Neurofeedback Treatment and Posttraumatic Stress Disorder

Effectiveness of Neurofeedback on Posttraumatic Stress Disorder and the Optimal Choice of Protocol

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Abstract: Neurofeedback is an alternative, noninvasive approach used in the treatment of a wide range of neuropsychiatric disorders, including posttraumatic stress disorder (PTSD). Many different neurofeedback protocols and methods exist. Likewise, PTSD is a heterogeneous disorder. To review the evidence on effectiveness and preferred protocol when using neurofeedback treatment on PTSD, a systematic search of PubMed, PsychInfo, Embase, and Cochrane databases was undertaken. Five studies were included in this review. Neurofeedback had a statistically significant effect in three studies. Neurobiological changes were reported in three studies. Interpretation of results is, however, limited by differences between the studies and several issues regarding design. The optimistic results presented here qualify neurofeedback as probably efficacious for PTSD treatment.

Key Words: PTSD, neurofeedback, psychopathology

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Posttraumatic Stress Disorder

Posttraumatic stress disorder (PTSD) is characterized by the development of specific symptoms after exposure to an exceptionally traumatic event (American Psychiatric Association, 2013a; WHO ICD-10, 1994). Symptoms include reexperiencing, avoidance, and hyperarousal. In the new fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-5*), a fourth cluster of symptoms that pays more attention to behavioral symptoms has been added. It includes symptoms of negative cognitions and mood (American Psychiatric Association, 2013b). PTSD is a heterogeneous disorder; the type of trauma experienced differs from one sufferer to the other, and the clinical presentation, that is, predominance of different symptoms and symptom severity, varies both from one individual to another and, especially in the more chronic cases, over time (American Psychiatric Association, 2013a).

The 12-month prevalence of PTSD differs between countries, with 3.5% in the United States and lower estimates of around 0.5% to 1% in Europe, Australia, Africa, Asia, and in Latin American countries (Hinton and Lewis-Fernandez, 2011). Far from all those exposed to trauma develop PTSD, Breslau et al. (1998) found that the conditional risk of PTSD following exposure to trauma was 9.2% and that this conditional probability varied depending on different factors such as severity of trauma (Breslau et al., 1998). There is a high level of comorbidity among individuals with PTSD, especially depression, anxiety, and substance use disorders (Sareen et al., 2007), as well as higher levels of physical health problems, suicidal behavior, distress, and poor well-being as compared with non-PTSD individuals (Sareen et al., 2007). Many cases of PTSD remit in the first 12 months after the trauma (40%), but more than one third of cases may persist for more than 60 months (Breslau et al., 1998).

Treatment of PTSD consists of psychotherapy, pharmacotherapy, and social support (National Institute of Clinical Excellence [NICE], 2005). Current evidence and practice guidelines recommend trauma-focused cognitive behavioral therapy and eye movement desensitization and reprocessing as effective treatment modalities. However, dropout from these psychological therapies is an important issue of consideration (Bisson et al., 2013; NICE, 2005). Pharmacological treatment can be effective in PTSD, and selective serotonin reuptake inhibitors are at present considered the most effective drugs. However, large gaps in the evidence base still exist and research suggests that a substantial part of patients (41%) fail to respond to pharmacotherapy (NICE, 2005; Stein et al., 2006). Likewise, psychotherapy is reported to be successful in approximately 60% of cases (Bradley et al., 2005).

Psychopathology and Core Neurocognitive Networks

Methodological advances in the study of psychopathology, especially the use of functional magnetic resonance imaging (fMRI), are pushing forward new ways of viewing psychiatric and neurological disorders, including PTSD (Menon, 2011). These are disorders characterized by altered perception, cognition, and emotion processes that all rely on the functioning of large-scale brain networks, rather than on specific brain areas of dysfunction as originally thought. So far, three stable intrinsic connectivity networks have shown to be particular important to proper functioning: the default mode network (DMN), central executive network (CEN) and salience network (SN). Menon (2011) suggests a "triple network model," hypothesizing that dysfunctioning of these three core networks plays a significant role in a broad range of psychopathology.

