Title and Identification Information

Study title: Using biofeedback during exergaming to attenuate alpha oscillations to improve postural control in people living with Parkinson's.

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Introduction and Study Overview

Background information

1. Background

Overview:

Complaints of impaired balance are common in, and troublesome for, people with Parkinson's (PwP). Accordingly, there is an urgent need to develop ways of improving balance beyond the ability of currently available therapies. New approaches need to target brain activity that controls movement and balance. Electroencephalography (EEG) is a device that measures the electrical activity of the brain (brain waves). There are several frequencies of brain waves when we are awake: alpha (medium), beta (fast), and theta (slow). Alpha frequencies of brain activity are linked to maintaining balance, with more alpha activity being associated with poorer balance. EEG neurofeedback treatment involves placing electrodes on a person's head to monitor and change brain activity by giving cued audio or visual feedback. It has been used in PwP to show improvements in balance and walking. Other preliminary research in PwP has shown that exercise can also improve balance. In this project, we want to find out whether greater and longer-lasting clinical benefits as well as more improvement in QoL measures, can be achieved if we use a specially designed exercise game as the feedback to change alpha brain activity. The use of gaming to motivate PwP in rehabilitation programs has recently been shown to improve short-term functional balance.

Detailed review:

Impaired balance and gait function culminates in increased falls risk for PwP. Between 45-68% of PD patients fall annually, with 50-86% falling recurrently. Falling carries a 30% mortality risk at 1 year, and 20% are institutionalised. To address this, we need to develop a rehabilitative intervention that will serve to prevent falls in PwP and address the heavy psychological burden that is imposed on PwP. Various non-invasive approaches to improve balance have been trialled in PwP. Neurofeedback utilises a brain-computer interface (BCI), to allow an individual to voluntarily learn how to self-regulate brain activity using an external real-time representation of on-going brain activity. EEG driven biofeedback is effective in modulating neural networks and can selectively target brain areas associated with movement control. Previous studies in PwP have shown that balance and postural control (gait) can be improved by utilising passive biofeedback techniques at rest to modulate neural oscillations.

Other non-invasive interventions in PwP include the use of exercise. Recent evidence from animal studies illustrates that high-intensity exercise can provide relief from motor symptoms in Parkinson's, corroborated by a randomised clinical trial showing that aerobic exercise but not stretching, improved motor function measured 6 months post intervention. However, despite physical exercise offering a potential feasible and cost-effective treatment option, adherence to physical activity is difficult to ensure, partly attributable to challenges with engagement as well as the cognitive deficits in PwP (i.e. apathy, lack of motivation). Recent technological advances have led to the development of computer games that incorporate physical activity (exergaming), which is suggested to lead to higher levels of intrinsic motivation and thus potentially improve adherence. Emerging data in PwP has illustrated that exergaming alone improves short-term functional balance. Additionally, exergaming in PwP has also been shown to reduce problematic (see paragraph below) rhythmic alpha brain activity and recruit cognitive processes, as demonstrated by its effectiveness in simultaneously improving measures of both apathy and motivation. The ability to reduce alpha levels of brain activity and simultaneously boost cognitive processing is particularly interesting when considered in the context of recent findings that have explored the neural and cognitive contributions upon balance control. These findings have illustrated the critical role that alpha

