Effects of the HiBalance-program: Linking Clinical Signs and Symptoms to Changes in the Brain in People With Parkinson´s Disease

NCT03213873

Documents approved by the ethical committee in Stockholm, Sweden 21nd December 2017

The effects of challenging and progressive balance training on brain structure, function and recovery in people with Parkinson´s disease

This study is a part of the larger study BETA-PD (Balance, Elderly, Training and Activity in Parkinson's Disease) which has the long-term goal to reduce the risk of falling in people with Parkinson's disease (PD) by improving balance, gait and physical activity level. The BETA-PD study consists of several steps (see Figure 1 and preliminary results): method development and laboratory studies, an efficacy study, an effectiveness/implementation study and neuroplasticity studies. Ethical approval has previously been granted for steps 1 through 3, and we are here applying for performing step 4.

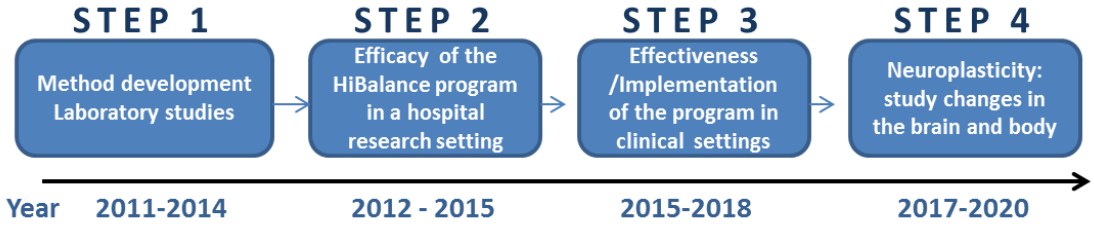

Figure 1. A graphical overview and time line of the steps in the BETA-PD study.

Purpose and aims

The BETA-PD project aims to translate knowledge from basic neuroscience into applied research and clinical understanding and implement the evaluation methods and a highly-challenging balance training program into clinical practice. Our **main hypothesis** is that highly challenging exercise will lead to greater gait and balance ability, increased levels of physical activity and an improved health related quality of life. We also hypothesize that neuroplasticity changes will be seen in corresponding areas of the brain, neuropsychological changes on cognitive test measures, and that exercise will inhibit the degeneration of dopaminergic neurons in the brain through the mediation of neurotrophic factors. Since there is currently no cure for PD, such a finding would revolutionize the way in which we treat the condition and possibly also other neurodegenerative disorders. This would in turn give new hope to patients of improved quality of life through extended years of functional independence and better health.

The main aim of this part of the project is to explore ***neuroplasticity*** in the people with PD, by linking improvements in clinical signs and symptoms to structural, functional and biomolecular changes in the brain after a period of balance training.

The **specific aims** of the project are to:

1. Characterize the neuroanatomical and biochemical features of PD in comparison to healthy controls by linking physical (balance control and motor impairment) and cognitive (executive and visuospatial function, and memory) functions to structural and functional features in the brain as well as to specific (wet) biomarkers in the cerebrospinal fluid and blood plasma (Cross-sectional studies).
2. Determine which methods may be used, and how, to characterize neuroanatomical and biomolecular correlates of improved physical and cognitive functions, by means of neuroimaging techniques, neuropsychological testing, as well as biomarkers in cerebrospinal fluid and blood plasma (Feasibility / pilot).
3. Determine the effects of the HiBalance program on neuroplastic changes in people with mild to moderate PD and to compare the effects to a group of people with PD receiving speech and communication training (RCT-study).

SURVEY OF THE FIELD

Parkinson's disease (PD) is a neurodegenerative disorder for which there is no curative treatment today. Balance and walking impairments are present even in the early stages of PD and have been shown to be associated with restrictions in everyday activities and reduced quality of life. Not only is postural instability one of the most disabling symptoms of PD, but it also increases the risk of falling. An estimated 38-68% of people with PD fall repeatedly, and they have a nine times increased risk of injurious falls, compared with the healthy elderly. Furthermore, elderly with PD have reduced levels of physical activity, which further contributes to social isolation and possibly also accelerates the progression of the disease. Speech is affected in up to 90% of people with PD, with low voice intensity, harsh voice quality and reduced articulatory precision, often also resulting in reduced communicative participation [1].

