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Marquise M. Bonn

Liliana Alvarez

Laura J. Graham

James W. Thompson

James P. Dickey

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Biofeedback as an intervention for persistent post-concussive symptoms: A randomized feasibility trial

Marquise M Bonn[1], Liliana Alvarez[2], Laura Graham[3], James W Thompson[4] and James P Dickey[5]

Abstract

Background: Case reports indicate that low-resolution electromagnetic tomography neurofeedback and heart rate variability biofeedback may improve physiological functioning in individuals with persistent post-concussive symptoms. However, it is unclear whether larger-scale studies are feasible.

Purpose: To evaluate the feasibility of a combined low-resolution electromagnetic tomography neurofeedback and heart rate variability biofeedback intervention for individuals with persistent post-concussive symptoms.

Methods: Individuals with persistent post-concussive symptoms were randomized into intervention and control groups, and their baseline and post-test assessments were compared to a healthy control group. Outcomes included self-report questionnaires, resting electroencephalograph and electrocardiograph recordings, and a driving simulation task. Participants in the intervention group completed three 20 min low-resolution electromagnetic tomography neurofeedback sessions per week and at-home heart rate variability biofeedback training every morning and night for 8 weeks. Feasibility was evaluated according to recruitment capability and sample characteristics, data collection procedures, suitability of the intervention and study procedures, management and implementation of the study intervention, and preliminary participant responses to the intervention.

Results: Thirty-three individuals were recruited and 24 completed this study (seven intervention participants, nine persistent post-concussive symptoms control participants, and eight healthy control participants). One-quarter of participants (four intervention participants and three persistent post-concussive symptoms control participants) experienced simulator sickness during the driving simulator task and had to withdraw from the study. Intervention participants had an 88% and 86% compliance rate for the low-resolution electromagnetic tomography neurofeedback and heart rate variability biofeedback sessions, respectively. Low-resolution electromagnetic tomography neurofeedback sessions took approximately 1 h to complete per participant. Preliminary analysis indicated that the intervention reduced electroencephalograph *z*-score deviation with a very large effect size ($d = 1.36$) compared to the other study groups.

Conclusions: Pilot studies evaluating the efficacy of low-resolution electromagnetic tomography neurofeedback and heart rate variability biofeedback should be performed to confirm these preliminary findings. However, the protocol should be modified to reduce participant fatigue and withdrawal. This trial was registered with Clinicialtrials.gov (NCT03338036; https://clinicaltrials.gov/ct2/show/NCT03338036?term=03338036&draw=2&rank=1).

Keywords

Concussion, Neurofeedback, Low-resolution electromagnetic tomography neurofeedback, LoRETA neurofeedback, Heart rate variability biofeedback, Persistent post-concussive symptoms

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[1]Health and Rehabilitation Sciences, Western University, Canada
[2]Occupational Therapy, Western University, Canada
[3]Physical Therapy, Western University, Canada
[4]Evoke Neuroscience Inc., USA
[5]Kinesiology, Western University, Canada

Corresponding author:
Marquise M Bonn, Health and Rehabilitation Sciences, Western University, 1151 Richmond Street, London N6A 3K7, Canada.
Email: mmayo23@uwo.ca

Introduction

Following a concussion, persistent symptoms are often disabling[1] and can result in difficulty continuing previously enjoyed past-times, resuming pre-injury physical activities or employment tasks, and reduced social interactions.[2]

Approximately 42% of people that experience a concussion do not return to work within 6 months of their injury, and 28% of those that do return to work are unable to return to their pre-injury work level.[3] Furthermore, once back at work, individuals who experience persistent post-concussive symptoms (PPCS) have an increased rate of unintentional injury[4,5] and risk of re-injury,[6] as well as an increased risk for severe motor vehicle collisions (requiring hospitalization[7]), and impaired driving performance.[8]

Individuals with a concussion history report more traffic accidents than those without,[9] which may be attributed to lasting impairments from their concussions. For example, individuals less than 3 months post-concussion exhibit poorer reaction times[10] and delayed perception of traffic hazards[8] during driving simulation tasks. Furthermore, asymptomatic individuals post-concussion cross over the roads edge more frequently than those that did not experience a concussion.[11] Of the asymptomatic individuals in this study, those that committed more driving errors also demonstrated poorer performance in verbal memory, memory speed, executive function, and cognitive flexibility tasks. These relationships are similar to those reported in the moderate to severe traumatic brain injury population.[12] However, little is known about the impact of PPCS on driving performance, and whether targeted interventions can improve driving performance.