oscillations play in governing balance in both healthy controls and patients with neurodegeneration. That is, high levels of alpha brain activity is associated with poorer balance. Furthermore, other research has shown that interventions that address cognitive processes such as confidence (i.e. fear of falling), are also effective in improving balance in PwP. Growing body of empirical research suggests that exercise and techniques to non-invasively modulate brain activity can provide a valuable adjunct to rehabilitate balance impairment in PwP. However, such interventions are heterogenous in nature and currently there is no consensus regarding the optimal approach. Specifically, exercise therapy has been shown to be effective in relieving motor symptoms in both, a) animal models of PD and, b) human clinical trials. These include a diverse set of interventions, including aerobic exercise, mixed exercises, tai-Chi, treadmill training, dance and resistance training. Overall, the effects of exercise have been corroborated by a meta-analysis to illustrate improvement in balance assessed using the Berg Balance Scale (BBS) (SMD, 0.23: 95%CI, 0.10-0.36; $P<0.001$), but not for decreasing the incidence of falls (overall effect of $Z=1.81$). Technology inspired exercise interventions (i.e. exergaming) have also been effective in improving balance in PwP above the levels obtained with exercise therapy alone. Meta analysis of trials revealed significant differences between exergaming and conventional exercise on the following measures: Timed up and go ($p=0.043$:), 6 minute walk test ($p=0.021$), BBS ($p= 0.001$) and functional gait assessment ($p=0.022$). Other technology driven approaches include neurofeedback, which is a technique that can non-invasively modulate neural network activity, for example, by targeting brain activity associated with movement. Recent research has highlighted the critical role that alpha oscillations in motor and parietal cortices play in maintaining balance and postural control. Furthermore, using neurofeedback to supress alpha activity has been shown in skilled athletes to induce “expert-like” patterns of cortical activity presumably reflecting motor learning. Thus, EEG driven biofeedback that targets alpha oscillations appears to hold potential promise as a treatment for motor symptoms in PD. However, current data regarding the potential clinical benefits of improving balance in PwP using neurofeedback is variable. Review of studies revealed a success rate between 47-100% regarding the ability to change brain activity. 6/11 of these studies included a clinical outcome. However, in these 6 studies, the lack of any consistency regarding

the outcome measure, adequate inclusion of clinical information and lack of explicit statistical reporting, preclude the ability to conduct a meta-analysis and provide data regarding the precise effect size of this intervention.

To-date no study has sought to augment balance rehabilitation by using an exercise intervention that can simultaneously target, the neural (alpha oscillations), physiological (exercise), and cognitive (motivation) impairments in PwP. This project represents a significant step change in our approach to using exercise as an intervention to improve balance

Study design

For the design of the study, the investigators will adopt a double-blinded randomised clinical trial. This means that patients will not know their group allocation and the research associate that will be analysing the data will also not know what treatment the patient received.

Participants will be allocated into either group 1 (experimental) or 2 (control-SHAM). Participants in both groups will both perform the exergame rehabilitation. The exergame, delivered in virtual reality, involves travelling down a road (to give optic flow) whilst dodging balls that move towards the participant by either shifting their body either to the left or right. Patients are also be instructed to stand still and catch stars that appear, and these will be used to score points and are associated with reward, ensuring motivation.

The difference between the two groups will be the neuro-feedback provided during the performance of the exercise game. That is, group 1 will receive real feedback of brain activity whilst group 2 will receive a placebo which is called SHAM feedback (it corresponds to a random recording that has no association/correlation with on-going brain (EEG) activity). All participants will be randomly assigned a unique key code via a random computer generator, this will be facilitated by the Data Monitoring and Ethics committee. The research technician, that will perform the analysis of the data, will not be privy to particular intervention of interest. After the random allocation, but before the intervention, all participants will receive a familiarisation procedure for their allocation. Once the participants have successfully undergone the eligibility screening (see section below for details), participants will be randomly allocated to one of two groups. The

research team will then conduct the familiarisation sessions before proceeding to the pre-intervention assessment (limit of stability at baseline). This will be followed by the 12-week training program (that requires attendance at 30 1/2hr sessions over the course of three months. This will be followed by the 12 week (end of program) post-intervention assessment to measure the limit of stability, and a further single follow-up at 6 months to assess for long-term retention of any benefits. The 12-week post-intervention testing sessions will occur within 72 hours, but no less than 24 hours following the preceding training session. For the Pre-assessments: this will include: (i) the Limits of Stability test, (ii) Sensory Organisation Test, (iii) Parkinson's Disease Questionnaire, (iv) Berg Balance Scale, (v) Section III of UPDRS, (vi) mBEST, and (vii) 3 Metre Timed up-and-go. For the Post-assessments, this will include: (i) the Limits of Stability test, (ii) Sensory Organisation Test, (iii) Berg Balance Scale, (iv) mBEST, and (v) 3 Metre Timed up-and-go test.