Balance control in Parkinson's disease

Balance control relies on the interaction between several physiological systems (musculoskeletal, neuromuscular, cognitive and sensory systems), environmental factors and the performed task [2]. Neuropathological changes in the brain affect many physiological systems essential for balance control. Balance disorders in PD cannot therefore be attributed to one single function but, are the result of impairments of multiple systems such as; impaired sensory integration, poorly timed and scaled anticipatory postural adjustments, reduced reactive control and motor coordination as well as decreased stability limits [2, 3]. Another critical aspect of balance control in PD is the ability to divide attention and simultaneously process multiple tasks (motor or cognitive), namely, multi-tasking. When performing a dual- or a multi-task activity, individuals with PD, compared with healthy individuals, are more inclined to shift attention away from the balance task, which may lead to falls [4]. Balance problems commonly leads to physical inactivity, which in turn results in increased unsteadiness and a vicious cycle involving less mobility, muscle weakness, falls and fractures [2]. Accelerometer data from our study shows that only 27% of individuals with mild to moderate Parkinson's disease meet the recommendations on physical activity [5].

Exercise and neuroplasticity

As PD progresses, balance problems gradually increase and are generally non-responsive to or worsen with levodopa treatment [3]. Several systematic reviews and meta-analyses have found various types of exercise, e.g. balance training, aerobic exercise and resistance exercise, to improve a wide range of symptoms in PD, including gait ability, balance, strength, depression and quality of life [6]. We recently developed a novel training program (the HiBalance program) that combines challenging balance exercises with cognitive tasks in a progressively more difficult manner [7]. In a subsequent RCT-study, we found the program to significantly improve balance performance, gait velocity, step length and dual-tasking ability. In addition, favorable transfer effects were seen in relation to physical activity levels as well as in the performance of activities of daily living [8].

Currently, there is a growing body of research highlighting the role of physical exercise as an essential part of managing PD, by means of neuroprotective mechanisms [9]. Neuroplasticity can be defined as a dynamic process by which the brain modifies neural pathways and synapses in response to environmental changes. Multiple mechanisms have been suggested to underlie neuroplasticity, including strengthening or weakening of synapses, synaptogenesis, neuronal sprouting and neurogenesis. Retrospective studies have shown that a higher level of physical activity earlier in life is associated with a reduced risk of acquiring PD later in life.

To this end, five animal [10-14] and four human [15-18] studies have experimentally investigated the effects of exercise on neuroplasticity in PD. Animal studies indicate that exercise may induce neural repair in PD and human studies have shown promising results on dopaminergic signalling and neuroadaptation, but these studies are limited to small sample sizes, conflicting results and validity issues, making it difficult to draw any firm conclusions. Importantly, no study has to date investigated functional brain changes and connectivity after exercise in humans with PD. Cerebrospinal fluid (CSF) and blood serum has been extensively studied to explore biochemical alterations in subjects with neurodegenerative disorders such as PD. However, only one study [16] has explored the potential mediating effects of brain-derived neurotrophic factor (BDNF) on improved physical functions in people with PD after a period of training.

In the last few years, the rapid development of functional MRI techniques has made it possible to characterize not only the structure of the brain, but also functional changes and networks in the brain. We therefore aim to utilize this sophisticated and non-invasive technique to relate improvements in balance and gait functions after training, to changes in the brain. As of yet, no-one has studied brain network changes after exercise in humans with PD. Such studies are warranted in order to understand whether improvements in specific networks may be obtained via an exercise-regime that has been shown to improve clinical features of PD.

Preliminary results

Method development (Step1): During the first years of the project we have tested the validity and reliability of the measurement methods that we use. For example, we have translated, culturally adapted and tested the validity and reliability of the new clinical balance test called the Mini-BEST test, for use in patients with PD as well as conducted methodology studies on physical activity measured with accelerometers in PD. This step has resulted in 5 publications and 3 manuscripts.

Laboratory (Step1): We have conducted kinematic and kinetic studies in movement laboratories (at Karolinska Institutet and at Sunnaas rehabilitation hospital) in which we have investigated straight walking, variability and turning strategies as well as the effect of levodopa on these strategies in individuals with PD (ON and OFF their medication) compared to controls. This step has resulted in 4 manuscripts and another 5 in pipeline.

Efficacy (Step2): We have developed the HiBalance program and showed the program to be feasible and effective to improve balance performance, gait velocity, step length, cognitive performance while dual-tasking, as well as beneficial transfer effects to everyday living, seen as increased physical activity and improved activities of daily living. Long-term results show that cognitive performance while dual-tasking persisted over a very long period of time while gait and balance effects diminished 10 to 14 months after the training period, suggesting that the training program may need to be repeated frequently.
We have also performed in-depth studies concerning the effects gait parameters and cognitive as well as factors associated with physical activity and fear of falling. Findings from a qualitative study, using semi-structured interviews with open-ended questions, suggest that being pushed to the limits of balance capacity provoked people with mild-moderate PD to re-think their individual motor and cognitive resources, a process that was further enabled by the PD-specific group setting. This step has resulted in 6 manuscripts/publications and another 4 in pipeline.