The SN includes the anterior insula and the dorsal anterior cingulated cortex (dACC), as well as subcortical areas including the amygdala and substantia nigra/ventral tegmental area. It is involved in integrating and regulating somatic, autonomic, and emotional information (Menon, 2011; Seeley et al., 2007). The CEN is anchored in the dorsolateral prefrontal cortex and the lateral posterior parietal cortex and subserves processes related to working memory and attentional control (Menon, 2011; Sridharan et al., 2008). The DMN involves the medial prefrontal cortex (mPFC), posterior cingulated cortex, and nodes in the medial temporal lobe and the angular gyrus. It controls various aspects of self-referential and mental processes (Menon, 2011). Unlike the SN and CEN, which become engaged when demand for external attention is high, the DMN shows less activity during stimulus-driven tasks. It will activate during internally focused processes. With this model, Menon states that dysfunction in any one of these three core networks can affect all three, leading to symptoms that go beyond the original deficit (Menon, 2011; Patel et al., 2012).

The identification of core neurocognitive networks helps in the understanding of a broad range of psychological disorders. Concurrently, identification of unique connectivity aberrations may facilitate the identification of reliable biomarkers that may serve as important, specific targets for therapeutic intervention and differential diagnosis of related disorders (Menon, 2011; Patel et al., 2012).

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Neurocircuitry of PTSD

As mentioned above, PTSD is a heterogeneous disorder with symptom severity varying across different symptom clusters. This in-group individual variability leads to inconsistency and heterogeneity in findings across studies. However, abnormal patterns of brain activity have been characterized in PTSD (Patel et al., 2012). Several brain regions implicated in the triple network model have been identified by use of voxel-wise whole-brain functional neuroimaging investigations as compromised in the neurocircuitry of PTSD, suggesting an over-engagement of the SN, failure to properly recruit the CEN, and altered functional connectivity within the DMN (Patel et al., 2012). On top of that, characteristically to PTSD, studies have found that people with PTSD exhibit less activation in the mPFC, contributing to a loss of top-down regulation of emotional systems. This may contribute to amygdala hyperactivation, a common feature of several anxiety disorders (Menon, 2011), but also a feature proposed to relate to trauma exposure more generally (Patel et al., 2012). Furthermore, hyperactivation in the hippocampus is found. These characteristic alterations result in difficulties in attention, arousal regulation, and inability to extinguish a fear response (Patel et al., 2012; Rauch et al., 2006).

Thus, finding ways to modify network connectivity may be a valuable tool in the treatment of PTSD.

How Does the Brainwave Pattern of a Patient With PTSD Look?

As discussed above, PTSD is associated with functional brain abnormalities, and fMRI studies have identified several involved brain structures. The real-time electrical activity in the brain as measured by electroencephalogram (EEG) is another way of gaining information about the functional neuroanatomy underlying the clinical symptoms. However, the small number of studies that have explored quantitative EEG (qEEG) patterns in patients with PTSD have elicited conflicting results; no consistent trend exists (Todder et al., 2012; Wahbeh and Oken, 2013). Because it is theoretically possible that two EEG measurements with similar visual raw EEG and/or qEEG patterns differ as to the inner brain electrical dipole distribution, Todder et al. (2012) applied both qEEG and low-resolution electromagnetic tomography (LORETA) analysis to a resting EEG measurement of 10 PTSD sufferers and 10 healthy controls. The study focused only on the theta band. They found no significant difference between the groups on the qEEG. However, the LORETA analysis revealed distinct patterns for PTSD patients as compared with controls, showing lower activity at 4 to 5 Hz mainly over the right temporal lobe and lower activity at 6 to 7 Hz over both right and left temporal lobes. The noteworthiness of this result is that it demonstrates the importance of exploring the current sources inside the brain and that it offers an alternative brain imaging method (*i.e.*, LORETA) that is less costly and complex and, although it possesses a lower spatial resolution, has a better time resolution than fMRI does.

Also, electrophysiological recordings related to the analysis of event-related potentials (ERPs) have shown promise as an alternative cost-effective method to fMRI to detect abnormal patterns of brain activity and neural processes related to information processing. A recent meta-analysis (Johnson et al., 2013) suggests that the ERP P3 has potential to be developed into a diagnostic aid in PTSD used in combination with biomarkers and clinical information as well as a means of evaluating treatment outcome. It relates to processes of attention and working memory and several P3 components have been found to be abnormal in PTSD.

Neurofeedback

Biofeedback is a means by which individuals can learn to control their physiology by providing them real-time report of biological activity (Niv, 2013). In the case of EEG biofeedback, that is, neurofeedback, the biological activity recorded is the person's brainwave activity. It is fed back to the person as an auditory or visual signal, rewarding the person each time progress is being made toward normalizing dysregulated neural activity (Demos, 2005). The mechanism is considered to be operant conditioning (Hammond, 2011).

