Semi-Automated Neurofeedback Therapy for Persistent Postconcussive Symptoms in a Military Clinical Setting: A Feasibility Study

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ABSTRACT Introduction: Neurofeedback therapy (NFT) has demonstrated effectiveness for reducing persistent symptoms following traumatic brain injury (TBI); however, its reliance on NFT experts for administration and high number of treatment sessions limits its use in military medicine. Here, we assess the feasibility of live Z-score training (LZT)—a variant of NFT that requires fewer treatment sessions and can be administered by nonexperts—for use in a military clinical setting. Materials and Methods: A single group design feasibility study was conducted to assess acceptability, tolerance, treatment satisfaction, and change in symptoms after a 6-week LZT intervention in 38 Service Members (SMs) with persistent symptoms comorbid with or secondary to mild TBI. Acceptance and feasibility were assessed using treatment completion and patients' satisfaction with treatment. To evaluate changes in symptom status, a battery of self-report questionnaires was administered at baseline, posttreatment, and 3-month follow-up to evaluate changes in psychological, neurobehavioral, sleep, pain, and headache symptoms, as well as self-efficacy in symptom management and life satisfaction. Results: Participants tolerated the treatment well and reported a positive experience. Symptom improvement was observed, including depressive, neurobehavioral, and pain-related symptoms, with effects sustained at 3-month follow-up. Conclusion: LZT treatment appears to be a feasible, non-pharmacological therapy amenable to SMs. Results from this pilot study promote further investigation of LZT as an intervention for SMs with persistent symptoms following TBI.

INTRODUCTION

Since 2000, nearly 380,000 US Service Members (SMs) have been diagnosed with a traumatic brain injury (TBI), of which approximately 82% were classified as mild (mTBI).[1] Symptoms of mTBI include impaired cognition (reduced attention, executive dysfunction), somatic complaints (headache, fatigue, sleep disturbance), and affective dysfunction (depression, anxiety, irritability, aggression).[2] Although most symptoms resolve within 3 months post-injury,[3] they persist beyond 3 months for 15–30% of patients.[4] Persistent postconcussive symptoms (PPCS)[5] can burden the individual, lead to a reduction in military readiness, and strain military health care resources.[6–9]

Neurofeedback Treatment for Persistent Postconcussive Syndrome

In light of evidence that posttrauma symptoms in mTBI may result from a disruption of neurological function,[3,10–16] it stands to reason that rehabilitation efforts focused on mitigating such disruptions and normalizing neural activity could benefit individuals exhibiting chronic symptoms associated with and comorbid to TBI.

Neurofeedback therapy (NFT) is a non-pharmacological intervention that produces few physical or psychological side effects.[17] It works by training patients to self-regulate their abnormal neural activity, as that underlies impaired cognition and behavior.[18] In addition to directly targeting underlying neural dysfunction, it has been suggested that NFT also improves self-efficacy, which may also underlie clinical improvement.[19] Generally, NFT uses behavioral principles to train patients in the form of positive reinforcement (eg, advancement in a video game, positive auditory or visual cues) for desirable neural modulation or negative punishment (eg, setbacks in a video game, negative auditory or visual cues) for undesirable neural modulation.[20,21] Studies have demonstrated that NFT improves somatic complaints[22] and cognitive functioning[23–25] following TBI and that it may be particularly effective for individuals for whom pharmaceutical interventions were ineffective.[26] Furthermore, a recent review of NFT in TBI reported improvements across a number of cognitive and neuropsychiatric symptoms, such as poor attention, memory, anxiety, depression, and impulsivity.[17]

Traditional applications of NFT may be limited for use in military clinical settings because of the number of sessions required to achieve results (~40) and the personnel resources needed for administration. Live Z-score training (LZT), a recently developed variant of NFT, does not share these limitations and has demonstrated efficacy in cognitive rehabilitation for several patient populations, including TBI.[27] LZT works by standardizing electroencephalographic (EEG)

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activity to a normative database, thus producing a Z-score that is used to provide immediate and appropriate feedback as patients attempt to normalize their EEG activity.[27] This real-time comparison to normative data permits patients to immediately adjust EEG normalization strategies and/or practitioners to immediately adjust feedback parameters to optimize and accelerate training. Several case studies of LZT have reported clinically meaningful symptom reduction in 20 sessions or fewer.[27] Furthermore, by comparison to standard NFT which is typically performed by a specially trained clinician to manually interpret EEG patterns and deliver feedback, LZT is semi-automated, such that a computer program compares real-time EEG to a normative database and provides automated feedback, with minimal input from a clinician in the form of pretreatment-specified parameters.