Implementation/effectiveness (Step 3): Initially a survey among 3000 physiotherapists has been performed to describe treatment characteristics, knowledge and skills with regards to PD. Preliminary results show that physiotherapists rarely treat patients with PD, but when they treat them gait and balance are the most common treatment. The survey also showed that physiotherapists have a self-expressed desire for increased education regarding PD and evidence-based PD-related treatments. We have conducted developmental workshops and are now in the process of developing a prototype of a mobile application for physiotherapists to assist them in the HiBalance program. We are now starting developmental workshops for people with PD to promote exercise and physical activity in this group. We have also performed a pilot study during the fall of 2015 and are now starting up the full implementation and effectiveness study.

PROJECT DESCRIPTION

Participants

Inclusion criteria will be a clinical diagnosis of "idiopathic" PD according to the definition of the Queens Square Brain Bank Criteria and Hoehn & Yahr scores 1-3. In addition, the subjects will have no history suggesting "atypical" PD symptoms, a Mini Mental State Examination (MMSE) <24 or any other existing neuromuscular disorders. Additional exclusion criteria for the imaging will include the presence of; pacemakers, deep brain stimulators and other metal implants, as well as claustrophobia. The implementation and efficacy part (step 3) is approved by the Regional board of ethics in Stockholm, dnr 2015/1804-32, 2015/570-32 and 2016/201-31/2. For the healthy control group, used to compare the anatomy and function of the brain of people with PD with healthy individuals, exclusion criteria will be: a MMSE <24 or any other existing neuromuscular disorders or other disorder that may interfere with their gait and balance performance as well as the exclusion criteria for the imaging.

Intervention programs

The HiBalance program is based on scientifically well-established principles of exercise training and postural control as well as current research on training in PD. The training will be conducted as a progressive individually adjusted group program in order to challenge the specific balance disorder of every participant and endorse progression. Four main subsystems underlying balance control (stability limits, anticipatory postural adjustments, sensory integration and motor agility) are used to target symptom-specific balance impairments. Over this period of time, the difficulty level will be increased in three consecutive blocks. To ensure highly challenging exercises, each task is individually adjusted, e.g. by altering the area of base of support, increasing movement speed/amplitude, restricting vision and varying the grade of multitasking. The intervention will be performed for an hour, 2 times/week in groups of six to eight participants for a total of 10 weeks and one home training session on their own. The control group will receive a group treatment (2 times/w for 10 w + 1 home training session) consisting of speech and communication therapy performed by a speech therapist. This intervention will be performed in a sitting position. The speech and communication treatment will aim at increasing vocal loudness and improving articulatory precision. Level of difficulty is gradually increased by progressing from using loud voice and clear speech in short and automatized utterances, to using the same technique in more complex sentences and situations. The group format is used to practice techniques in communicative situations and also to introduce increasing level of multitasking by combining speech training with cognitively more challenging tasks in the group training.

Procedures

In order to evaluate the effects of the HiBalance-program on neuroplasticity, we will first need to develop a study protocol which includes establishing an appropriate methodology. Previous research has found disruptions in several functional networks in the brain among people with PD; however, there is still a lack of knowledge regarding how specific networks involved in different cognitive (executive functions, memory and logical thinking) and motor tasks are affected. Additionally, a healthy control group, matched for age and sex, will be recruited and assessed only at baseline to compare the anatomy and function of the brain of people with PD with healthy individuals. Both groups will receive treatment (HiBalance program or speech and communication training) 3 times weekly for a total of 10 weeks, after which they will be re-assessed together with the control group in order to determine how improvements in clinical outcomes relate to neuroplasticity changes in the brain, including structural, functional and neuroprotective changes. Participants will be recruited through Karolinska University Hospital and via announcements in relevant forums like for instance the Swedish Parkinson Association. We have conducted a pilot study with 15 individuals with PD and a power calculation of that data show that we will need approximately 38 persons in each group to detect a difference with an 80% power (alfa 0.05, SD 3.1) of 2 points on the main outcome (Mini-BESTest). With an estimated dropout of 15-20% we will need to recruit approximately 50 participants in each group. The pilot study has also given us valuable insights into the measurements and procedures that we use for refining the design for the larger RCT.