Training may focus on increasing or decreasing the amplitude of a wave, modifying coherence (synchrony) or phase-lag (processing speed) between certain electrode sites (Demos, 2005; Hammond, 2014). An example of a protocol could be theta/beta training, which is upregulation of beta/sensorimotor rhythm activity with downregulation of theta. It aims to increase attention (Niv, 2013).

A variety of innovative neurofeedback approaches exists, for example, slow cortical potential training, infra-low-frequency neurofeedback, the low-energy neurofeedback system, LORETA neurofeedback training, as well as hemoencephalography training that focuses on influencing regional cerebral blood flow and fMRI neurofeedback that measures changes in blood flow through blood oxygenation levels (Demos, 2005; Hammond, 2014; Niv, 2013).

Clinical Efficacy and Use of Neurofeedback

Neurofeedback was developed initially in the United States in the 1960s and 1970s but is now being practiced in many countries around the world. PTSD is among the disorders addressed (Hammond, 2011; Othmer et al., 2013; Rubi, 2006). Most research suggests that significant improvements occur in 75% to 80% of cases (*e.g.*, Scott et al., 2005), enhancing brain functioning in a wide range of conditions such as attention deficit disorder (ADD)/attention deficit hyperactivity disorder (ADHD), learning disabilities, anxiety, depression, head injuries, insomnia, autism, and addictions (Hammond, 2011; Niv, 2013). Neurofeedback is also being used in nonclinical populations and seems to produce performance and cognitive enhancement (Gruzelier, 2014). In a recent systematic review of biofeedback for psychiatric disorders, 14 of the 20 (70%) included studies that had investigated EEG biofeedback reported a statistically significant clinical amelioration. Most had treated depression or anxiety disorders (Schoenberg and David, 2014). Despite these generally optimistic results, it is only in the treatment of ADD/ADHD that neurofeedback meets the criteria for being classified as an efficacious and specific treatment (Hammond, 2011; Niv, 2013).

The Underlying Mechanism of Neurofeedback

The evidence of how neurofeedback works and its impact on brain function is still insufficient, but there are different theories.

Neuroplasticity is a concept that is being supported by brain imaging techniques and research. It is particularly evident in the rapidly developing child or adolescent brain and if the event of physical trauma occurs to one part of the brain and other locations then take over the job. Although it takes more effort and cognitive training to achieve changes, adults continue to have a measure of plasticity (Demos, 2005). Neurofeedback may produce effects both on the synaptic level and by strengthening circuitry and may modulate (ab)normal brain oscillations directly (Ghaziri et al., 2013; Lubar, 1997; Niv, 2013; Ros et al., 2014, 2013).

In a recent magnetic resonance imaging study by Ghaziri et al. (2013), it was found that microstructural changes had occurred in white and grey matter after neurofeedback training. With a protocol aimed at enhancing sustained activity, they found improved visual and auditory sustained attention performance after 40 sessions of neurofeedback along with modifications in white matter pathways implicated in that skill and grey matter increases in areas involved in sustained attention.

In another sham-controlled study by Ros et al. (2013), one 30-minute session of alpha suppression training was preceded and followed by an fMRI scan. Only the neurofeedback group reduced their alpha amplitude significantly during training, and this dynamic EEG change was positively correlated with subsequent EEG resting state alpha change

(*i.e.*, lower resting-state alpha amplitude after neurofeedback as compared with before neurofeedback). This, in turn, was positively correlated with less mind wandering on a low-attention task and an increase in connectivity within regions of the SN involved in intrinsic alertness (the dACC). Clusters of DMN connectivity (the precuneus) were found to be positively associated with alpha synchronization.

Thus, neurofeedback seems to be able to induce functionally and anatomically specific brain changes. These changes have been shown to occur in core neurocognitive networks whose dysfunction have been implicated in a broad range of brain disorders and proposed to underlie psychopathology (*cf*., the triple network model; Menon, 2011; Ros et al., 2013).

Aims

Considering its proposed mechanism of action as well as the nature of PTSD, neurofeedback seems like a conceptually appealing approach. But how effective is neurofeedback in fact in relieving symptoms of and changing brain abnormalities in PTSD?