Accordingly, LZT shows promise for use in military medicine where effective rehabilitation of mTBI must be balanced with high incidence of TBI, few NFT-trained clinicians, time constraints, and cost-effectiveness. In this pilot study, we aim to assess the feasibility of LZT technology in a military clinical setting and describe changes in self-reported symptomatology in SMs with a history of mild TBI. Here, we report the acceptability (ie, the willingness to continue treatment after commencement), tolerance (ie, the ability to complete treatment), and treatment satisfaction of LZT by SMs after completing treatment and also evaluate changes in a variety of self-reported symptoms between pre- and posttreatment, including a 3-month follow-up.

METHOD

Design

This study was a single-group, pre-post intervention design to evaluate the feasibility of LZT as a rehabilitation treatment for PPCS and characterize changes in self-report symptoms following treatment, as this may inform future clinical effectiveness trials. Baseline (T1) evaluations were completed no more than 4 weeks before start of LZT; posttreatment (T2) evaluations were completed between 1 and 4 weeks after the final treatment; and a follow-up (T3) evaluation was completed between 11 and 15 weeks after the final treatment. This study was approved by the Madigan Army Medical Center's Institutional Review Board, which later consolidated into U.S. Army's Regional Health Command—Pacific Institutional Review Board.

Participants

Participants were recruited from Fort Carson Army Post and the surrounding Colorado Springs, CO community by posting recruitment material and provider referrals. Inclusion criteria included (1) active duty or Veteran status between 18 and 50 years of age; (2) documented history of mild to moderate TBI 3 months to 5 years post-injury (based upon documented loss of consciousness, alterations of consciousness, posttraumatic amnesia, and/or positive radiological findings in medical records); (3) current complaints of affective, somatic, or cognitive symptoms self-reported as being related to their injury; (4) presence of emotional dysregulation based on a score of $\geq$33 on the PTSD Checklist-Military version (PCL-M) and/or a score of $\geq$9 on the Patient Health Questionnaire (PHQ-9); (5) pass both the Word Memory Test and the Victoria Symptom Validity Test; (6) absence of unstable chronic medical and/or psychiatric condition for at least 6 months before enrollment (eg, uncontrolled symptoms associated with epilepsy, lupus, hypothyroidism, and neurocardiogenic syncope); and (7) absence of alcohol abuse indexed by a score below 6 on the AUDIT-C[28] (a screening tool for alcohol abuse) and/or medications known to interfere with either EEG readings or standard NFT (ie, benzodiazepines, nootropics, and narcotics [if used within the previous 24 hours]).

One hundred and seventy-two prospective participants were initially recruited. A total of 38 participants met eligibility requirements and agreed to take part in the treatment. Participants' medical status, standard of care TBI rehabilitation visits, and any adverse events were recorded at T1, each treatment session, and at T2 and T3. Medical records were used to confirm patient reporting.

Procedures

Evaluation assessments lasted 5–6 hours, split over 2 days, with each session no more than 7 days apart. Evaluation day 1 included a full neuropsychological battery. Evaluation day 2 included EEG recordings at rest and during a computerized cognitive task, self-reported symptom assessments, and physiologic stress testing (while viewing combat-related videos and performing high-load cognitive tasks). Neuropsychological, EEG, and physiological stress test results will be reported elsewhere, as the scope of this analysis is limited to feasibility. The average time period between day one of T1 and T2 evaluations was 61.59 days (SD = 9.78). The average time period between day one of T2 and T3 evaluations was 71.65 days (SD = 9.32).