Imaging and wet biomarkers

The neuroimaging techniques that will be used to link improvements in clinical features to changes in the brain include structural magnetic resonance imaging (MRI), which makes it possible to identify gross changes in brain anatomy, and functional MRI (fMRI) which makes it possible to study brain networks during activity and in the resting state. Resting state fMRI, which provides an index of connectivity across the whole brain, may be particularly suitable for studying brain connectivity in people with PD because it does not require the patient to perform any actions, thus minimizing the risk of random errors. The imaging will be performed at Karolinska University Hospital with a 3 Tesla MR camera. Moreover, diffusion tensor imaging (DTI), also assessed by means of MRI, will be used to determine the effects of exercise on brain connectivity. DTI can be used to map white matter fiber tracts, thus providing a picture of how different nodes or areas in the brain are interconnected. Taken together, fMRI and DTI complement each other in providing a picture of how different areas of the brain are interrelated.

During the fMRI-assessment, participants will perform different tasks that engage motor networks, cognitive networks, or a combination of cognitive and motor networks. A block-design, in which the experimental conditions are separated by resting periods, will be employed. In order to maximize the evoked response, and thus the detection power, an extended scanning time will be used for each block (experimental- and resting conditions). Participants will perform a version of the serial reaction time (SRT) task in order to explore implicit motor sequence learning. The cognitive task will consist of N-back, a task primarily assessing working memory before entering the scanner, all participants will practice the task on a laptop until they can answer continuous trials satisfactorily. The time inside the scanner is approximated to 45-60 minutes per test occasion.

In addition to the imaging tasks, a selection of neuropsychological tasks will be performed outside the scanner to assess potential cognitive training-related changes: Executive functions: The Trail Making Test (TMT) trial 4 from Delis-Kaplan Executive Function System (D-KEFS), The Color-Word Interference Test from D-KEFS and Verbal Fluency (VF) from D-KEFS; Attention/working-memory: Digit Span from Wechsler Adult Intelligence Scale - Fourth Edition (WAIS-IV), The Trail Making Test (TMT) trial 1-3, and 5 from D-KEFS, Deary-Liewald Reaction Time Task; Episodic memory: Ray Auditory Verbal Learning Test (RAVLT), Brief Visuospatial Memory Test - Revised (BVMT-R) and finally Visuospatial functions: Copy condition from BVMT-R and lastly the Boston naming test. The neuropsychological test battery will approximately require 50-60 minutes per test occasion.

Furthermore, biomolecules will be assessed from 150-200 ul cerebrospinal fluid (CSF) or plasma, before and after the exercise intervention and analyzed with ELISA commercial analyzing kit. These molecules include brain-derived neurotrophic factor (BDNF), α-Synuclein, and amyloid β_{1-42}. BDNF is an important signaling molecule for cell survival in the central nervous system. α-Synuclein is a pathological hallmark of PD, and it will be used in this study as a diagnostic marker for PD, as well as to evaluate the therapeutic effects of the exercise program. Amyloid β_{1-42}, correlates with cognitive decline in people with PD, and will be used to evaluate the potential therapeutic effects of the training. All spinal fluid samples will be performed by a licensed physician. Contraindications to lumbar puncture include: Increased intracranial pressure, bleeding disorders or treatment with warfarin or high-dose heparin and local infection. People with any of these symptoms will not undergo the test. Approximately 5-10% of participants may suffer from headaches after the lumbar puncture. This is usually harmless and symptoms commonly subside after 30-60 minutes of rest in the supine position.

Clinically oriented tests

Gait will be assessed with an electronic walking system (GAITRite®, CIR Systems Inc., PA) which measures temporal and spatial gait parameters. Participants will walk at different speeds in order to evaluate cadence, phases of the gait cycle, step frequency, step length and step width. Walking ability will also be assessed with Walk-12, which is a 12 item self-rating scale. The Mini-BESTest, a 14 item scale that has been validated for people with PD, will be used to assess balance control. Fear of falling will be assessed with the Falls Efficacy Scale-International (FES-I), and balance confidence during activities of daily living with the ABC-scale. We will also use the Unified PD Rating Scale (UPDRS) Motor part (III) to evaluate rigidity, tremor, balance, and gait and UPDRS part II scale to assess Activities of Daily Living. Physical activity will be assessed with wearable sensors/accelerometers (ActiGraph GT3X) and with the Frändin-Grimby activity scale. Health related quality of life will be assessed with the Parkinson's Disease Questionnaire (PDQ-39 and EQ-5D). Depression will be evaluated with the Hospital Anxiety and Depression Scale (HAD), and cognitive status with the Mini Mental State Examination (MMSE).
We will also include speech and voice assessment to evaluate the effect of the control treatment (speech and communication training). The Dysarthria test [19] will be used to assess speech function (including respiration and phonation, oral-motor- and velopharyngeal function and articulation). This test also includes assessment of prosody and intelligibility as well as a section for self-reported data on speech and communicative participation. In addition, a standardized speech recording including production of sustained phonation, text reading and production of spontaneous speech will be made in a sound-proofed booth using a