Different neurofeedback protocols exist. In PTSD, no consistent brainwave pattern has been found, and bearing in mind the general heterogeneity across studies as well as the fact that PTSD is a heterogeneous disorder, an additional question is: Which neurofeedback approach is presently the most ideal choice for PTSD?

This review was carried out to answer these questions.

MATERIAL AND METHODS

A systematic literature search was undertaken using the PubMed, PsycInfo, Embase, and Cochrane databases on dates between April 16 and April 30, 2014. The following search profile was used: "Neurofeedback" OR "EEG biofeedback" OR "neurotherapy" combined by AND with "PTSD" OR "post-traumatic stress disorder."

Articles were found among the search results based on relevance as judged by title and abstract. References of selected studies were also examined. Articles were restricted to those written in English and using human subjects. Only studies enrolling patients with a diagnosis of PTSD based on the World Health Organization International Classification of Diseases or DSM criteria were included. Studies that used neurofeedback along with other treatment modalities were also included. Case studies were excluded.

RESULTS

Five published articles were identified that had investigated the effectiveness of neurofeedback with PTSD and that met inclusion criteria for this literature review. Only one is a randomized controlled trial (RCT); the rest are uncontrolled studies (see Table 1).

Demographics

Sample sizes were small in all five studies, with the largest study holding 29 subjects. Only two studies included women, with a percentage of 30% and 86%, respectively (Kluetsch et al., 2013; Pop-Jordanova and Zorcec, 2004). The three studies applying alpha/theta training all treated combat-related PTSD (Peniston and Kulkosky, 1991; Peniston et al., 1993; Smith, 2008). Another study focused on children with insecure attachment and trauma-related PTSD (Pop-Jordanova and Zorcec, 2004), and one study included participants with PTSD related to childhood abuse (Kluetsch et al., 2013). Comorbidity such as alcohol abuse and depression was reported in two studies (Kluetsch et al., 2013; Peniston et al., 1993).

EEG Neurofeedback Protocols

Varieties of alpha/theta training were applied in three studies (Peniston and Kulkosky, 1991; Peniston et al., 1993; Smith, 2008), and an additional study focused on the alpha wave (Kluetsch et al., 2013). Anxiety disorders in general are mostly targeted with protocols designed to regulate alpha or both the alpha and the theta waves, and most of the studies report a good clinical outcome (Hammond, 2005, 2011; Moore, 2005; Schoenberg and David, 2014).

One study did sensorimotor rhythm (SMR) training (Pop-Jordanova and Zorcec, 2004). SMR neurofeedback has been found to facilitate thalamic inhibitory mechanisms, and it is associated with enhanced attention performance and less motor activity (Egner and Gruzelier, 2001; Sterman, 1996). It has been applied to seizure disorders and proven effective and specific in the treatment of ADHD, when combined with downregulation of lower frequencies (theta; Niv, 2013; Sterman, 1996; Timmers, 2014).

Duration of training and number of sessions varied from 30 minutes (Kluetsch et al., 2013; Peniston and Kulkosky, 1991; Peniston et al., 1993) to an hour (Smith, 2008) and from a single session (Kluetsch et al., 2013) to a series of 30 sessions (Peniston and Kulkosky, 1991; Peniston et al., 1993; Smith, 2008).

Effect on Targeted Symptomatology

Neurofeedback had a positive clinical effect in all five studies (see Table 2). Three of them (Kluetsch et al., 2013; Peniston and Kulkosky, 1991; Smith, 2008) reported statistically significant reduction in targeted symptomatology. In some instances (Peniston and Kulkosky, 1991; Smith, 2008), improvement was large; for example, in the study of Peniston and Kulkosky in 1991, *t*-scores on the Minnesota Multiphasic Personality Inventory went from above 70, 80, even 90 to *t*-scores below 70 and, on most scales, even below 60 in the study group (a *t*-score of 50 represents the mean average of a "normal" population; Hammond, 2005). However, some measures of clinical improvement failed to show a change (Kluetsch et al., 2013; Smith, 2008).

Two studies did a follow-up 30 months (Peniston and Kulkosky, 1991) and 26 months (Peniston et al., 1993) after training. All participants in both studies had had frequent (two to three episodes/week) anxiety-evoking nightmares/flashbacks before training. By the end of follow-up, only 3 of 15 (Peniston and Kulkosky, 1991) and 4 of 20 (Peniston et al., 1993) participants had had episodes of symptom relapse.