Feasibility Measures

Participants were expected to complete a minimum of 15 treatment sessions; however, they were encouraged to participate in as many treatment sessions as possible up to 20 within 6 weeks. Treatment acceptability was quantified by evaluating early (i.e., within the first 5 sessions) voluntary withdrawal rates of less than 25%. For treatment tolerance, we established a 60% minimum for participant completion of at least 15 treatment sessions within a 6-week period. To evaluate participants' perceptions of the treatment, we created an End-of-Treatment survey with 8-items using a 5-point scale related to recovery progress, time commitment, and perception of the treatment. Participants were administered this survey after completion of T3 evaluations. Those who did not complete the entire study but completed at least one treatment session were offered the opportunity to complete the survey.

Self-Reported Symptoms

Outcome metrics were selected in an effort to assess the variety of distinct symptoms frequently reported following TBI, spanning physical, psychosocial, and cognitive domains. Two assessments were used for both study inclusion and as outcome measures: the PCL-M,[29,30] consisting of 17-items to assess PTSD-related symptoms; and the PHQ-9,[31] a 9-item questionnaire to assess depressive symptoms. Symptoms were assessed with a battery of self-assessment questionnaires that include Neurobehavioral Symptom Inventory (NSI),[32] a 22-item questionnaire, was used to assess the number and severity of postconcussive neurobehavioral symptoms (we used total score, number of different symptoms reported, and the somatosensory, affective, cognitive, and vestibular subscales for analysis); Medical Outcomes Study Sleep Scale (MOS-Sleep), a 12-item questionnaire to evaluate reported sleep disturbances and quantity; Chronic Pain Grade questionnaire (CPG), a 7-item questionnaire to measure chronic pain[33] (we used the pain intensity and disability scores); Migraine Disability Assessment Scale (MIDAS)[34] to assess pain related to headaches and migraine; Satisfaction with Life Scale (SWLS)[35] to evaluate global life satisfaction; and Self-Efficacy for Symptom Management Scale (SEsX)[36] to assess self-efficacy for symptom management.

Treatment Protocol

Treatment sessions took place over a maximum 6-week period. The LZT treatments were performed using BrainMaster Technologies, Inc[27] EEG hardware and acquisition software. Treatment was delivered using a video selected by participants from a complement of videos included in the BrainMaster BrainAvatar software system. Participants were positioned in a seated position 100 cm from the video display; audio was provided through an external speaker. During the video, EEG data were acquired through the BrainMaster Discovery 24E amplifier and recorded using 19 electrodes placed using the 10–20 system of electrode placement. Data from each channel were segmented into 10 different frequency bands randing from 1.0 Hz to 30.0 Hz (Delta, Theta, Alpha, Alpha1, Alpha2, Beta, Beta1, Beta2, Beta3, High Beta), each with a measure of phase, coherence, asymmetry, absolute power, relative power, and ratios to other frequency bands. The continuous EEG data recorded in each of these frequency bands and metrics were compared continuously in real-time to normative data to provide continuous Z-scores. For the normative database, we employed the Applied NeuroScience BrainMaster Z-Score Dynamic Link Library. When patients met specific Z-score criteria (eg, when EEG was approximating or within normative values) as described below, they received positive feedback in the form of visual and audio cues on the video.

The following clinician-specified criteria were established before training (for greater detail, see Collura et al.[27]): "target window" (the number of standard deviations from the mean of the normative database) was set at ± 0.9 standard deviations; percent ZOK ("PZOK"; the percent of all Z scores that fall within the target window at the current time) threshold was adjusted as needed so that the selected threshold was exceeded between 40 and 60% of the time; and percent ZMO ("PZMO"; the overall movement of Z score outliers that fall outside the "target window") was adjusted based upon patient performance such that reinforcement frequency fell within 10–15 per minute. Positive reinforcement was provided when the above three criteria were met. All administrations were performed by research staff who had been trained by an NFT expert on the LZT protocol and equipment. Staff performing the treatment administrations had no prior experience with EEG or NFT.

Setup time for treatment sessions was typically fewer than 10 minutes. Treatment duration began at 10 minutes and progressed to 30 minutes by treatment 6 or 7. Treatments could be shortened or breaks given based on patient tolerance. After the completion of the treatment, participants were encouraged to take a brief nap after each study treatment session to minimize expected side effects of fatigue and/or headache.