head-mounted microphone. Analyses of the speech recording include voice sound level (dB SPL), mean fundamental frequency and measurements of speech rate.

Time plan

As displayed in Figure 1, step 3 is ongoing. A pilot has been conducted and the larger study is starting up and is planned to go on until 2018. Step 3 is currently financed by Forte and Vårdal until 2017. The pilot/feasibility study for this step (4), will start recruiting patients during the fall of 2016. The full RCT of step 4 is planned to start in late 2017 and go on until 2019. During 2020 we will analyse and disseminate the results.

Significance

The results from this project will have an immediate application and clinical relevance for individuals with PD and other neurological diseases. This project spans domains of pre-clinical, clinical and implementation research, combines expertise from multiple professions and involves the collaboration between research institutions and both hospital and primary care units. By mapping how improvements in clinical outcomes relate to neuroplastic changes in the brain and specific biomarkers we aim to evaluate the therapeutic effects of exercise in this group of patients. Our choice of study design aims to fill gaps in the knowledge concerning not only *what* to implement but also *how* to implement evidence-based PD training in clinical practice. Our evaluation methods and training program also aim to narrow the gap between research findings and everyday clinical practice and will, in the very near future, have the potential to reach a large number of patients.

With an improved balance and gait, increased level of physical activity and an improved health related quality of life, individuals participating in the program will not only reduce their risk of falling, but also gain other health benefits related to an active lifestyle and, thereby, a good and active ageing. Additionally, the underlying neuroanatomical correlates of improvements gained through exercise remains a poorly understood area among individuals with PD. Such knowledge could contribute to further evidence-based development of our and other highly-challenging training programs for those with progressive neurological conditions Since there is currently no cure for PD, positive findings would revolutionize the way in which we treat this debilitating condition and possibly also other neurodegenerative disorders which would in turn provide new hope to patients of a longer life with better health, higher independence and improved quality of life.

Project organization

The project is an interdisciplinary collaboration between several departments and groups. The investigators and collaborators of this project possess unique knowledge necessary for both clinical and laboratory research and implementation of the results. With the combined knowledge and resources we are excellently placed to translate basic human research into applied research and clinical understanding. We also have the clinical knowledge and the patients to transfer the results directly to the clinic in a multidisciplinary way.

Erika Franzén is an expert in balance control and movement in elderly and Parkinson's disease, in both clinical and laboratory settings. Dr. Franzén has both a clinical (Karolinska University Hospital and Stockholms sjukhem) and a university position (associate professor) at KI and is financed by Vetenskapsrådet, Vårdal and Forte. Associate professor **Maria Hagströmer** is a physical therapist and an expert in physical activity, exercise and health with a special knowledge in measurement of physical activity using wearable monitors. Professor **Per Svenningsson** is a world leading researcher and neurologist who specializes in PD. His

research deals with the invention of new therapeutic agents, studying receptor dynamics, developing biomarkers for PD, and more. Professor **Staffan Holmin** with a specialty in neuroradiology and neurosurgery, is an expert in neuroimaging and head of radiology at the Karolinska University Hospital in Solna and Professor at Department of Clinical Neuroscience. His research focuses on developing neuroradiological methods to reveal and treat neurological diseases. PhD **Martin Benka Wallén** is a physical therapist and a medical student, working as a postdoc in the BETA-PD project. He has a background in clinical stress research, with extensive knowledge in physiology and neuroscience. Over the last four years, he has mainly been involved with studies on balance and physical activity in people with PD. **Urban Ekman** is a registered psychologist and PhD, who has written a thesis on the neuroanatomical and functional correlates of cognitive decline in people with PD. He works clinically part-time and part-time as a postdoc at KI. Additionally, a postdoc and a research assistant is working with step 3 and a PhD student has been recruited for the project (**Hanna Johansson**, MSc, half-financed by Forskarskolan i Vårdvetenskap, KI) who will work with step 3 and the pilot in step 4. **Ellika Schalling**, assistant professor and speech and language pathologist, KI and Karolinska university hospital, with an expertise in PD. We also collaborate with Professor **Martin Lövdén** and postdoc **Alexander Lebedev** concerning the imaging and specially the fMRI set-up and acquisition.

