.[18] This treatment technique has been effectively used since the 1960s in many conditions, including ADHD, epilepsy, alcoholism, PTSD, stroke, depression, fibromyalgia and autism.[19]

Neurofeedback has been used in phobic and psychiatric populations to decrease anxiety. In a randomized controlled trial (RCT), females with spider phobia underwent functional magnetic resonance imaging (fMRI) neurofeedback, which decreased self-rated anxiety levels as compared to cognitive reappraisal controls and decreased insular activity.[20] In a pre- and post-test study, high frequency beta neurofeedback training in a PTSD population showed decreased self-rated anxiety.[21] Finally, in a quasi-randomized study of psychiatric patients with prominent anxiety symptoms, alpha EEG biofeedback decreased Taylor's Manifest Anxiety Scores in all anxiety groups.[22]

The objective of the present systematic review is to determine the effect of neurofeedback therapy on anxiety in an adult chronic illness population. According to the Shifting Perspectives Model, coping with chronic illness can change throughout the course of the illness as influenced by external and internal variables.[23] Neurofeedback targets the internal variables (operant brainwaves conditioning) in an attempt to decrease anxiety.[16] Thus, in addition to its ability to decrease anxiety, neurofeedback is able to provide the appropriate level of intervention based on the patient's own biofeedback.[19] Furthermore, patients with chronic illnesses often cite their complex medication regimen as a barrier to care.[24] Neurofeedback can benefit this population by thinning their pharmacopeia. This review will determine efficacy by compiling and analyzing the studies that have reported on neurofeedback therapy for anxiety in chronic illness populations. To guide this review, it is necessary to define key terms further:

Chronic illness is any condition lasting longer than one year, with progressive physical and/or mental deficits that lead to decreased quality of life.[1-3] For the purposes of this review, chronic illnesses will include chronic pain in addition to medical diagnoses.[5,6] In an effort not to overlap with past systematic reviews, ADHD, depression, PTSD, addiction, and other mood and psychiatric disorders will not be included in our definition of chronic illness.[18,25-27]

Anxiety is a psychological condition that can manifest affectively, cognitively and somatically.[28] Anxiety manifests affectively through pathological worry and emotional lability.[28,29] Cognitively, anxiety can cause decreased concentration and frequent rumination.[29] Somatic symptoms of anxiety include increased heart rate and autonomic activation, sleep difficulties, fatigue and restlessness, and altered immune function.[12,28,29] Anxiety also causes neurobiological abnormalities that can be seen in brain scans and functional differences that manifest in EEG changes.[15,16,18] For the purposes of this review, chronic illness and anxiety are viewed as synergistic.[7,8,13]

Neurofeedback, neurotherapy and EEG *biofeedback* are used synonymously to indicate a technique where electrodes, numbering two to 19, are placed on the scalp to monitor EEG brain activity.[18,30,31] When input falls into acceptable and healthy parameters, the system generates pleasant stimuli to reinforce the change.[30,31] This operant conditioning is continued over numerous sessions to reinforce transient changes in brain function using the patient's own input as a guide.[30]

Alpha EEG wave patterns are categorized based on frequency in Hertz (Hz): delta (<4 Hz) usually seen during sleep, theta ($4-8$ Hz) associated with thoughtfulness, alpha ($8-12$ Hz) associated with relaxation, beta ($13-30$ Hz) associated with alertness and gamma ($30-100$ Hz) associated with

cognitive processing.[30,32] The goal of neurofeedback is to alter the wave amplitudes of certain bandwidths.[30] In individuals experiencing anxiety, the alpha range is targeted to optimize a state of relaxed wakefulness, often through alpha/theta training.[30]

Numerous neurofeedback set ups can be used. Targeted symptom-responsive approaches allow the selection of a brainwave target based on symptomatology.[30] Quantitative EEG approaches work by selecting a structured frequency target to address EEG abnormalities. Nonlinear dynamical and low-energy neurofeedback system (LENS) approaches are often used to optimize non-clinical brain function.[30] Finally, fMRI-based neurofeedback approaches provide feedback from deeper brain structures, such as the insula and amygdala in emotional regulation.[31]

A search of the *JBI Database of Systematic Reviews and Implementation Reports*, Cochrane Database of Systematic Reviews, Medline and CINAHL found no existing or proposed systematic reviews of the treatment of anxiety with neurofeedback in a chronic illness population.