Data Analysis

We quantified early voluntary withdrawal and completion rates to provide descriptive results for acceptability and tolerance, respectively, and qualitatively analyzed perceptions of treatment. Scores from the self-report questionnaires were individually submitted to repeated measures ANOVAs with time (T1, T2, and T3) as the within-subjects factor. Planned comparisons were computed to compare T1 to T2; T1 to T3; and T2 to T3. Greenhouse-Geisser corrections are reported for analyses with sphericity violations. To explore what factors may best predict long-term changes in self-reported symptoms, we computed Pearson correlation coefficients between sustained changes in symptoms (T3—T1) and age, number of treatments, and number of lifetime TBIs. We also examined the relationships between long-term changes in self-efficacy and self-reported symptoms. All aforementioned statistical analyses were performed using SPSS v24.0. Because of the small sample size of this feasibility study, we interpreted significant and nonsignificant effects that have at least medium effect sizes (Cohen, 1988[37]).

RESULTS

Participants

Thirty-seven participants met criteria for mild TBI (<30 minutes LOC), and one participant met criteria for moderate TBI (due to abnormal imaging). The moderate TBI participant had fewer than 30 minutes of LOC and fewer than 24 hours of PTA, both supporting a classification of mild TBI, but the participant had a positive CT for subarachnoid hemorrhage. This participant was included in the analyses below after confirming that he/she was not an outlier (ie, ± 2 SD) on any outcomes. All patients who volunteered for treatment were active

TABLE I. Participant Demographics

	Time 1	Completers	Non-Completers	*p*
N	38	27	11	
Age	33.395 (8.046)	36.00 (7.580)	27.00 (5.177)	<0.001
Gender (male)	31 (81.6%)	23 (85.2%)	8 (72.7%)	0.369†
Race				0.279†
African American	7 (18.4%)	3 (11.1%)	4 (36.4%)	
Asian	1 (2.6%)	1 (3.7%)	0 (0.0%)	
White	29 (76.3%)	22 (81.4%)	7 (63.6%)	
Other	1 (2.6%)	1 (3.7%)	0 (0.0%)	
Ethnicity (Hispanic)	3 (7.9%)	2 (7.4%)	1 (9.1%)	0.402†
Rank				0.088†^
E2–E3	3 (7.9%)	1 (3.7%)	2 (18.2%)	
E4–E8	29 (76.3%)	20 (74.1%)	9 (81.8%)	
W4	1 (2.6%)	1 (3.7%)	0 (0.0%)	
O2–O3	3 (7.9%)	3 (11.1%)	0 (0.0%)	
O4–O6	2 (5.2%)	2 (7.4%)	0 (0.0%)	
Number lifetime TBIs	5.947 (3.510)	5.444 (3.609)	6.546 (3.357)	0.390
Months since most recent injury	14.054 (13.163)	14.692 (13.053)	12.546 (13.938)	0.657

Notes. Mean (SD) or number (%).
†Indicates *p*-value of chi-square analysis.
^Comparison between enlisted and officer (including warrant officer) ranks.

duty SMs. Twenty-seven patients completed the required minimum of 15 treatment sessions over 6 weeks. Comparisons of demographic characteristics between completers and non-completers (Table I) revealed that age significantly differed between the two groups, $t(36) = -3.596$, $p = 0.001$. Results from a post hoc univariate ANCOVA indicated that the relationship between age and treatment completion is independent of rank, $F(1,35) = 8.754$, $p = 0.006$, $\eta_p^2 = 0.200$.

Treatment Acceptance and Tolerance

Treatment was acceptable, as all 38 participants completed at least 5 treatment sessions. After the fifth treatment session, 13.2% (5 of 38) withdrew voluntarily from treatment—two due to dislike of treatment (nausea; increase in preexisting headaches) and three due to unavailability for treatments—15.8% (6 of 38) withdrew involuntarily due to service-related reasons, which is expected in this population—three due to not receiving permission for release from duty, two were removed by the PI for exacerbation of preexisting migraines, and one due to training assignments. In terms of treatment tolerance, 71.1% of participants (27 of 38) who began treatment completed a minimum of 15 sessions. Between T2 and T3 evaluations, one participant was lost to follow-up, one participant was excluded for starting an exclusionary medication (nootropics), and two participants withdrew involuntarily upon expiration of term of service. In total, 38 participants completed T1 evaluations, 27 completed T2 evaluations, and 23 completed T3 evaluations (Fig. 1).