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Hypotheses and analysis plan for the main paper of the EXPANd trial: Behaviour and brain-related effects of a highly challenging balance training in individuals with mild to moderate Parkinson's disease

Date : 2020-11-02

This is a complementary description of the hypotheses and analyses to be made as part of the main paper of the RCT in the EXPANd trial. This trial was registered at clinical trials.gov NCT03213873 before data collection. More information on the trial can also be found in our study protocol Franzen et al. (2019).

Design

Double-blind RCT

Group of primary interest: the HiBalance training

Active control group: the HiCommunication training

95 participants with mild to moderate PD

Aims

There are two main aims of this paper.

1) To investigate the interaction effects of time and group on balance, gait and executive functions

2) To investigate the correlations between change in balance, gait and executive functions and change in brain derived neurotrophic factor (BDNF) and brain activity.

Hypotheses

Primary outcome

• H1. We hypothesize an interaction effect of time and group such that the HiBalance group will improve their balance performance to a greater extent than the active control group (HiCommunication group) measured with the Mini-BESTest (def. improvement = increased score)

• H2. Gait velocity (def. improvement = increased velocity), as measured with a pressure sensitive gait mat (GAITRite®)

• H3. Step length (def. improvement = increased step length), as measured with a pressure sensitive gait mat (GAITRite®)

• H4. Habitual physical activity measured as steps per day with an accelerometer (Actigraph GT3x) (def. improvement = increase in steps/day)

Secondary outcomes

Gait ability and physical activity

We hypothesize an interaction effect of time and intervention group such that the HiBalance group will improve to a greater extent than the active control group on the following outcomes:

Cognitive function

• H5. We hypothesize an interaction effect of time and group such that the HiBalance group will show a greater improvement than the active control group on a composite measure of executive functions. We will base the composite measure on three test measures from the Delis-Kaplan Executive Function System: The verbal fluency test - letter fluency (FAS), The verbal fluency test - category switching (number switches) and the Color-Word Interference Test - switch condition, as well as one test measure from Wechsler Adult Intelligence Scale: Digit Span Total score (forward + backward + sequence) (def. improvement = increased score).

BDNF

• H6. We hypothesize an interaction effect of time and intervention group such that the HiBalance group will show a greater increase than the active control group on mature BDNF.

Brain activity as measured by fMRI during an implicit sequence learning task (the SRTT)

We hypothesize that there will be:

• H7. a group by time interaction effect such that the HiBalance group will show a greater increase in striatal activity, compared to the active control group

• H8. group by time interaction effects in the following frontal areas/ROIs: the primary motor cortex, the premotor cortex, the supplementary motor cortex, the anterior cingulate cortex and the dorsolateral prefrontal cortex (DLPFC). The primary motor cortex, the premotor cortex and the supplementary motor cortex were primarily chosen for their involvement in motor function and the DLPFC and the anterior cingulate cortex were primarily chosen for their involvement in cognitive functions, with important interconnections assumed.

Correlations of individual difference values (pre-post) of behavioural outcomes and BDNF

We hypothesize that there will be:

• H9. a stronger positive correlation between the difference values of the Mini-BESTest and the difference values in mature BDNF within the HiBalance group than within the active control group.

• H10. a stronger positive correlation between the difference values in gait velocity and the difference values in mature BDNF in the HiBalance group than in the active control group

• H11. a stronger positive correlation between the difference values of the composite measure of executive function and the difference values of mature BDNF in the HiBalance group than in the active control group.

Correlations of individual difference values (pre-post) of behaviour outcomes and brain activity

We hypothesize that there will be:

• H12. a stronger positive correlation between the difference values in Mini-BESTest and the difference values of striatal activity within the HiBalance group than within the active control group

• H13. a stronger positive correlation between the difference values in gait velocity and the difference values in striatal activity within the HiBalance group than within the active control group

• H14. a stronger positive correlation between the difference values of the composite measure of executive function and the difference values in striatal activity within the HiBalance group than within the active control group

• H15. stronger correlations between the difference values of the Mini-BESTest and the difference values of activity in the aforementioned ROIs (in H8) within the HiBalance group than within the active control group

• H16. stronger correlations between the difference values of gait velocity and the difference values of activity in the aforementioned ROIs (in H8) within the HiBalance group than within the active control group