Inclusion criteria
Types of participants
The current quantitative review will consider studies that include any adult aged 18 years or older living with a chronic illness and reporting any level of anxiety. The focus of this systematic review will be on the treatment of anxiety in chronic medical conditions, including fibromyalgia, multiple sclerosis, cancer and stroke. Although psychological conditions may be chronic, their treatment with neurofeedback has been well documented in the literature. Past systematic reviews have explored neurofeedback, focusing on ADHD, PTSD and depression, therefore, these conditions will be excluded from the current review.[25,33]

Types of intervention(s)
The review will examine studies that evaluate any type of neurofeedback, including but not limited to the NeurOptimal system (New York, NY, US), the LENS and mixed alpha/theta and alpha/beta protocols.[32,34,35] There will be no exclusion based on the frequency, intensity or duration of the therapy.

The experimental interventions will include any method/protocol of neurofeedback. The control group can consist of no treatment, any alternative treatment or another method/protocol of neurofeedback.

Outcomes
The current review will consider studies that include the primary outcome of anxiety and/or secondary outcomes of distress, stress and coping. Any validated tool measuring these outcomes will be considered.

Given our interest in the comorbidity between chronic illness and anxiety, some of the scales measure anxiety within illness-specific parameters. Examples of this include the Fibromyalgia Impact Questionnaire, PTSD Symptom Scale – Self-Report, the Symptom Checklist-90-Revised and the Millon Clinical Multiaxial Inventory III.[36,37] Although not ideal, some papers have self-rated Likert type anxiety scales through which participants can rank their anxiety on a scale of one to 10.[34]

Types of studies
The current review will consider both experimental and epidemiological study designs, including RCTs, non-RCTs, quasi-experimental, before and after studies, prospective and retrospective cohort studies, case control studies and analytical cross sectional studies. This review only considered studies that were published in English.

The review will also consider descriptive epidemiological study designs, including case series, individual case reports and descriptive cross sectional studies.

Search strategy
The search strategy aims to find both published and unpublished studies. A three-step search strategy will be utilized in this review. An initial limited search of MEDLINE, CINAHL and PsycINFO will be undertaken followed by analysis of the text words contained in the title and abstract, and of the index terms used to describe the article. A second search using all identified keywords and index terms will then be undertaken across all included databases. Third, the reference list of all identified reports and articles will be searched for additional studies. To be thorough, no date limit will be placed on the search strategy.

The databases and sources to be searched include the following: MEDLINE, CINAHL, PsycINFO,

Epistemonikos, Scopus, Embase, Web of Science, Trip Database and Cochrane Central Register of Controlled Trials.

The search for unpublished studies will include: Dissertation Abstracts, Google Scholar, Clinical-Trials.gov and grey literature databases/gateways (e.g. OpenGrey, Grey Literature Report, Grey Source).

Initial keywords to be used will be: "EEG biofeedback," neurofeedback, neurotherapy, "chronic illness," "mood disorder∗," anxiety, stress, distress, "generalized anxiety disorder," coping.

Assessment of methodological quality

Quantitative papers selected for retrieval will be assessed by two independent reviewers for methodological validity prior to inclusion in the review using standardized critical appraisal instruments from the Joanna Briggs Institute Meta-Analysis of Statistics Assessment and Review Instrument (JBI-MAStARI).[38] Any disagreements that arise between the reviewers will be resolved through discussion, or with a third reviewer.

Data extraction

Quantitative data will be extracted from papers included in the review independently by two reviewers, using the standardized data extraction tool from JBI-MAStARI.[38] The data extracted will include specific details about the interventions (e.g. duration, content and method of delivery), populations, study methods and outcomes of significance to the review question and specific objectives. For missing information or to clarify unclear data, the authors of primary studies will be contacted. Any disagreements that arise between the reviewers will be resolved through discussion, or with a third reviewer.