Electroencephalograph (EEG) biofeedback, often called neurofeedback, has been used for decades as a non-invasive technique to improve brain function.[13] It was initially based on electrical activity at the surface of the brain, but has evolved to localizing the source of activity using low-resolution electromagnetic tomography (LoRETA). LoRETA neurofeedback improves attention and impulse control,[14] executive function,[15] agreeableness, feelings of confidence and composure,[16] and reduces stress.[17] It has also been used to modulate the symptoms of attention deficit hyperactive disorder,[18] post-traumatic stress disorder,[19] depression,[20] epilepsy,[21] and mild to severe traumatic brain injury.[22] For individuals with cognitive impairment and dementia, LoRETA neurofeedback has improved memory, attention, and global cognitive processing outcomes.[15] Accordingly, LORETA neurofeedback may be a suitable intervention for individuals with PPCS as they often experience memory, attention, and cognitive processing difficulties.[23]

Heart rate variability (HRV) biofeedback is often used in conjunction with LoRETA neurofeedback training[24–26] because the neuroanatomical networks and structures that affect and control HRV are influenced by neurofeedback, and vice versa.[24] HRV is the natural beat-to-beat variability in heart rate. It represents autonomic function and sympathetic-parasympathetic balance.[27] A review of evidence-based applications for HRV biofeedback indicates that HRV biofeedback may improve the management of hypertension, chronic muscle pain, depression, anxiety, post-traumatic stress disorder, and insomnia.[28] In individuals with a severe traumatic brain injury, HRV biofeedback improves cognitive functioning, problem solving, and emotional regulation.[29,30] Combining HRV biofeedback and LoRETA neurofeedback can reduce anxiety and depression in some individuals with a concussion,[31] and ultimately may reduce PPCS.[24,25]

Although previous literature indicates LoRETA neurofeedback may be beneficial for individuals with PPCS, it is unclear whether evaluating this intervention is feasible in this clinical population. For instance, recruitment in previous literature involved organizations affiliated with neurofeedback,[14] or individuals on wait lists for other treatment,[20] possibly increasing their willingness to participate. Drop-out rates in previous literature also vary from less than 1%[32] to 20%.[19] Accordingly, a feasibility trial is necessary to understand the best way to systematically evaluate LoRETA neurofeedback for individuals with PPCS.

Evaluating the effects of this intervention on changes to PPCS may help healthcare providers implement patient-centered care. Additionally, changes in EEG, standard deviation of the normal-to-normal interval (SDNN), and driving outcomes provides objective changes that healthcare providers can use when evaluating patient progress. Driving outcomes are practically important as fitness to drive (as assessed by a healthcare practitioner) following a concussion is influenced by type and severity of symptoms.[33] If healthcare providers could use objective measures (i.e. EEG and HRV outcomes) to determine if an individual is fit to drive, then it may reduce uncertainty and variability when allowing patients to drive following a concussion.

Intervention complexity and targeted outcome measures, including driving performance, recruitment of persons with a brain injury, and compliance, may all impact whether it is feasible to evaluate this intervention. Therefore, the purpose of this study was to evaluate the feasibility of a LoRETA neurofeedback and HRV biofeedback intervention to improve self-reported symptoms, EEG z-score deviation, HRV, and driving performance on a driving simulator. Specifically, this study evaluated feasibility based on recruitment capability and sample characteristics, data collection procedures, suitability of the intervention and study procedures, management and implementation of the study intervention, and preliminary participant responses to the intervention.[34]

Materials and methods

This study was informed by the intervention feasibility framework described by Orsmond and Cohn,[34] and sought to answer the following guiding questions: (1) Can we recruit and retain an appropriate and representative sample of participants? (2) Are the data collection procedures and outcome measures appropriate to evaluate the efficacy of the intervention for the intended population?

Table 1. Description of the five feasibility objectives and the guiding questions used in this study, as outlined in the Orsmond and Cohn (2015) framework.