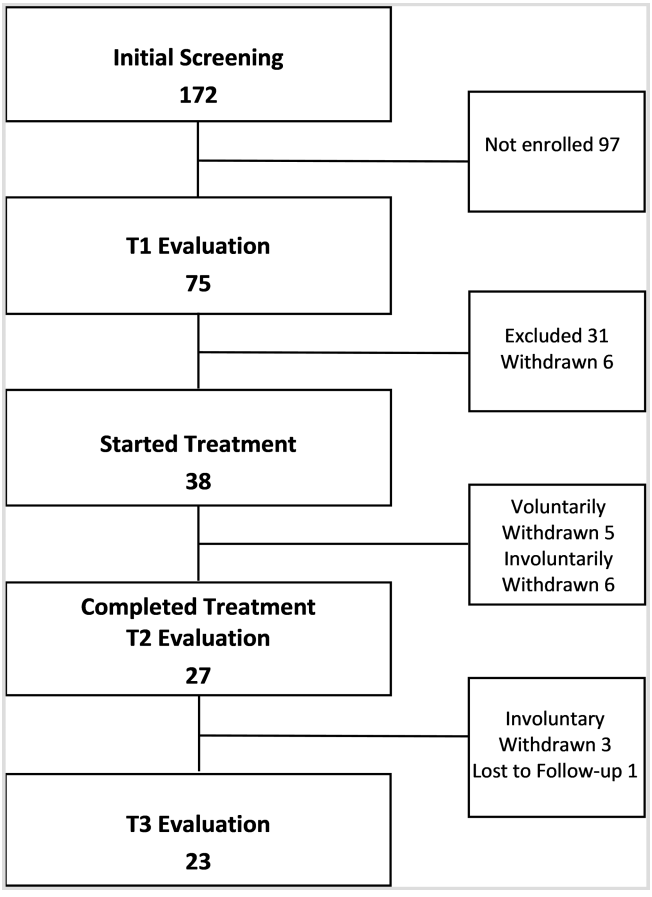

FIGURE 1. Participant flow diagram.

A total of 33 participants completed the End-of-Treatment survey (Table II): 27 treatment completers (≥15 completed treatments) and 8 non-completers (≥5 and <15 completed treatments). Overall, participants reported positive (>2.0) perceptions of the treatment and attributed many positive changes to the treatment, particularly improvements in memory (57.6% of respondents) and concentration/attention (81.8% of respondents). Groups differed on the item *"I am*

TABLE II. Participants' Perceptions of Treatment, N = 33

Survey Items	M (SD)[^]
This treatment program helped my recovery process	2.82 (0.917)
I thought the time commitment to the program was worth the effort to attend	3.36 (0.742)
I was able to find the time to attend or to get the support from my command	3.24 (0.969)
I found the process and the feedback program to be appropriately challenging	3.27 (0.876)
If there was an opportunity to do more of this kind of therapy, I would do it	2.94 (1.029)
I am glad I participated in this program	3.76 (0.435)
I would recommend this program to other service members	3.70 (0.467)
I felt this treatment program helped me in the following areas:	N (%)[†]
Concentration/attention	27 (81.8%)
Memory	19 (57.8%)
Visual tasks	13 (39.4%)
Calmness	13 (39.4%)
Decision-making	11 (33.3%)
Listening	10 (30.3%)
Headaches	7 (21.2%)
Social relationships	5 (15.2%)
Real world tasks	4 (12.1%)
Sleep	3 (9.1%)
Math	3 (9.1%)
Vocabulary	2 (6.1%)

[^] Scores range from 0 (low) to 4 (high).
[†] Number (%) of respondents indicating "yes."

glad I participated in this program," $t(24) = 3.361$, $p = 0.003$ (*df* reflects correction for unequal variance). Treatment completers reported a lower rating, M = 3.68 (SD = 0.476), than non-completers, M = 4.00 (SD = 0.00).