Data synthesis

Quantitative papers will, where possible, be pooled in statistical meta-analysis using JBI-MAStARI. All results will be subject to double data entry. Effect sizes expressed as odds ratio (for categorical data) and weighted mean differences (for continuous data) and their 95% confidence intervals will be calculated for analysis. Heterogeneity will be assessed statistically using the standard Chi-square and also explored using subgroup analyses based on the different quantitative study designs included in this review. Where statistical pooling is not possible, the findings will be presented in narrative form, including tables and figures to aid in data presentation where appropriate.

References

1. World Health Organization. Global status report on non-communicable diseases 2014. Geneva: WHO Press; 2014.
2. Denton FT, Spencer BG. Chronic health conditions: changing prevalence in an aging population and some implications for the delivery of health care services. Can J Aging 2010;29(1):11–21.
3. Ontario Ministry of Health and Long-term Care. Preventing and managing chronic disease: Ontario's framework Kingston, Ontario: Queen's Printer for Ontario; 2007.
4. World Health Organization. Fact sheets: chronic diseases-World Health Organization; 2016 ; Available from: http://www.who.int/topics/chronic_diseases/factsheets/en/. [Updated January 1, 2016; cited June 30, 2016].
5. McLellan AT, Lewis DC, O'Brien CP, Kleber HD. Drug dependence, a chronic medical illness: implications for treatment, insurance, and outcomes evaluation. JAMA 2000;284(13):1689–95.
6. Tracey I, Bushnell MC. How neuroimaging studies have challenged us to rethink: is chronic pain a disease? J Pain 2009;10(11):1113–20.
7. Roy-Byrne PP, Davidson KW, Kessler RC. Anxiety disorders and comorbid medical illness. Gen Hosp Psychiat 2008;30(3):208–25.
8. Friedmann E, Thomas SA, Liu F, Morton PG, Chapa D, Gottlieb SS, et al. Relationship of depression, anxiety, and social isolation to chronic heart failure outpatient mortality. Am Heart J 2006;152(5):940.e1–8.
9. Alwahhabi F. Anxiety symptoms and generalized anxiety disorder in the elderly. A review. Harv Health Lett 2003;11(4):180–93.
10. Putwain D. Researching academic stress and anxiety in students: some methodological considerations. Br Educ Res J 2007;33(2):207–19.
11. Liu Y, Croft JB, Wheaton AG, Perry GS, Chapman DP, Strine TW, et al. Association between perceived insufficient sleep, frequent mental distress, obesity and chronic diseases among US adults, 2009 behavioral risk factor surveillance system. BMC Public Health 2013;13(1):84.
12. Burges Watson IP, Brüne M, Bradley AJ. The evolution of the molecular response to stress and its relevance to trauma and stressor-related disorders. Neurosci Biobehav Rev 2016;68:134–47.
13. Yohannes AM, Willgoss TG, Baldwin RC, Connolly MJ. Depression and anxiety in chronic heart failure and chronic obstructive pulmonary disease: prevalence, relevance, clinical implications and management principles. Int J Geriatr Psychiatry 2010;25(12):1209–21.

14. Baldwin DS, Anderson IM, Nutt DJ, Allgulander C, Bandelow B, den Boer JA, et al. Evidence-based pharmacological treatment of anxiety disorders, post-traumatic stress disorder and obsessive-compulsive disorder: a revision of the 2005 guidelines from the British Association for Psychopharmacology. J Psychopharmacol 2014;28(5):404–39.

15. McEwan BS, Eiland L, Hunter RG, Miller MM. Stress and anxiety: structural plasticity and epigenetic regulation as a consequence of stress. Neuropharmacology 2012;62(1):3–12.

16. Mathersul D, Williams LM, Hopkinson PJ, Kemp AH. Investigating models of affect: relationships among EEG alpha asymmetry, depression, and anxiety. Emotion 2008;8(4):560–72.

