The Effectiveness of Biofeedback for Individuals With Long-term Post-concussive Symptoms
NCT03338036

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Study Protocol:

1.1 Participants

Thirty-one individuals were recruited to participate in this study; which was approved by Western University Health Science Research Ethics Board (Appendix A). Participants with PPCS had to be 18 years of age or older, have previously suffered a clinically diagnosed concussion, completed the BrainEx 90 concussion rehabilitation program, and still experiencing ongoing symptoms. They also had to be fluent in English, hold a valid driver's license, and be capable of using hand-held devices. Healthy participants also had to be 18 years of age or older, have not suffered a concussion in the last two years, be fluent in English, and hold a valid driver's license. Participants were withdrawn from the study if they were unable to complete the entire baseline assessment. This resulted in the loss of seven participants that experienced a worsening of symptoms and could not complete the driving simulator task. Therefore, 16 participants with PPCS were randomized into the intervention and control groups, and eight healthy individuals were part of the healthy control group. This resulted in seven participants in the intervention group (48.6 ± 13 years old, four females), nine participants in the PPCS control group (54.6 ± 7.6 years old, six females), and eight healthy control participants (50.1 ± 15.5 years old, four females).

Information about the participants' PPCS were collected during the baseline assessment. All PPCS individuals (intervention and control participants) reported that they continued to experience headaches, along with a variety of other symptoms. Seven (of eight) intervention participants reported experiencing emotional changes (anxiety, anger, inability to regulate emotions), and four (of eight) reported experiencing balance problems. Additionally, three (of eight) intervention participants reported experiencing dizziness, light sensitivity, memory problems, difficulty focusing, and feelings of overstimulation. Eight (of 10) PPCS controls reported experiencing noise sensitivity, six reported experiencing light sensitivity, and five reported experiencing emotional changes (anxiety, anger, inability to regulate emotions) and balance problems.

1.2 Intervention Protocol

1.2.1 Baseline and Follow-Up Assessment

Participants were initially contacted via email about interest in the study; their response prompted an informational email. They then met with a study investigator at the iMobile Research Lab at Western University, where together they reviewed the letter of information. Once all questions were answered and they signed the consent form, the baseline assessment began.

The participant was first measured and fitted with a 19-lead EEG cap (Electro Cap International, Eaton, Ohio). Each electrode placement corresponded to specific locations on the scalp according to the 10-20 International System for electrode placement (80). The leads were then filled with a water-soluble conducting gel (Electro-Gel, Electro Cap International, Eaton, Ohio). An abrasive gel (NuPrep) was used as skin preparation for the attachment of an electrode to

each earlobe. Additionally, one electrode was also taped to the participants chest, below the left clavicle, for ECG monitoring.

The participant then completed three individual brain function assessments. First, they sat still and silent for five-minutes for eyes open EEG recordings. As sensitivity to light and screens can be problematic for individuals suffering PPCS, they were instructed to look at a spot on the wall. Afterwards, they had a three-minute resting EEG measurement taken with their eyes-closed. Finally, they performed a 10-minute reaction time test, where they pressed a button on a handheld toggle when a large blue circle appeared. Before they completed the actual reaction time test, they had to pass a pre-test that had the same rules, but provided immediate feedback about whether the responses were correct/incorrect in pressing/not pressing the button. All of this was completed with the study investigator in the neighboring room so as to not distract or stress the participant. There was a one-way window for the study investigator to observe the participant, and the participant was informed that they could either wave or call on the investigator if they had any questions or issues.

Brain function assessment was followed by a break. Afterwards, the participant completed the RPQ and GAD questionnaires (Appendices B and C), and then proceeded to the driving simulation task. This was performed on a CDS-200 DriveSafety simulator, which includes a steering wheel and dash display from a Ford Focus, a gas and brake pedal, and three computer screens for viewing. The simulator was adjusted for the participants comfort, ensuring that they were the appropriate distance from the screens, and they were comfortable with the height and tilt of the steering wheel and distance to the pedals.