Feasibility objective	Main guiding question	Evaluation approach
Recruitment capability and sample characteristics	• Can we recruit appropriate participants?	• The number of potential eligible participants was based on the number of recruitment emails. • The recruitment rate was calculated as the number of recruited individuals versus lost to follow-up. • Contexts for obstacles to recruitment were identified from communications with potential participants, as were reasons for ineligibility. • Participant characteristics were captured by a questionnaire.
Data collection procedures	How appropriate are the data collection procedures and outcomes measures for the intended population and purpose of the study?	• Suitability of data collection procedures was evaluated using the number of completed baseline and post-test assessments, and if participants took breaks between assessments. • The number of participants that did not complete the baseline assessment informed the capacity to complete data collection procedures.
Suitability of the intervention and study procedures	• Are the study procedures and intervention suitable for and acceptable to participants?	• Adherence rates were calculated using the average number of sessions completed. • Contexts for obstacles to adherence were identified from communications with participants to understand the time and capacity necessary to complete the intervention. • Adverse or unexpected events were explored with participants by discussing missed sessions.
Management and implementation of the study intervention	• Does the research team have the resources and ability to manage the study and intervention?	• Training, space, and time requirements were captured to explore the resources required to perform this study. • Financial requirements were identified to evaluate if the study could be conducted within the designated budget. • Technology and equipment used was identified to understand if they were sufficient.
Preliminary evaluation of participant responses to the intervention	• Does the intervention show promise of being successful with the intended population?	• Intervention's preliminary success was based on EEG z-score deviation and SDNN change.

EEG: electroencephalograph; SDNN: standard deviation of the normal-to-normal interval.

(3) Are the study procedures and the intervention suitable for participants? (4) What resources are required to manage the study and intervention? (5) Does the intervention show promise of being efficacious in the intended population? Table 1 outlines the study objectives, main guiding questions, and the approach used to assess the feasibility of this intervention.

Participants

People with a physician-diagnosed concussion that completed a recognized and publicly funded combined physiotherapy and occupational therapy brain injury treatment program (BrainEx90 at Parkwood Institute in London, Ontario) within the past 6 years were invited to participate in one of two groups: the experimental group or the PPCS control group. Participants were included if they: experienced at least one persistent symptom after completing BrainEx90; were 18 years of age or older; were fluent in English; had a valid driver's license; and had the physical ability to use hand-held tablet devices. People that met the same inclusion criteria, but with no history of a brain injury in the past 2 years and never attended BrainEx90, were invited to participate as part of a healthy control group. It was not possible to perform a power analysis to identify an appropriate sample size as the expected differences in HRV or EEG from biofeedback were not known. Rather, we identified an appropriate feasibility sample size of five participants per group to match a similar study evaluating brain injury and driving.[35] We tried

to recruit 10–12 participants per group to account for possible attrition.

Recruitment

Graduates of the BrainEx90 program were e-mailed a brief outline of the study and invited to meet with the researcher for more information before consenting to participate. Healthy controls were recruited via email from Western University and London, Ontario. This study was approved by Western University's Health Science Research Ethics Board, and registered on ClinicalTrials.gov (NCT03338036; https://clinicaltrials.gov/ct2/show/NCT03338036?term=03338036&draw=2&rank=1). All participants provided written informed consent.

Measures

After participants provided consent, the research team randomized individuals with PPCS into the intervention or PPCS control group before their baseline assessment. All participants completed the same battery of assessments at baseline and following the -week intervention. Assessments included the Rivermead Post-Concussion Questionnaire (RPQ[36]), the Generalized Anxiety Disorder 7-Item Scale (GAD-7; [37]), resting EEG and electrocardiograph (ECG) measures, and a 10 min driving simulation task. An evidence-based simulator sickness mitigation protocol was implemented throughout the driving simulator sessions including lighting adjustments, room temperature control, and three acclimation drives progressively introducing increasingly visually complex settings.[38] Participants were monitored for motion sickness following each acclimation and driving task via the Adapted Motion Sickness Assessment Questionnaire,[39] adjusted to a 0–10 point scale,[40] which assesses participant's feelings of discomfort in four domains: sweatiness, queasiness, dizziness, and nausea.

Participants in the intervention group performed HRV biofeedback training sessions every morning and night at home for 8 weeks with an Android tablet (either a Craig 7″ 1GB 6.0 "Marshmallow" Tablet, New York, New York or a Samsung Galaxy Tab A 7″ 8 GB Android 5.1 "Lollipop" Tablet, Seoul, South Korea), and a HRV training tool (similar appearance to an Apple Watch, but placed between the wrist and elbow; Evoke Waveband, Evoke Neurosciences, New York, NY). Each training session comprised a 5 min breathing exercise guided by a mobile application (Mindja, Evoke Neurosciences, New York, NY). Participants also recorded the date and time of each completed HRV session in a logbook.