17. Weiner DK, Ernst E. Complementary and alternative approaches to the treatment of persistent musculoskeletal pain. Clin J Pain 2004;20(4):244–55.

18. Hammond DC. Neurofeedback with anxiety and affective disorders. Child Adolesc Psychiatr Clin N Am 2005;14(1):105–23.

19. Hammond DC. What is neurofeedback? J Neurother 2006;10(4):25–36.

20. Zilverstand A, Sorger B, Sarkheil P, Goebel R. fMRI neurofeedback facilitates anxiety in females with spider phobia. Front Behav Neurosci 2015;9(148):1–12.

21. Walker JE. Anxiety associated with posttraumatic stress disorder – the role of quantitative electroencephalograph in diagnosis and guiding neurofeedback training to remediate the anxiety. Biofeedback 2009;37(2):67–70.

22. Bhat P. Efficacy of Alfa EEG wave biofeedback in the management of anxiety. Ind Psychiatry J 2010;19(2):111–4.

23. Patterson BL. The shifting perspectives model of chronic illness. J Nurs Sch 2001;33(1):21–6.

24. Bayliss EA, Steiner JF, Fernald DH, Crane LA, Main DS. Descriptions of barriers to self-care by persons with comorbid chronic diseases. Ann Fam Med 2003;1(1):15–21.

25. Cortese S, Ferrin M, Brandeis D, Holtmann M, Aggensteiner P, Daley D, et al. Neurofeedback from attention-deficit/hyperactivity disorder: meta-analysis of clinical outcomes from randomized controlled trials. J Am Acad Child Adolesc Psychiatry 2016;55(6):444–55.

26. Linden DE. Neurofeedback and networks of depression. Dialogues Clin Neurosci 2014;16(1):103–12.

27. Reiter K, Andersen SB, Carlsson J. Neurofeedback treatment and posttraumatic stress disorder: effectiveness of neurofeedback on posttraumatic stress disorder and the optimal choice of protocol. J Nerv Ment Dis 2016;204(2):69–77.

28. Brenes GA. Age differences in the presentation of anxiety. Aging Ment Health 2006;10(3):298–302.

29. Harvard Health Letter. Are your daily concerns a sign of an anxiety disorder? [Internet]. 2014. Available from: http://www.health.harvard.edu/mind-and-mood/are-your-daily-concerns-a-sign-of-an-anxiety-disorder- [cited June 30, 2016].

30. Luctkar-Flude M, Groll D. A systematic review of the safety and effect of neurofeedback on fatigue and cognition. Integr Cancer Ther 2015;14(4):318–40.

31. Marzbani H, Marateb HR, Mansourian M. Neurofeedback: a comprehensive review on system design, methodology and clinical applications. Basic Clin Neurosci 2016;7(2):143–58.

32. Alvarez J, Meyer FL, Granoff DL, Lundy A. The effect of EEG biofeedback on reducing postcancer cognitive impairment. Integr Cancer Ther 2013;12(6):475–87.

33. Schoenberg PLA, David AS. Biofeedback for psychiatric disorders: a systematic review. Appl Psychophysiol Biofeedback 2014;39(2):109–35.

34. Hammond DC. Neurofeedback treatment of restless leg syndrome and periodic leg movements in sleep. J Neurother 2012;16(2):155–63.

35. Peniston EG, Kulkosky PJ. Alpha-theta brainwave training and beta-endorphin levels in alcoholics. Alcohol Clin Exp Res 1989;13(2):271–9.

36. Nelson DV, Bennett RM, Barkhuizen A, Sexton GJ, Jones KD, Esty ML, et al. Brief research report: neurotherapy of fibromyalgia? Pain Med 2010;11:912–9.

37. Saxby E, Peniston EG. Alpha-theta brainwave neurofeedback training: an effective treatment for male and female alcoholics with depressive symptoms. J Clin Psychol 1995;51(5):685–93.

38. The Joanna Briggs Institute. Joanna Briggs Institute Reviewers' Manual: 2016 edition Australia: The Joanna Briggs Institute; 2016.