Effect on Neurobiological Parameters and Association With Symptomatology

Changes in brainwave activity and/or fMRI connectivity were investigated in three studies (Kluetsch et al., 2013; Peniston et al., 1993; Pop-Jordanova and Zorcec, 2004). Two of the studies reported significant changes (Kluetsch et al., 2013; Peniston et al., 1993). Changes in brainwave activity as well as in symptomatology were reported in these two studies, but although it was investigated by Kluetsch et al. (2013), none of them made a significant correlation between brainwave changes and symptom changes.

However, a significant link between changes in network connectivity and calmness was found. Kluetsch et al. (2013) found that reduced alpha amplitude during neurofeedback training was associated with a posttraining alpha "rebound" and that this increased resting alpha synchronization was associated with network connectivity changes: Greater SN connectivity with the right insula, decreased connectivity with the dACC, as well as an increased connectivity with several brain regions within the DMN, indicating less outward directed attention and greater reflective and self-regulatory capacities, respectively (Menon, 2011; Ros et al., 2013). Several of these connectivity changes were found to be associated with increased calmness.

Peniston et al. (1993) were successful in increasing brainwave synchrony from pre-to-last-session measures. The same study observed, during the last neurofeedback session, a crossover pattern wherein theta waves gradually increased and alpha waves decreased. Progression from one brainwave to another, that is, a decrease in alpha and increase in theta, happens naturally when we go from wakefulness into the presleep state

TABLE 1. Study Demographics, Design, and Outcome Measures

Author (Year)	Peniston and Kulkosky (1991)	Peniston et al. (1993)	Pop-Jordanova and Zorcec (2004)	Smith (2008)	Kluetsch et al. (2013)
Sample					
Patient group	PTSD (chronic (12–15 yrs) combat related)	PTSD (chronic (12–15 years) combat related) and alcohol abuse	PTSD (insecure attachment + trauma: death of family member, car accident, war conditions)	PTSD (combat related)	PTSD (childhood abuse) + comorbidity (*e.g.*, depression, other anxiety disorders, eating disorders)
N	29 (15 NF *vs.* 14 TAU)	20	10	10	21
% male	100	100	70	100	14
Age (yrs)	36.1 *vs.* 37.25 (mean)	37.2 (mean)	9 (mean)	26–63 (range)	39.9 (mean)
Medicated (yes/no)	Yes	Not reported	No	Yes, $n = 3$; no, $n = 7$	Yes, $n = 11$; no, $n = 10$
Design					
Randomized (yes/no)	Yes	No	No	No	No
NF approach	Alpha/theta	Alpha/theta	SMR	Two phased: (1) bipolar uptraining (15–18 Hz and 12–15 Hz) + theta (4–7 Hz) suppression and (2) alpha/theta (5–8 Hz) training followed by bipolar uptraining	Alpha desynchronization
Electrode placement	O1	F7, F8, 01, 02	Not reported	C3-Fpz, C4-Pz (bipolar), and Pz (alpha-theta)	19-channel EEG (signal at Pz for NF control)
No. of sessions	30	30	20	1: 10 and 2: 20	1
Duration (mins) of NF (per session)	30	30	50	1: 30 and 2: 20 + 10	30
Other treatment modalities	Pretraining: 8 × 30-min temperature biofeedback, autogenic training and breathing techniques	Pretraining: 5 or 6 × 30-min temperature biofeedback, autogenic training and breathing techniques	Traditional treatment + EDR biofeedback	No	No
Control group	TAU	No	No	No	No
Follow-up	30 mos	26 mos	No	No	No

Outcome measures and measures used					
	MMPI-indexed personality changes	Synchronization (% of synchrony per quadrant pair (phase 1, F7–F8; phase 2, F8, 02]; phase 3, 01, 02; phase 4, F7, 01)	Skin electric resistance (KΩ)	PTSD induced symptoms of depression and attention measured by HAMD and TOVA	Changes in alpha amplitude from pre-NF baseline to (1) "raining alpha change" (alpha during NF) and (2) "resting alpha change" (post-NF baseline)
	Medication consumption	Brainwave amplitude changes (mean alpha, beta, and theta amplitudes [uV])	Brainwave changes (μV)		Short-term changes in resting state fMRI connectivity within the SN and DMN measured by pre- and post-NF fMRI scans
	PTSD symptoms reported by monthly telephone contact	PTSD symptoms reported by monthly telephone contact	PTSD symptoms		State anxiety and arousal measured by STAI and Thayer