• H17. stronger correlations between the difference values of the composite measure of executive function and the difference values of activity in the aforementioned ROIs (in H11) within the HiBalance group than within the active control group

We also expect greater improvements in the HiBalance group compared to the active control group, on the following outcomes:

• Balance confidence as measured by the ABC-scale (def. improvement = increased score)

• MDS-UPDRS III motor part (def. improvement = decreased score)

• MDS-UPDRS total (def. improvement = decreased score)

• Physical activity as measured with the Frändin-Grimby scale (def. improvement = increased score)

• EQ5D-VAS, a measure of self-rated health (def. improvement = increased score)

• PDQ-39 summary index, a measure of difficulties in daily life associated with PD (def.improvement = decreased score)

• HADS anxiety subscale (def.improvement = decreased score)

• HADS depression subscale (def.improvement = decreased score)

• SRTT, a measure of implicit motor sequence learning (def. improvement = greater difference in RT between sequence trials and random trials)

We also expect greater improvements in active control group (HiCommunication) compared to the HiBalance group, on the following outcome:

• Voice intensity, as measured in mean dB during reading of a short story (improvement = higher mean dB). A c-weighted dB outcome will be used as this suppresses low frequent noise.

Analyses

Analyses of behavioural outcomes

The outcomes listed below will be analysed with multilevel models with group, time and the interaction between group and time as independent variables. The models will be specified with the pre and post values as level 1, clustered within the individuals i.e., level 2, with group as a factor on level 2. We will allow for random intercepts but not random slope (due to only two time points). The alpha level will be set to 0.05 for all outcomes. If assumption of normality is not fulfilled, generalized multilevel models will be used and transformations of data will be avoided when possible.

Multiple imputation for cluster level analyses will be used to impute missing values. The primary analyses will be based on the imputed values and all participants included in the study with at least one observed pre or post value will be included. Complementary, we will also perform analyses including solely participants with both pre and post observed values.

• The Mini-BESTest, a measure of balance performance

• Gait velocity, a measure of gait ability measured by a pressure sensitive mat (GAITRite®)

• Step length, a measure of gait ability measured by a pressure sensitive mat (GAITRite®)

• Steps per day, a measure of physical activity level measured by an accelerometer (Actigraph GT3x)

• A composite measure of tests of executive function from the Delis-Kaplan Executive Function System and the Wechsler Adult Intelligence Scale. The composite outcome will be calculated based on a factor analysis on the pre-intervention scores. The final combination of tests to form the composite measure might be modified based on evaluation of the factor model, primarily the fit indices.

• MDS-UPDRS III, a measure of motor ability in PD

• MDS-UPDRS total, a measure of PD symptoms

• The ABC-scale, a measure of balance confidence

• Frändin-Grimby, a measure of physical activity level

• SRTT, a measure of implicit motor sequence learning

• EQ5D, a measure of health and health related quality of life

• PDQ-39, a measure of difficulties in daily life associated with PD

• HADS, a measure of symptoms of depression and anxiety

• dBC during text reading, a measure of voice intensity

Analyses of BDNF

• Mature BDNF will be analysed with multilevel models with group, time and the interaction between group and time as independent variables. The models will be specified with the pre and post values as level 1, clustered within the individuals i.e., level 2, with group as a factor on level 2. We will allow for random intercepts but not random slopes. If assumption of normality is not fulfilled, generalized multilevel models will be used and transformations of data will be avoided when possible. Alpha level will be set to 0.05.

• Multiple imputation for cluster level analyses will be used to impute missing values. The primary analyses will be based on the imputed values and all participants included in the study with at least one observed (pre or post) and usable BDNF sample will be included. Complementary, we will perform analyses including solely participants who had observed and usable BDNF samples for both the pre and post assessments.

Preprocessing and analyses of the fMRI data

Preprocessing

• MRIQC will be used for initial quality control of images.

• The standardized pipeline fMRIPrep will be used for the preprocessing of images. When available, the two T1 images from each individual's pre and post scan will be merged and used as a longitudinal template for co-registration with the functional images. Mapping to standard space will be done using the MNI template 2009c. For individuals with field maps, these will be included in the fMRIPrep pipeline.

• Manual inspection will be done on the MRIQC and fMRIPrep output to determine whether the individuals' data is of sufficient quality for inclusion in the analyses.