Self-Reported Symptoms

As shown in Table III, several self-reported symptoms were significantly different between T1, T2, and T3. PHQ-9 and NSI scores were reduced at T3 relative to T1 and T2. Scores for all subscales of the NSI were smallest at T3, as well as the number of distinct symptoms reported. CPG scores indicate that while the intensity of pain did not differ between evaluations, the extent of disability attributed to pain was significantly reduced at T2 and T3 relative to T1. MIDAS score was also reduced at T3 compared to T1. Although many self-reported symptoms were significantly reduced following treatment, PCL-M, MOS-Sleep scale, and SWLS scores did not change over the course of the study. SEsX scores increased following treatment, with greater scores at T2 and T3 than T1.

As shown in Table IV, the number of treatments completed was strongly associated with reduced PCL-M and NSI scores. Age was also strongly related to higher SEsX scores. We also observed that increased SEsX scores from T1 to T3 were associated with decreased NSI and increased SWLS scores.

DISCUSSION

The goals of this study were two-fold: to assess the feasibility of LZT as a rehabilitation treatment for persistent symptoms secondary to or comorbid with mild to moderate TBI among SMs and to characterize changes in self-reported symptoms following treatment, as this may inform selection of outcome measures in future clinical trials. Treatment was accepted and well tolerated by participants, and there was an overall positive assessment of all aspects of the treatment. Additionally, the reduction of many self-reported symptoms following treatment and sustained changes at follow-up suggest that LZT may be an effective treatment of PPCS in SMs. This type of therapy may be especially appealing to both providers and patients in military settings given their shared preferences for non-pharmaceutical interventions[38,39] and the safety profile of LZT—in the current study, only mild, temporary, and mostly expected adverse effects were reported.

Treatment acceptance was high, with zero early withdrawals from treatment; only two patients overall withdrew due to dislike of the treatment. In total, 27 of the 38 participants, or 71.1%, completed treatment. Attrition rate was 13.2% (5 out of 38), accounting for only those participants who voluntarily withdrew from the study, for either dislike of treatment or scheduling unavailability. Notably, age differed between participants who completed at least 15 treatments and those who completed fewer, suggesting that older individuals are more likely to complete the program. We explored the possibility that the relationship between age and treatment completion may be explained by the relationship between age and rank; however, our analysis of covariance showed that age is independent of rank in terms of treatment completion. Our comparison between enlisted and officer ranks revealed a marginal effect wherein officers are more likely to complete treatment. It is also worth noting that the three study participants who were unable to complete treatment because of inability to be released from duty were E5/African American/27yo; E4/African American/21yo; and E4/Hispanic/28yo. Although we are underpowered and unable to draw conclusions with a sample size of three, we believe this pattern wherein young, enlisted minorities were the only three participants out of 38 who were unable to complete treatment because of the inability to be released from duty raises questions about barriers to care. Additionally, nearly 16% of those who began treatment withdrew for service-related reasons unrelated to treatment tolerance or acceptability; further investigations are needed to interrogate the barriers to care in military clinical settings.

The acceptability and tolerability of LZT in our sample are corroborated by the positive perceptions of treatment. Overall, participants reported the program worthwhile and appropriately challenging. They also reported that they were, on average, glad to have participated and would likely recommend the treatment to other SMs. Interestingly, non-completers reported greater appreciation for having participated, although the rating difference (0.31 points on a Likert