NF indicates neurofeedback; TAU, treatment as usual; MMPI, the Minnesota Multiphasic Personality Inventory; EDR, electrodermal; HAMD, Hamilton Depression Rating Scale; TOVA, Test of Variables of Attention; STAI, Spielberger's State Anxiety Inventory; Thayer, Thayer's Activation-Deactivation Adjective Checklist.

and the period in which the brainwave crossover pattern is found is thought to reflect states of consciousness wherein dreamlike images may be evoked, the so-called twilight states (De Gennaro et al., 2001; Demos, 2005; Foulkes and Vogel, 1965; Peniston et al., 1993). By promoting these twilight states, alpha/theta training is thought to bring forth the possibility to relive and resolve previously repressed traumatic events. This is supported by patients' reports of their clinical experiences with neurofeedback: Trauma-related memories were described as essentially anxiety-free episodes both during and several months after training (Demos, 2005; Peniston et al., 1993), and, more importantly, episodes of flashbacks and nightmares disappeared altogether in most cases (Peniston and Kulkosky, 1991; Peniston et al., 1993).

The results by Kluetsch et al. (2013) (increased resting alpha synchronization as well as calmness) are in line with the results from the studies applying alpha/theta training (Peniston and Kulkosky, 1991; Peniston et al., 1993; Smith, 2008).

DISCUSSION

Taken together, the results suggest that PTSD sufferers can have their brainwave activity as well as their fMRI connectivity of core neurocognitive networks changed by neurofeedback training and that alleviation of symptomatology occurs.

The results by Peniston et al. (1993) (*i.e.*, brainwave changes and symptom relief) are in accordance with the theories about neurocognitive networks and newer ways of explaining psychopathology discussed above (see *Psychopathology and Core Neurocognitive Networks*). Recent research has related the EEG changes of the transition from wakefulness to presleep to fMRI neural activity. Using an alpha/theta neurofeedback protocol on 45 healthy subjects, Kinreich et al. (2014) induced EEG changes and recorded the simultaneous fMRI activity with an aim to unveil the brain dynamics underlying the transition. Study results linked successful neurofeedback sessions, that is, the aforementioned brainwave changes including the crossover pattern, to decreased activity in external monitoring brain regions and to an opposition between the anterior and posterior parts of the SN, reflecting shifting from extrapersonal- to intrapersonal-based processing respectively (Menon, 2011).

Limitations

Several limitations must be taken into account when viewing the results. First of all, only five studies met criteria for inclusion in this review, and of these, only one was an RCT; the remaining four were uncontrolled studies. This problem applies more broadly to the field of neurofeedback research, where relatively few studies are well-designed, controlled studies (Niv, 2013). How big this problem is, is however being questioned because nonrandomized observational studies have been found to yield results similar to those obtained in RCTs (Benson and Hartz, 2000; Hammond, 2005). Nevertheless, other limitations regarding design exist. In this review, all included studies had small sample sizes, thus limiting sample power. In particular, one study (Pop-Jordanova and Zorcec, 2004) failed to comprehensively explain their methodology; for example, no information about electrode placement was provided. This lack of systematic communication seems to be a general tendency in the field (Schoenberg and David, 2014). Another issue is that neurofeedback covers a broad range of therapies. Even though an alpha/theta protocol was applied in three of the five studies, only two used the same clinical procedure. In neurofeedback research, in general, different protocols have been found to produce different outcomes. Some argue that this suggests that neurofeedback effects are specific, not simply placebo (Niv, 2013). Studies that include investigations of pre-to-post brain activity changes help elucidate the specific effects of the neurofeedback intervention (Kluetsch et al., 2013; Peniston et al., 1993; Ros et al., 2013). Still, with the absence of standardization,