First-level analyses (individual-level analyses)

• General linear models will be used to analyse the time-series of brain activity acquired during the SRTT for each voxel, individual and available scan. Independent variables will be the experimental timeline convoluted with the canonical hemodynamic function (HRF) (explanatory variable) and 24

motion parameters as well as aCompCor acquired from the fMRIPrep outcome (nuisance regressors). Activity during random blocks will be contrasted to activity during sequence blocks, creating statistical contrast maps for each individual and scan. Structure adaptive smoothing will be performed with default maximum bandwidth.

• Two masks, based on anatomical atlas, will be created and applied to each individual's statistical map(s), one for striatum and one for the remaining ROIs (the primary motor cortex, the premotor cortex, the supplementary motor cortex, the anterior cingulate cortex and the DLPFC).

• Random field theory for small regions with alpha set to 0.05 will be used for thresholding the statistical maps. Thresholding will be done separately for statistical maps of striatum and for statistical maps of the remaining ROIs.

Second-level analyses (group-level analyses)

• To test hypothesis H7, a multilevel model with group, time and the interaction between group and time as independent variables will investigate the group by time interaction effect in in the masked statistical map of the *striatum* using a voxel by voxel analysis. There will be no imputation on the fMRI data, but all participants included in the study with at least one (pre or post) times series of brain activity deemed to be of sufficient quality in manual inspection described under "Preprocessing", will be included.

• To test hypothesis H8, multilevel model with group, time and the interaction between group and time as independent variables will investigate group by time interaction effects in the masked statistical map including *the primary motor cortex, the premotor cortex, the supplementary motor cortex, the anterior cingulate cortex and the DLPFC* using voxel by voxel analyses. There will be no imputation on the fMRI data, but all participants included in the study with at least one (pre or post) times series of brain activity deemed to be of sufficient quality in manual inspection described under "Preprocessing", will be included.

• The multilevel models will be specified with the pre and post scans as level 1, clustered within the individuals i.e., level 2, with group as a factor on level 2. We will allow for random intercepts but not random slopes.

Correlations between mature BDNF, brain activity and behaviour outcomes

• For the correlations between mature BDNF and behaviour, we will calculate the within-group correlations between change values (pre-post) in the MiniBESTest, gait velocity and the composite measure of executive function with change values (pre - post) of mature BDNF, using Spearman's rank order correlation. We will correct for multiple comparisons by using the false discovery rate method with alpha set to 0.05. The correlations will be calculated on individuals with data from both the pre and post assessment.

• For the correlations between brain activity and behaviour, we will correlate the within-group change values (pre-post) in the MiniBESTest, gait velocity and the composite measure of executive function respectively, with change values (pre - post) of activity in the ROIs of striatum, the primary

motor cortex, the premotor cortex, the supplementary motor cortex, the anterior cingulate cortex and the DLPFC respectively, using Spearman's rank order correlation. We will calculate the mean activity on the top 10% active voxels of each ROI for each individual's first level contrast map(s). We will correct for multiple comparisons by using the false discover rate with alpha set to 0.05. The correlations will be calculated on individuals with data from both the pre and post assessment.

• To test hypotheses H9:H17, we will perform tests as for whether the within-group correlations between behavioural outcomes and mature BDNF and brain activity change values described above, are significantly larger in the HiBalance group than in the HiCommunication group. This will be done using Fischer's Z significance test. We will correct for multiple comparisons by using the false discover rate set to p = 0.05. The corrections will be done separately for our more primary hypotheses i.e., the correlations between mature BDNF and striatal activity with the behavioural outcomes respectively, and the remaining correlations stipulated. • In addition to testing for group by time effects in mature BDNF, we will investigate group by time interactions for the outcomes proBDNF and the ratio proBDNF/matureBDNF using the same multilevel models as specified for matureBDNF but with an exploratory approach i.e., no hypotheses.

• In addition to testing for group by time effects in the brain areas listed above, we will investigate group by time interactions with a whole brain voxel by voxel analysis, after thresholding with random field theory. We will then correlate change values (pre-post) in the voxels/clusters with significant time by group interactions (alpha = 0.05) with the change values of MiniBESTest, gait velocity and executive function, using Spearman's rank order correlation. Fisher's Z tests will be used to compare the correlation coefficients over the groups.

Planned exploratory analyses

Other information of importance

The preregistration at clinical trials.gov NCT03213873 was done before any data collection. The present document of more detailed hypotheses and analyses was formulated after data collection but before analyses. All assessors were blinded throughout pre and post assessments and the author performing the analyses will remain blind to group allocation during the statistical analyses (the two groups have been assigned arbitrary names by a person not involved in the analyses).

References

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