Objectives and Hypotheses

Primary Goal

1. Examine whether exergaming with neurofeedback reduces falls risks in people living with Parkinson’s by improving neural control of balance and motor responses.

Secondary

2. Examine whether the amplitude of alpha waves is modulated by neurofeedback; and if so, does the change in alpha correlate with the reduction in fall risks?

Hypotheses

1. We predict that Group 1 will show reduced fall risk in comparison to Group 2 as reflected by improvement in objective and questionnaire-based measures of postural control, gait, and balance.
2. We predict that in Group 1 alpha waves will be gradually attenuated as a consequence of neurofeedback; indicating that neurofeedback can be used to modulate alpha waves to reduce fall risks in people living with Parkinson’s.

two balance questionnaires (Berg Balance Scale and mBEST) and each balance score (posturography). These are the Sensory Organisation Test (composite score equilibrium), the Motor Control Test (Forward and Backward Weight Symmetry; and Forward and Backward latency composite) and the Rhythmic Weight Shifting Test (Left/Right, Front/Back weight shift velocity and directional control composite scores).

Sample Size Determination

Based on data provided by Shih and colleagues who implemented the LOS as the primary outcome measure in PwP (Cohen's d = 0.74), a sample size calculation using G*Power statistical software estimated a sample size of five participants per group would be sufficient for 85% power (a = 0.05) while using a conservative estimated SD change of ±5. However, practically it is unlikely that this is a large-enough sample size to detect change between the real and sham (biofeedback and exercise conditions). Given the paucity of literature using a testing paradigm of exercise+ SHAM feedback and exercise + real feedback, we used our pilot data, indicates an effect size of 0.44. Accordingly, setting alpha at 0.05, our sample size calculation indicates that we need approximately 38 participants / group. We increase the sample size to 50 participant/group to account for 24 drop outs across both groups.

Statistical Methods

1. Analyses for the primary goal.

We will use a 2 (Phase: Pre vs Post) x 2 (Groups: Experimental vs SHAM-control) mixed model for repeated measures ANOVA for the individualised calculated falls risk. This will include three balance-related questionaries (Berge Balance Scale, mBEST, and 3 Metre Timed up-and-go test) with posturography balance score, which includes the Sensory Organisation Test (composite score equilibrium), the Motor Control Test (Forward and Backward Weight Symmetry; and Forward and Backward latency

composite) and the Rhythmic Weight Shifting Test (Left/Right, Front/Back weight shift velocity and directional control composite scores).

2. Analyses for the secondary goal

These analyses will be based on the training sessions.

a) A 3 Session Block (total number of session per ppt/3) x 2 Group (1 vs 2) one-way ANOVA for average alpha attenuation (this was calculated by comparing their average alpha waves with their baseline alpha waves which was recorded for 20 seconds in each participant in each session).
b) To assess whether alpha attenuation correlates with changes in balance, we will run a Pearson correlation between the average alpha attenuation and the balance measurements (e.g., composite equilibrium scores).

Handling missing data

No missing data are expected because of the way session block is defined.

Blinding/Unblinding (Details of any blinding and unblinding processes).

For the design of the study, the investigators will adopt a double-blinded randomised clinical trial. This means that patients will not know their group allocation and the research associate that will be analysing the data will also not know what treatment the patient received.

Data Presentation (TLF specifications; Statistical software and versioning).

R version 4.1.3 (2022-03-10)

Ethical and Regulatory Considerations

Ethical approval was granted by the Leicester Central NHS Ethics Research Committee, IRAS 324686