TABLE III. ANOVA Results

	df	F	*p*	η_p^2	Mean (SD) T1	Mean (SD) T2	Mean (SD) T3	Planned Comparisons
PCL-M	1.478, 32.508	2.309	0.128	0.095	42.870 (12.768)	41.696 (15.369)	38.000 (13.246)	—
PHQ9	2,44	9.992	<0.001	0.312	12.739 (3.887)	11.430 (4.869)	8.830 (4.217)	b**, c**
NSI total	2,44	6.974	0.002	0.241	40.609 (13.486)	36.739 (15.327)	31.391 (12.576)	b*, c**
NSI somatosensory	2,44	3.549	0.037	0.139	10.522 (4.551)	9.565 (4.470)	8.522 (3.976)	b†, c*
NSI affective	2,44	5.700	0.006	0.206	14.000 (4.862)	13.217 (5.161)	11.000 (4.553)	b**, c**
NSI cognitive	2,44	6.406	0.004	0.226	9.913 (3.383)	8.217 (3.965)	7.261 (3.493)	a*, c**
NSI vestibular	2,44	1.580	0.216	0.067	3.261 (2.598)	3.087 (2.539)	2.565 (2.212)	b*, c†
NSI number of symptoms	2,44	6.216	0.004	0.220	12.130 (4.434)	11.044 (5.628)	9.087 (4.842)	b*, c**
MOS-sleep	1.574, 34.632	1.004	0.360	0.044	37.783 (5.334)	37.870 (6.622)	39.174 (5.598)	c†
CPG intensity	2,44	0.932	0.401	0.041	48.696 (14.728)	45.650 (13.686)	46.670 (14.873)	—
CPG disability	2,44	5.427	0.008	0.198	48.841 (26.123)	38.990 (29.067)	35.650 (28.612)	a*, c**
MIDAS	1.571, 34.553	2.039	0.154	0.085	92.435 (80.082)	89.826 (92.103)	67.826 (85.160)	c*
SWLS	2,44	1.307	0.281	0.056	24.044 (6.270)	23.304 (6.588)	24.522 (5.591)	—
SEsX	2,44	6.649	0.003	0.232	71.652 (21.083)	76.480 (27.871)	83.170 (24.066)	b*, c**

Notes. a = T1 vs T2; b = T2 vs T3; c = T1 vs T3.
** $p < 0.01$.
* $p < 0.05$.
† $p < 0.1$.

TABLE IV. Correlation Results

Self-Reported Symptom Questionnaires^	Treatments Completed	Age	SEsX^	Lifetime TBIs
PCL-M	**−0.405**†	−0.138	−0.325	−0.096
PHQ-9	−0.239	0.056	−0.311	−0.155
NSI total	**−0.354**†	−0.175	**−0.395**†	−0.133
NSI somatosensory	−0.306	0.071	−0.104	0.125
NSI affective	−0.285	−0.211	**−0.536****	−0.187
NSI cognitive	−0.300	−0.182	**−0.422***	−0.157
NSI vestibular	**−0.379**†	−0.040	−0.049	−0.154
NSI number symptoms	−0.331	−0.109	**−0.411**†	−0.115
MOS-sleep	−0.058	0.126	0.086	0.090
CPG intensity	−0.060	−0.078	−0.150	0.098
CPG disability	−0.238	0.106	−0.140	−0.002
MIDAS	−0.242	0.276	0.066	0.059
SWLS	−0.095	−0.093	**0.409**†	−0.290
SEsX	0.036	**0.381**†	—	0.070

Notes. N = 23.
Variables entered into the analysis reflect the change in symptom scores between T1 and T3.
** $p < 0.01$.
* $p < 0.05$.
† $p < 0.1$.

scale) is likely not clinically meaningful. Participants also directly attributed improvements in cognitive performance to the treatment. Interestingly, the cognitive functions they reported as most improved as a direct effect of treatment are memory and concentration/attention, which are two of the most commonly reported impairments following mild to moderate TBI.[40,41]

Previous studies of NFT for mild TBI have indicated improvements in somatic complaints[22] and cognitive functioning.[23–25] Additionally, NFT has been posited to reduce symptoms associated with PTSD,[42–44] depression,[45] and anxiety.[46] In an effort to evaluate whether LZT has potential to reduce symptoms in patients with TBI, we described and compared changes in symptoms related to PTSD, depression, somatic complaints, affective dysregulation, vestibular dysregulation, cognitive impairment, pain, and sleep disturbances. We found significant improvement in depressive symptoms, somatic symptoms, affective dysregulation, cognitive function, and pain-related disability. Interestingly, with the exception of pain-related disability,