Participants in the intervention group completed LoRETA neurofeedback sessions three times a week for 8 weeks in a private room at Parkwood Institute in London, Ontario. Typically, each participant completed their sessions on the same days and times each week. Initial assessments identified all deviant frequency bands within each Brodmann area (compared to age-based normative values) in each participant. These initial assessments informed individualized LoRETA neurofeedback training protocols, where a maximum of 12 Brodmann areas with at least one frequency band equal to or greater than two standard deviations above or below normal were selected for training. Each participant continuously trained the same Brodmann areas throughout the study. LoRETA neurofeedback sessions were completed using 4D source training (eVox, Evoke Neurosciences, New York, New York) and were broken up into 10 2 min exposures, for a total of 20 min of training, with breaks as required. Participants were instructed to "relax, focus, and turn on the green light". The light, presented on a computer screen in front of them, and turned green when participants were appropriately activating the target Brodmann areas. The goal was to have the green light on for 70–80% of the time, creating a balance of reward and challenge. Accordingly, when participants activated the green light >80% of the time, the stringency of their target (the magnitude of the acceptable deviation) was reduced, making it more difficult.

Following each LoRETA neurofeedback training session, participants completed a 5 min HRV biofeedback session on a desktop version of the Mindja app. This HRV biofeedback session counted as one of their two daily HRV biofeedback sessions.

Data collection and analysis

During the baseline assessment, all participants were fitted with a 19-lead EEG cap (Electro Cap International, Eaton, Ohio), with electrode placement corresponding to the 10–20 International System.[41] All leads linked ears as reference and AFz as ground, and connected to an amplifier (Evoke Neurosciences, New York, NY). An electrode was also taped inferior to the left clavicle to record the ECG. Data were recorded with the amplifier at a sampling frequency of 250 Hz.

Participants completed a 3 min resting EEG and ECG recording with their eyes closed. Following the EEG and ECG, participants completed the RPQ and GAD-7. Next, participants completed a driving simulation task on a CDS-200 Drivesafety™ high-fidelity simulator (DriveSafety, Murray, Utah). This included one of two 10 min simulator assessment drives, each containing the same pseudo-randomized scripted and potentially hazardous events.[38] Driving simulation metrics were collected at 50 Hz and included mean lane deviation and reaction times associated with two targeted scripted hazardous events: an unexpected pedestrian crossing in front of the vehicle, and a car suddenly pulling out of an adjacent driveway.

Participant EEG results were presented using z-scores of the EEG amplitude for frequencies between 2 and 30 Hz (0.1 Hz resolution) at all 47 Brodmann areas.[42] This yielded a rich dataset of 1288 EEG z-scores. However, to support preliminary evaluation of participant responses to the intervention and interpretation of EEG data, average standard deviation of power (at baseline and follow-up) was calculated across all frequencies (from 2–30 Hz) and between left and right for each Brodmann area with at least one frequency band greater than two standard deviations outside of normal. As fewer than 1% of normative z-scores are expected to be greater than three standard deviations,[43,44] data greater than three standard deviations was excluded from EEG z-score analysis.[45] Normality was assessed using boxplots. Parametric (analysis of variance) or non-parametric (Kruskal–Wallis) statistics, as appropriate, were performed (SPSS 25, IBM Corp., Armonk, NY) to evaluate the statistical significance of differences from baseline to post-test between the three participant groups.

HRV was quantified using the SDNN parameter.[29] The change in SDNN between groups (from baseline to post-test) was analyzed using a Kruskal–Wallis non-parametric test analysis (SPSS 25, IBM Corp., Armonk, NY) because the data were not normally distributed.

Results

Recruitment capability and sample characteristics

It took 8 weeks to recruit 24 participants for this study (Supplemental Appendix A). We do not know the number of individuals that received this email while still experiencing PPCS. The most frequently cited reason for refusing to participate was an unwillingness to commit to an 8-week intervention (three individuals). All individuals in the intervention and PPCS control groups that successfully completed the baseline assessment also successfully completed the post-test assessment (100% recruitment rate), while one healthy control participant was lost to follow-up (90% recruitment rate).