TABLE 2. Study Results

Study (Year)	Results	Symptom Change?	Neurobiological Change?
Peniston and Kulkosky (1991)	MMPI: All 15 NF significantly improved on all 10 clinical scales, TAU only on one. On the PTSD subscales, only NF group ↓ mean score significantly. Medication: Significant differences between groups. All 15 NFs had ↓ medication use, only 1 TAU had ↓ use, whereas 10 TAU ↑ total psychotropic drug dosage. Follow-up: Significant differences between groups. Only 3 of 15 NF relapsed, all TAU reported relapse of PTSD symptoms.	↑↑	Not reported
Peniston et al. (1993)	Synchronization: sign ↑ (from ~1%–2% to ~73%, slightly less at phase 3). Brainwave amplitude changes: Significant ↑ in theta and beta, but not in alpha. The resulting alpha-theta crossover pattern, where theta waves ↑ and alpha waves ↓ across the posttreatment trials, was a statistically reliable interaction. Follow-up: Four participants had relapse of PTSD symptoms. These four subjects reported only a few (one to three) instances of recurrence of nightmares or flashbacks and described the episodes as essentially anxiety-free. Note: information about alcohol consumption/symptoms was not reported	↑	↑↑
Pop-Jordanova and Zorcec (2004)	EDR: Skin electric resistance of the group ↑ from ~5752 to ~5949 KΩ (reflecting ↑ relaxation). Brainwave changes: SMR ↑ from 6344 to 7176 μV (group mean), followed by relaxation, motor control, and ↓ beta. PTSD symptoms: eliminated in all 10 children	↑	↑
Smith (2008)	HAMD: Significant ↓ in depression. Scores from mean rank of 15.5 to 5.5. TOVA: Significant, positive change in commissions, variability, and *d'* scores but not in omissions or response time. Additional information: Two subjects were titrated off of Zoloft. Three subjects (experiencing stressful life events during and after the study) reported return of depression 20–30 days after NF.	↑↑	Not reported
Kluetsch et al. (2013)	Training alpha change: significant ↓; and resting alpha change: significant ↑. (The greater the ↓ in training alpha change, the greater the ↑ in resting alpha change afterward.) Functional connectivity: –For the SN, significant ↑ with the RMI, LPI, BST gyri, left dACC, and the RIF gyrus. –For the DMN, significant ↑ with bilateral sgACC and BMF gyri and sign. ↓ with the RMT gyrus and PCC. –No significant change in state anxiety but significant ↑ in calmness. Additional analysis: Relationship between changes in alpha amplitude and network connectivity: –For the SN: the greater the ↓ in training alpha change, the greater the ↑ in SN connectivity with the right insula. Also, t he stronger the ↑ in resting alpha change, the larger the ↑ in SN insula connectivity but the larger the ↓ in connectivity with the RSF gyrus, A/MC gyrus, RST gyrus, and the right dACC.	↑↑	↑↑

(Continued on next page)

TABLE 2. *(Continued)*

Study (Year)	Results	Symptom Change?	Neurobiological Change?
	–For the DMN: the stronger ↓ in training alpha change, the greater the ↑ in connectivity in the LA gyrus and the right putamen but the greater the ↓ in the RMF gyrus and left precuneus. A strong ↑ in resting alpha change was associated with ↑ connectivity with bilateral PCC, the RMF gyrus, and (only global alpha) the left mPFC but with ↓ connectivity in the RPC gyrus.		
	Relationship between calmness and changes in alpha amplitude: Nonsignificant for the alpha amplitude ↓ during neurofeedback but a *trend* toward a significant correlation with the resting alpha change (↑ alpha from first to second baseline correlated with ↑ calmness; global: $p = 0.07$ and Pz $p = 0.08$).		
	Relationship between calmness and connectivity changes: ↑ in calmness was associated with ↑ in SN connectivity with LPI, LST gyrus, LMT gyrus, LIF gyrus, RSF gyrus, and (although a little below the predefined extent threshold) a cluster in the RPI. Regarding the DMN: ↑ calmness associated with ↑ connectivity with the LSF gyrus, bilateral dorsomedial PFC, and the RMF gyrus but with ↓ connectivity with the left sgACC, the LMT gyrus, and the left claustrum.		
	Results were not significantly changed by participants' use of medication or comorbid diagnosis of depression.		

↔ = no change, ↑↑ = significant improvement ($p < 0.05$), ↑ = improvement (statistical significance not reported).

Note: MMPI indicates Minnesota Multiphasic Personality Inventory; TAU, treatment as usual; NF, neurofeedback; EDR, electrodermal; HAMD, Hamilton Depression Rating Scale; TOVA, Test of Variables of Attention; RMI, right middle insula; LPI, left posterior insula; BST, bilateral superior temporal; RIF, right inferior frontal; sgACC, bilateral subgenual anterior cingulated; BMF, bilateral middle frontal; RMT, right middle temporal; PCC, posterior cingulated cortex; RSF, right superior frontal; A/MC, anterior/nid-cingulate; RST, right superior temporal; LA, left angular; RMF, right middle frontal; RPC, right postcentral; LST, left superior temporal; LMT, left middle temporal; LIF, left inferior frontal; RPI, right posterior insula; LSF, left superior frontal.

found also among studies in this review, a difficulty pooling results remains.