all of these outcomes were significantly improved at 3-month follow-up compared to baseline and posttreatment evaluations while no differences were observed between baseline and posttreatment evaluations. Pain-related disability was the only self-reported outcome that improved between baseline and posttreatment time points. Because of the use of a single-group design wherein we cannot compare changes to a control group, we cannot conclusively attribute any changes in outcomes to the treatment; however, our observation that several symptoms improved following treatment provide additional support for the potential of LZT to effect positive changes in TBI-related symptoms. Additionally, because we did not control for concurrent treatments, we cannot dissociate the effects of LZT from other forms of treatment; 15 of the 23 participants who completed the follow-up evaluation received standard of care treatments concurrent with LZT (eg, vision therapy, physical therapy, speech therapy, cognitive rehabilitation, behavioral health). As a post hoc analysis to investigate the influence of concomitant treatments, we compared changes in outcomes between the two groups: participants receiving additional standard of care treatments ($n = 15$) and participants not receiving additional treatments ($n = 8$). We found no difference in outcomes associated with concomitant treatment. Additionally, our finding that the number of treatment sessions is associated with reduction in PTSD symptoms, depressive symptoms, and somatic, affective, cognitive, and vestibular symptoms lends indirect support to the possibility that there is a causal relationship. Furthermore, if any changes in self-reported symptoms are in fact due to LZT, our data suggest that these effects are more prominent several months after treatment completion and are subject to a linear dose-response relationship. This pattern should be explored in future clinical trials of the comparative effectiveness of LZT.

We observed enhanced self-efficacy of symptom management between follow-up and pre- and posttreatment evaluations, and this enhancement predicted better outcomes for symptom reporting and life satisfaction. These results suggest that LZT could potentially influence recovery from mild TBI both directly via neural mechanisms as proposed and indirectly via symptom management behaviors mediated by enhanced self-efficacy. Previous research suggests that enhanced self-efficacy interacts with normalized neural activity to further enhance treatment effects.[19] In corroboration with these previous reports, our data suggest that the strategies and perceived abilities to control neurophysiological mechanisms that are learned through NFT are integral components of treatment success. Furthermore, in our study, the difference in self-efficacy between baseline and follow-up was also strongly correlated with age, indicating that age may moderate the relationship between self-efficacy and treatment effects. Given the known significance of self-efficacy in recovery from TBI[36] and the relationship we observed between age and treatment completion, we propose that the relationships among these variables are critical to explore in clinical trials of LZT in SMs with TBI. Pending results from further investigation, it may be beneficial to apply age-specific treatment protocols to increase tolerance for younger adults and/or to simultaneously target self-efficacy to increase the overall effectiveness of LZT.

Limitations and Future Directions

Although we found that non-NFT expert research staff could efficiently administer the LZT protocol, we have questions about whether a universal target window, PZOK, and PZMO protocol for all participants were appropriate. Although LZT could be administered by non-NFT experts, the initial assessment to determine the LZT parameters in addition to periodic reassessments across multiple sessions may require a provider who specializes in neurofeedback in order to achieve maximum treatment effectiveness. For example, widening the target window "[provides] the brain with too much freedom in which to operate,"[27] effectively limiting training capacity. Conversely, a narrower target window would implicitly force the brain to develop a strategy for normalizing EEG activity to receive reinforcements. Accordingly, the ability to flexibly adjust the criteria allows for optimization of individual treatments. Future investigations exploring the implementation of LZT into military clinical settings may consider a "hub-and-spoke" model, wherein a single NFT expert may develop the treatment plans (either in clinic or remotely), with treatment implementation executed by technicians.[47]

The aims of this pilot study were to assess the feasibility of LZT in a military clinical rehabilitation setting and describe changes in symptom status following treatment to determine if LZT has potential for improving self-reported symptoms in SMs with PPCS. As previously discussed, we cannot conclusively attribute changes in symptoms following LZT to the treatment because of the single-group design, nor can we rule out potential confounding effects of concurrent treatments. The results provide support for the development of a randomized controlled trial to compare the effectiveness of LZT to standard of care for treatment of PPCS in a mild TBI population. We have demonstrated here that the treatment protocol is easily administered by non-NFT expert research technicians, is well accepted and tolerated by patients, and has potential to improve symptoms.

CONCLUSION

LZT is a clinically practical treatment that shows promise for improving PPCS symptoms in SMs. We found that LZT treatment was easily administered by non-NFT experts, was experienced positively by SMs, and could be readily implemented in military clinical settings. Although we found tentative support, future experimental trials are needed to conclusively establish the effectiveness of LZT for reducing symptoms of PPCS.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest.

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