When evaluating baseline PPCS, all PPCS participants (intervention and control PPCS groups) reported that they continued to experience headaches, along with a variety of other symptoms. Out of seven intervention participants, 86% reported experiencing emotional changes (anxiety, anger, inability to regulate emotions), and 57% reported experiencing balance problems. Additionally, 43% of the intervention participants reported experiencing dizziness, light sensitivity, memory problems, difficulty focusing, and feelings of overstimulation. Out of nine PPCS controls, 89% reported experiencing noise sensitivity, 67% reported experiencing light sensitivity, and 56% reported experiencing emotional changes (anxiety, anger, inability to regulate emotions) and balance problems.

Data collection procedures

All participants completed the RPQ and the GAD-7 without asking for any additional clarification. Most of the individuals with PPCS chose to have a break after they completed the RPQ and GAD-7 questionnaires, and between each driving simulator acclimation drive. These breaks varied between 2 and 5 min. None of the healthy controls took breaks between any of the assessments. Seven individuals (four intervention participants and three PPCS control participants) reported increased sweatiness, queasiness, dizziness, and/or nausea while completing the driving simulation task. These seven individuals completed all acclimation drives, but experienced a worsening of symptoms following the last acclimation drive or during the driving simulation assessment, prompting them to voluntarily withdraw from the study.

Suitability of the intervention and study procedures

All participants in the intervention group that completed the baseline assessment completed the 8-week intervention (100% compliance). Participants attended 88% of their LoRETA neurofeedback sessions (21 ± 2.6 of the 24 possible sessions). One participant attended 17 sessions, and two participants attended all 24 sessions. Participants usually completed their sessions on the same dates and times (e.g. every Monday, Wednesday, and Friday at 9:30am). On each Friday session, the schedule for the following week was confirmed and changes to dates or times were made as needed (often to adjust for other commitments).

Participants often took breaks, such as getting a drink of water or sitting silently between exposures during LoRETA neurofeedback training, but some individuals completed all of the 2 min exposures consecutively. Some participants expressed fatigue during the intervention, particularly within the first 4 weeks. Some of these participants opted to miss session(s) in order to rest before reengaging in the subsequently scheduled session.

On average, participants in the intervention group completed 86% of their HRV sessions (96.7 ± 10.1 of the 112 possible sessions). Participants completed between 83 (two participants) and 111 HRV sessions (one participant). The most frequent causes for missed sessions were forgetting to perform the training and having technical difficulties with the app, although these issues were relatively infrequent. Some participants anecdotally reported that they forgot to log their HRV sessions in their logbook.

Management and implementation of the study intervention

Researchers allotted a 1 h block for each LoRETA neurofeedback intervention. This provided ample time for each participant to perform their neurofeedback training

(including breaks), the 5 min HRV training session, and for the researcher to prepare the equipment for the next participant. Funds were provided for parking at the hospital for participants to complete the training sessions. A prepaid Western University parking pass valuing $7.00 was provided for participants to complete the baseline and post-test assessments.

One of the researchers completed two neurofeedback training sessions to gain experience with this intervention. Training included technical support for understanding and using equipment, along with guidance on implementing LoRETA neurofeedback and HRV biofeedback. Evoke Neurosciences helped create the intervention plan and provided technical support throughout the study. Evoke Neurosciences also analyzed the raw EEG and ECG data, and provided the researchers with summary reports for each participant.

One researcher performed all of the baseline and post-test assessments, as well as the majority of the neurofeedback sessions (1 week's assessments were performed by another member of the research team). The intervention group was divided into two 8-week blocks (four participants completed the first block, and three completed the second block), to accommodate scheduling with a sole researcher.

The app for performing HRV training (Mindja, Evoke Neurosciences) at home was only compatible with Android devices, so five Android devices were purchased for participants to use for this study.

Preliminary evaluation of participant responses to the intervention

Data from a healthy control was removed after boxplot inspection revealed the individual's baseline EEG assessment data was an extreme outlier (Brodmann areas with average z-scores greater than five compared to a normative database).

The Kruskal–Wallis test identified a significant difference in EEG z-score deviation change between groups ($\chi^2(2) = 34.05$, $p < 0.05$; Figure 1). The intervention group had the greatest EEG normalization in their target areas (greatest decrease in z-score deviations at post-test compared to baseline; mean rank of 42.15), followed by the healthy control group (mean rank of 81.45), and the PPCS control group (mean rank of 83.32). Post-hoc analyses revealed that the intervention group's EEG average z-scores significantly decreased compared to the PPCS control ($p < 0.05$) and healthy control ($p < 0.05$) groups, with a very large effect size ($d = 1.36$). There were no significant differences between the PPCS control and healthy control groups ($p < 0.05$; Figure 1).