The Ideal Choice of Protocol

Reaching a conclusion on what protocol to preferably use for PTSD is limited by issues regarding study design as well. The many differences in demographics among the included studies, for example, differences in age, sex, medication, and trauma exposure, are all factors that, along with the heterogeneous symptomatology of PTSD, may influence results. Clinicians already make this conclusion and adjust accordingly, individualizing therapy to match each specific patient (Demos, 2005). This strategy is in line with the emerging concept of personalized medicine. The US National Institute of Mental Health (NIMH) has recently launched new guiding principles for the research and understanding of mental illness, the Research Domain Criteria Project. This approach focuses on the underlying pathophysiology rather than symptomatology and emphasizes the importance of adapting a transdiagnostic perspective (Castellanos et al., 2013; NIMH, 2014). The example of PTSD is very illustrative in this context. Based on the new *DSM-5* criteria, calculations reveal that there are 636,120 ways to have PTSD. Bearing this in mind, it is maybe not so surprising that research based on the diagnosis of PTSD yields nonspecific findings (Galatzer-Levy and Bryant, 2013).

Personalized Protocols and Technical Advances

One way this problem is being addressed is by personalizing protocols to fit each individual patient. The assessment process before training, as well as modifications based on the person's response to the treatment, is one way to determine what protocol to use (Demos, 2005). One ADHD study found that children benefitted from protocol modification based on their individual neurophysiological profiles (Wangler et al., 2011). However, these modifications were made by very experienced neurofeedback researchers, meaning that translation into general clinical practice would probably require setting practitioner-training standards at very high levels (Brandeis, 2011).

The more recent advances in the field of neurofeedback such as LORETA may hold promise of a solution to the problem of heterogeneity as they address this issue directly and allow clinicians to integrate knowledge about a patient's symptoms to locations and systems in the brain. Existing literature about dysregulation of core neurocognitive networks can be used and linked to patients' complaints to confirm anatomical location (Thatcher, 2011). At the International Society for Neurofeedback and Research 2013 Annual Conference, a case series of eight veterans with PTSD and traumatic brain injury treated with LORETA Z Score neurofeedback was presented (Foster and Veazey-Morris, 1965 LORETA Z score neurofeedback in the treatment of veterans with PTSD and TBI, 2013. Retrieved from http://www.isnr.org/conference/ISNR_2013_Annual_Conference_Abstracts.pdf). Results were remarkable in most cases, with symptoms decreasing up to ten percent per session. The hope is that these methods will have the potential to reduce the number of sessions needed, lower the dosage of psychotropic medication given, and provide an alternative treatment approach to complex cases (Hammond, 2014; Thatcher, 2011).

CONCLUSION

PTSD is a debilitating disorder. Because of its complex symptomatology and psychopathology and high degree of comorbidity, it can be difficult to treat and current therapies are not effective for all people. A growing body of research suggests that, to a great extent, psychopathology can be understood by evaluating dysfunctioning of core

neurocognitive networks. Although heterogeneity exists, common or domain-general as well as domain-specific patterns of altered brain function have been found in PTSD.

Neurofeedback is a noninvasive, alternative treatment modality that is being used in a wide range of conditions, including PTSD. However, only a limited number of studies have investigated the effectiveness of neurofeedback on PTSD. Although all published studies find symptom amelioration and, when investigated, brain activity changes after training, several limitations exist. As of yet, data are still insufficient to qualify neurofeedback as efficacious for PTSD treatment (La Vaque et al., 2002) and more and better organized research is needed to establish which neurofeedback approach is the most ideal choice. The optimistic data that have been presented here will hopefully be supported by results from recent advances in the field and reap the benefits of the new guiding principles of research in mental illness.

DISCLOSURE

Søren Bo Andersen is co-owner of Learning Assessment and Neurocare Centre (LANC), an independent multidisciplinary lifespan clinic specializing in the assessment and management of individuals with ADHD, ASD, and other complex neurodevelopmental conditions. LANC also offers qEEG assessments as well as neurofeedback training.

Other authors declare no conflict of interest.

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