The simulation drive began with three acclimation drives, which are part of an evidence-based simulator sickness mitigation protocol in the iMobile laboratory (24). The acclimation drives included driving straight down the road at 50 km/hour with no other vehicles on the road, driving around a city block involving four consecutive left-hand turns while navigating traffic, and lastly driving around a city block involving four consecutive right-hand turns while navigating traffic. Between each acclimation drive, participants were screened for symptoms of simulator sickness using a modified version of the motion sickness assessment questionnaire (81). Participants rated feelings of sweatiness, dizziness, and potential to vomit on a scale of 1 (not at all) to 10 (severely). Participants also had the option to take breaks between drives as needed.

Finally, participants performed one of two simulator drives. Participants were informed that the drive was supposed to simulate driving in the real world, so they were informed that other drivers may not obey traffic laws as expected. The two simulator drives contained identical elements, but in different orders. Both drives ended at a highway on-ramp, and they were instructed to either go towards London or Toronto, depending on which simulation drive they were completing. The drive was approximately 10 minutes in length, and included five scripted events: an unexpected pedestrian crossing the street in front of the car; a car making a rapid lane change in front of the driver; a sudden change in traffic lights from green to yellow (go-no-go); a way-finding task (appropriately picking the ramp to London or Toronto based on earlier instruction); and a car suddenly pulling out of a driveway in front of the participant. As we are interested in measures of driving performance that are directly related to safety, we evaluated the participant's responses related to two of the scripted events that involve responding to critical roadway information: the unexpected pedestrian crossing the street in front of the car

and a car suddenly pulling out of a driveway in front of the car. In specific, we quantified the participants' reaction times between the onset of the scripted event (e.g. first appearance of the pedestrian) until the participant responded by steering or braking. We also evaluated whether the participants were in a collision during their driving simulator task. Involvement in a collision ended the driving simulation, which may have prevented the participant from completing the pedestrian crossing or car pull-out scripted event. The mean lane deviation for the duration of the driving simulation task was also evaluated, using the average deviation from the center of the lane.
After eight weeks, all participants returned to complete another brain function assessment, RPQ and GAD, and driving simulator acclimation and drive. The final simulator drive was the alternate drive they had not completed in their baseline assessment. For example, if they completed Drive 1 in their baseline test, then they would complete Drive 2 in their follow-up assessment.

1.2.2 LoRETA Neurofeedback and HRV Biofeedback Intervention

Participants in the intervention group received an Android tablet (either a Craig 7" 1GB 6.0 "Marshmallow" Tablet, New York, New York or a Samsung Galaxy Tab A 7' 8GB Android 5.1 "Lillipop" Tablet, Seoul, South Korea) and heart rate variability training tool (Evoke Waveband, Evoke Neurosciences, New York, New York) upon completion of their initial assessment. They were shown how to use the equipment, and instructed that they should perform a HRV biofeedback session every morning and night for eight weeks. Each HRV biofeedback session involved placing the Waveband just below their elbow, opening the application on their tablet (Mindja, Evoke Neurosciences, New York, New York), and doing a 5-minute exercise in which they were cued to breathe at their resonant frequency (approximately six breaths per minute; 82). Points were awarded as their HRV improved. Participants were also provided with a log book to record the dates and times of their completed sessions.
LoRETA neurofeedback is based on measuring EEG signals, comparing them to age-matched population norms, and providing feedback to normalize deviant signals. We performed these measurements using a 19-lead EEG cap (Evoke Neurosciences, New York, New York). Assessments were completed at the iMobile research laboratory at Western University, London, Ontario, and interventions were completed in a private room at Parkwood Institute, London, Ontario. Each participant in the intervention group was scheduled to participate in three sessions per week (usually Mondays, Wednesdays, and Fridays), for 8 consecutive weeks. This totaled an expected 24 LoRETA neurofeedback sessions and 112 HRV biofeedback sessions (24 of which to be completed with the study investigator during the regularly scheduled neurofeedback training sessions). Typically, their sessions were at the same time of day.
Based on their initial assessment, an individualized LoRETA protocol was developed for each participant. This involved identifying the Brodmann areas of the brain and the EEG frequencies that were most deviant from age-based normal values, and targeting them for biofeedback. The set of Brodmann areas and frequencies were constant for each of the participants throughout the study. Each LoRETA neurofeedback session was broken up into 10 exposures of two-minute duration, for a total of 20 minutes of training. Participants were instructed to "relax, focus, and turn on the green light", which would appear on a computer screen in front of them. The light turned green when the participants were appropriately activating the target cerebral areas at

the appropriate amplitude. Throughout the duration of the study, as participants achieved more success (having the green light on >80% of the time), the stringency of their target (the magnitude of the deviation) was reduced, making it more difficult. The goal was to have the green light on for 70-80% of the time, creating a balance of reward and challenge.
Following the 20-minute LoRETA neurofeedback training, participants completed a five-minute HRV biofeedback session. The same HRV biofeedback exercise was completed as described above (which included a five-minute guided breathing exercise at a rate of approximately six breaths per minute). This HRV biofeedback session counted as one of their two daily HRV biofeedback sessions, and was recorded in their log books.