The average standard deviation of power across all frequencies (from 2 to 30 Hz) and between left and right for each Brodmann area each participant trained, at baseline and post-test, is listed in Table 2. Participant pre- and post-test standard deviations of power, and change in standard deviations for each Brodmann area with at least one frequency band greater than two standard deviations outside normal, are presented in Supplemental Appendix B.

There were no significant differences in change in SDNN from baseline to follow-up between groups ($\chi^2(2) = 0.17$, $p = 0.92$). The median SDNN decreased 4 ms in the intervention group, decreased 7 ms in the PPCS control group, and did not change in the healthy control group. There were no significant between-group differences in driving simulator outcomes or GAD-7 results.[46] However, there were significant reductions in headache, nausea, and dizziness self-report ratings in the intervention

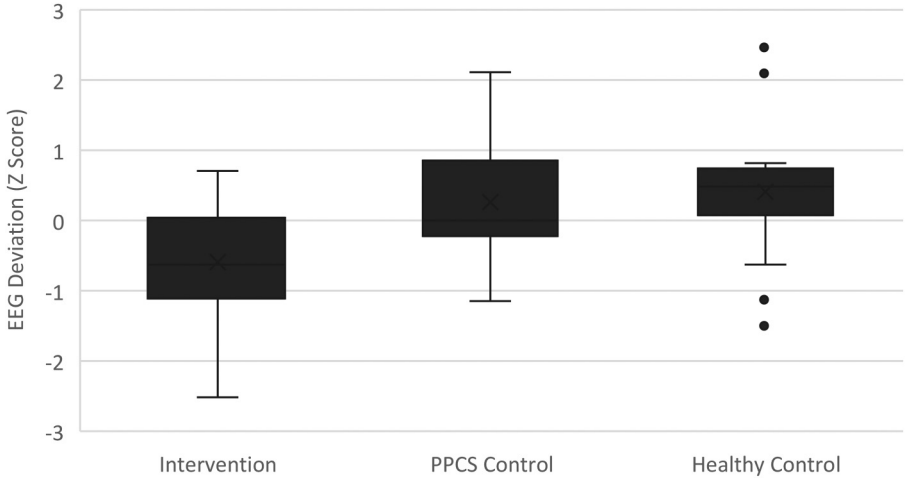

Figure 1. Average difference in the EEG z-score deviation change between groups. Boxes reflect the interquartile range, whiskers reflect the minimum and maximum values, and dots represent outliers. Significant differences are demonstrated between the intervention group and the PPCS control ($p < 0.05$) and healthy control groups ($p < 0.05$).
EEG: electroencephalograph; PPCS: persistent post-concussive symptoms.

Table 2. Participants average pre- and post-test standard deviations of power, and change in standard deviations for all Brodmann areas with at least one frequency band greater than two standard deviations outside normal.

Participant	Brodmann areas	Average baseline standard deviation	Average post-test standard deviation	Change in standard deviation
Intervention	10, 22, 23, 30, 32, 39, 40, 42	−0.47	−0.69	−0.23
Intervention	5, 7, 10, 11, 22, 31, 42	0.35	−0.83	−1.19
Intervention	10, 11, 21, 22, 23, 30, 31, 38, 42	0.74	−0.33	−1.07
Intervention	9, 10, 11, 32	0.23	−0.42	−0.65
Intervention	7, 10, 11, 19, 23, 31, 39	−0.40	−0.11	0.29
Intervention	7, 9, 10, 22, 23, 31, 39, 40, 44	1.88	0.55	−1.33
Intervention	10, 21, 22, 32, 40, 42	1.69	1.02	−0.67
Control	10, 11, 21, 22, 38, 42	0.09	0.46	0.57
Control	10, 11, 21, 22, 38, 42	0.11	1.12	1.01
Control	10, 11, 22, 42	0.01	−0.13	−0.13
Control	7, 21, 23, 24, 31, 32, 38	0.47	0.26	−0.21
Control	13, 21, 22, 39	−0.11	−0.42	−0.31
Control	19, 22, 23, 31, 39, 42	0.76	0.14	−0.62
Control	5, 6, 7, 21, 22, 30, 31	−0.55	−0.46	0.09
Control	10, 11, 21, 22, 38, 42	0.25	1.87	1.63
Control	19, 21, 22, 39, 42	−0.27	−0.26	0.01
Healthy	5, 7, 22, 42	4.45	0.82	−3.63
Healthy	10, 21, 22, 32, 38, 39, 40, 42	0.20	0.48	0.28
Healthy	23, 30, 31	2.39	3.03	0.64
Healthy	22, 42	−0.37	0.05	0.42
Healthy	10, 11, 32	2.66	2.96	0.30
Healthy	5, 7, 13, 21, 22, 31, 42, 44	0.63	1.21	0.58
Healthy	6, 10, 11, 22, 24, 29	0.35	−0.23	−0.57
Healthy	10, 11	−0.27	2.01	2.28

group compared to the healthy control group, and the PPCS control group compared to the healthy control group (Supplemental Appendix C).

Discussion

Case reports have highlighted the potential for LoRETA neurofeedback and HRV biofeedback to help reduce the number and severity of PPCS,[24,25] however, varying recruitment strategies and attrition rates made it unclear whether larger trials were feasible. The purpose of this study was to evaluate the feasibility of a LoRETA neurofeedback and HRV biofeedback intervention to improve symptoms, EEG *z*-score deviation, HRV, and driving performance on a driving simulator, in individuals with PPCS. The results of this study showed that larger randomized studies evaluating the efficacy of LoRETA neurofeedback and HRV biofeedback are feasible, as all feasibility objectives (recruitment capability, data collection procedures, acceptability of the intervention, resources, and preliminary effects) were met. The results suggest the need to modify the intervention for additional pilot testing ahead of starting a large-scale study. Modifications should include an altered number of LoRETA neurofeedback sessions and number of target Brodmann areas, extending the baseline assessment over a 2-day period, evaluating more safety-relevant driving outcomes, and using an application that is compatible with all devices.

A lack of standardized implementation guidelines may contribute to the lack of systematic evaluation on the benefits of LoRETA neurofeedback and HRV biofeedback on PPCS. Typically, neurofeedback practitioners create individualized LoRETA neurofeedback protocols, which can result in variations between protocols. Our implementation of three neurofeedback sessions per week was recommended by a licensed neurofeedback practitioner, however other biofeedback studies have used different numbers and frequencies of sessions. For example, one study used two to three LoRETA neurofeedback sessions per week for 20 sessions[47] while another study used daily neurofeedback sessions.[32] As some of our participants experienced fatigue from our protocol (resulting in some missed sessions), three sessions per week may not be the optimal number of sessions for this population. Future investigation on the ideal number of LoRETA neurofeedback sessions may be warranted to inform larger scale studies as well as neurofeedback practitioners' approach to creating individualized LoRETA neurofeedback protocols.

Individuals with PPCS often experience early cognitive fatigue,[48] and this study has highlighted the importance of pacing cognitive activities. This includes the number of

LoRETA neurofeedback and HRV sessions per week, along with the baseline and post-test assessment protocol. Since seven participants were unable to complete the driving simulation task, performing these assessments on separate days may increase the proportion of participants that can complete the protocol. As supporting evidence, some individuals said that they were too tired following the ECG and EEG brain function assessment, questionnaires, and acclimation drives, to complete the full driving simulation task. Fatigue may have influenced simulator sickness[49] and subsequent voluntary withdrawal. Furthermore, since the baseline testing was performed at Western University (an unfamiliar area for many individuals), participants may have experienced stress and fatigue from navigating to the test site.[48] Although the researchers took this into account by providing thorough and detailed written instructions (along with the researcher's phone number for immediate assistance), it still may have increased participants' fatigue before the study started.

In addition to early-onset fatigue, this population often experiences memory difficulties.[23] Memory difficulties were taken into account by maintaining consistent times and dates for sessions, and by confirming each participant's schedule the week prior. This helped participants remember their LoRETA neurofeedback training sessions, but did not help with their at-home HRV biofeedback training. Participants anecdotally stated that they forgot to perform their training, or forgot to record their at-home training in their logbooks, especially near the beginning of the study. Future studies should consider using an app that can store participant's usage, and potentially send reminders to perform their HRV biofeedback to help increase compliance.[50] Furthermore, the Mindja app was only compatible with Android devices. The research team purchased devices for intervention participants to use, which represented a significant infrastructure expense. Using an application that is compatible with all devices would reduce infrastructure expenses and may increase the ease of implementation.