1.2.3 EEG Collection and LoRETA Neurofeedback

EEG was collected using the eVox System (Evoke Neuroscience, New York, New York), which is a portable hardware and software system for measuring electrophysiological data and performing various biofeedback sessions (surface neurofeedback, LoRETA neurofeedback, and HRV biofeedback). The eVox system consisted of a laptop, an amplifier, a response button, and a 19-lead EEG cap. When using the system, the cap was placed on the participant so that the 19 electrodes were situated on the head according to the 10-20 International System for electrode placement (80). The cap was then connected to the amplifier, which measured the EEG and ECG data and wirelessly transmitted them to the laptop. This setup was utilized for the LoRETA neurofeedback and also the EEG data collection.

1.2.4 Driving Simulator Collection

Performance on the CDS-200 DriveSafety simulator was collected and stored from the entire drive, with metrics collected at 50 Hz. This included vehicle speed, heading, and position within the lane. In addition, information was collected during each scripted event (e.g. the unexpected pedestrian crossing onto the roadway). Data collected also included metrics such as the distance to objects in the scripted events, and activation of the steering wheel, brake and gas pedal.

1.3 Data Analysis

1.3.1 RPQ and GAD

Total scores on the GAD for each participant were summed and change from baseline to follow-up was calculated. Comparisons of this change were analyzed between the intervention, PPCS control, and healthy control groups using a one-way analysis of variance (ANOVA). RPQ outcomes were tallied as two scores, similarly to previous research (41). The headache, nausea and dizziness scores were tallied, and the remaining questions were tallied separately. The statistical significance of differences from baseline to follow-up between the three participant groups in both RPQ sub scores were assessed using one-way ANOVAs.

1.3.2 Driving Simulation Task

Three parameters were assessed during the driving simulation, including the reaction time for two of the specific scripted events (the unexpected pedestrian crossing and the car pulling out in front of the driver's simulated vehicle). Reaction times were assessed by evaluating the time difference between the start of the hazardous event and when the participant applied pressure

to the brake or suddenly changed their lane deviation (i.e. swerving). Additionally, average lane deviation was calculated using the magnitude of deviation from the center of the lane at 50 Hz throughout the drive. This was measured in meters, and averaged over the span of the participant's drive. The statistical significance of differences from baseline to follow-up between the three participant groups were analyzed using a one-way ANOVA.

1.3.3 HRV and EEG

HRV was represented by the SDNN parameter (48). SDNN was expressed as a change from baseline to follow-up, and analyzed using a one-way ANOVA.

Participants' EEG results included the z-scores of the EEG amplitude for frequencies between 2 and 30 Hz at all 47 Brodmann areas (83). This yielded a rich data set with a total of 1288 EEG parameters per participant. Brodmann areas with the most deviation (12 areas maximum) were identified for all participants in the initial assessment, and were the chosen intervention target areas. Mean changes from baseline to follow-up within the designated target Brodmann areas, at all frequencies (2-30 Hz), were calculated. The statistical significance of differences from baseline to follow-up between the three participant groups were analyzed using a one-way ANOVA.

Statistical Analysis Plan:

All statistical analyses were performing using commercial software (SPSS 25, IBM Corp., Armonk, NY). All one-way ANOVA analyses followed the same protocol. Outliers were assessed using boxplots, and identified outliers were considered on a case-by-case basis. Normality of the distribution was assessed using a Shapiro-Wilks test. Levene's statistic was used to evaluate homogeneity of variances, and if the threshold for homogeneity of variances was not met, a Welch ANOVA and Games-Howell post hoc was used. If the homogeneity of variances assumption was met, a Tukey post hoc was used. The threshold for significance was set at $p = 0.05$ for all tests. Normality of distribution and homogeneity of variances are assumed unless otherwise stated.