Preliminary analysis showed that the intervention group's EEG z-score deviation decreased compared to the PPCS and healthy control groups. However, we observed that individuals with reduced EEG z-score deviation did not always experience improved symptoms or driving simulation performance, as there was a large amount of variation between individuals (Supplemental Appendices B and C). This means that some participants improved following the intervention, but others did not. This is clinically relevant as guidelines recommend the need to create individualized treatment interventions, where evidence has shown other PPCS interventions do not work for all persons with PPCS.[51,52] Therefore, similarly to many other PPCS rehabilitation practices, this intervention may not be effective for everyone with PPCS.

The HRV data suggests that the intervention may have varying effects: there were no significant differences between groups in SDNN over time; however, the intervention group's average SDNN did not decline as much as the PPCS control group over time. As higher HRV and SDNN values demonstrate a protective effect against cardiovascular disease,[53] the intervention may have helped mitigate continuing HRV decline that the PPCS control participants demonstrated.

Future HRV biofeedback and LORETA neurofeedback pilot studies should continue to systematically implement HRV biofeedback and LORETA neurofeedback. Implementing one to two weekly LORETA sessions may reduce participant fatigue and increase compliance. Both fatigue and reasons for missed sessions should be documented and considered during analyses. Researchers should plan for 1 h sessions to allow ample time for breaks and setting up between participants. Additionally, researchers should plan to allow time for breaks following completion of self-reported assessments. If this assessment battery is involved, then baseline and follow-up assessments should be performed over 2 days to help reduce participant's fatigue, which may increase their likelihood of completing the driving simulator task.[54] Future LoRETA neurofeedback and HRV biofeedback studies should investigate the number of Brodmann target areas, where including fewer than 12 deviant Brodmann areas per participant may help to reduce fatigue and help participants focus on abhorrent Brodmann areas.[55] Lastly, a power analysis performed on our findings suggest that a minimum of 22 participants per group is required. Accordingly, we recommend that future studies should recruit 28 participants to each study arm to account the 33% attrition rate demonstrated in this study.

Limitations

This study was not performed without limitations. First, it was performed on a relatively small number of individuals that were continuing to experience PPCS following the completion of a multidisciplinary outpatient rehabilitation program. Additional pilot testing is necessary to confirm these preliminary findings, and the results of this study may not be generalizable to everyone experiencing PPCS. It is also unclear whether training 12 Brodmann areas simultaneously resulted in the maximum benefit for participants. Other studies have used similar criteria for defining which sites to target for LoRETA neurofeedback, but have trained a smaller number of sites concurrently.[32] Additionally, this intervention focused on the same Brodmann area training sites for each participant throughout the intervention, while other studies updated the training sites between sessions.[32] While there are merits to maintaining consistent training sites, it may not be optimal for recovery. There may have also been reporting

inaccuracies for HRV sessions where participants were responsible for reporting their completed sessions.

Lane deviation may not reflect safety-relevant behavior during the driving simulation task, therefore other driving metrics may be more appropriate. For example, a scenario with one slow lane deviation in each lateral direction may have the same average lane deviation as a different scenario with more frequent and abrupt lane deviations, although the implications for safety are different.[56] Accordingly, outcomes such as abruptness of lane deviations or number of lane deviations, may be more appropriate.[57]

Conclusion

The methods used in this study are feasible to implement when investigating the impact of LoRETA neurofeedback and HRV biofeedback on PPCS. Preliminary results of this study indicate that LoRETA neurofeedback may reduce EEG *z*-score deviations in individuals with PPCS. Considering that a relatively large proportion of participants withdrew from this study, we recommend that future studies consider conducting baseline assessments over a 2-day period. This may increase retention by reducing the number of individuals that experience driving simulator sickness. Different driving outcome measures should also be considered to capture more safety-relevant behavior. Future studies should also investigate the ideal number of LoRETA neurofeedback sessions, as the results of this study indicate that three sessions per week may have increased participant fatigue. The number of target Brodmann areas should be similarly investigated. Lastly, future studies should also consider using a HRV app that is compatible with all devices, tracks usage and reminds the participants about training sessions. This may improve accuracy when tracking participation and potentially increase compliance. Pilot studies should be performed to confirm the trends observed in this study, and provide stronger evidence about the potential benefits of combined HRV biofeedback and LoRETA neurofeedback for individuals with PPCS.

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Data availability

The data used to support this study are available from the corresponding author upon request.

Declaration of conflicting interests

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ORCID iDs

Marquise M Bonn https://orcid.org/0000-0002-2097-6786
Laura Graham https://orcid.org/0000-0003-0809-9618
James P Dickey https://orcid.org/0000-0002-4101-835X

Supplemental material

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