Study protocol - Version 2, 13/10/2020

The effect of training on brain activity during postural control tasks in older adults

Protocol identification number

S62917

Study type

Interventional

Principle investigator

Prof. Alice Nieuwboer

Sub-investigator

Veerle de Rond, MSc

1 General information

Sponsors:	European Union's Horizon 2020 research and innovation programme under the Marie Sklowdowska-Curie grant agreement No. 721577
Research Unit:	Neurorehabilitation Research Group, Faculty of Kinesiology and Rehabilitation Sciences, KU Leuven
Principal investigator:	Prof. Alice Nieuwboer Tervuursevest 101, 3001 Heverlee Tel: 016/32.91.19 E-mail: alice.nieuwboer@kuleuven.be
Sub-investigator:	Veerle de Rond, MSc Tervuursevest 101, 3001 Heverlee Tel: 016/37.28.39 E-mail: veerle.derond@kuleuven.be
Study period:	01/10/2020 – 01/01/2022

2 Summary of the protocol

2.1 Participants

40 healthy older adults

2.2 Study type

Monocentric study at the faculty of Movement and Rehabilitation Sciences, observational study, academic study.

2.3 Measurements

- Screening tests to evaluate motor and cognitive function
- Clinical measuring scales for the evaluation of balance
- Task that requires weight-shifting
- Measurements of cortical activity by means of functional Near-Infrared Spectroscopy (fNIRS)

2.4 Duration experiments

One session of ± 3.5 hours, including 25 min of training, and one session of ± 1.5u. There will be a period of 24 hours between both sessions.

2.5 Location experiments

Faculty of Movement and Rehabilitation Sciences (KU Leuven).

3 Background and rationale

In 2015, about 900 million people in the world were aged 60+. By 2050, this population will increase up to more than 2 billion[1]. Older people show deficits in balance control[2] and dynamic weight shifting, as more time is needed to perform weight-shifts and the movement becomes less fluent and accurate[3]. In addition, mediolateral weight-shift performance has been linked not only to ageing, but also to balance and falls[4, 5]. An observational study even showed that incorrect weight-shifting accounted for 41% of falls[6], making it one of the main causes of falls in the older population. Previous work reported prevalence rates of 33% up to 50% of healthy older adults who fall at least once a year[7, 8]. Falling has serious consequences for quality of life and mortality[9]. As such, investigating potential methods to delay or reduce falling is of utmost importance to prevent immobility and a sedentary lifestyle in healthy ageing.

Studying the neural basis of whole body movements is of great importance to increase our insight of gait and balance. The gold standard method is functional Magnetic Resonance Imaging (fMRI) during motor imagery of stance, which identified increased Blood Oxygenation Level Dependent (BOLD) activity in the brainstem, basal ganglia, cerebellum and cerebral cortex during 'postural control'[10]. A major drawback of brain scanning is that it occurs in a supine position. In contrast, functional near-infrared spectroscopy (fNIRS) allows measuring brain activity while being upright, albeit at a much lower temporal and spatial resolution[11]. However, mobile fNIRS systems now permit a wider brain coverage than hitherto possible to examine the neural correlates of postural stability, at least at the cortical level. fNIRS has also been validated against fMRI[12], is more resistant to head motion compared to other EEG[12] and is feasible for use in older adults[13, 14].

Recent systematic reviews showed that postural control in older adults can be improved with training[15]. However, little is known about the ability and maintenance of re-learning to weight-shift, let alone about its underlying mechanism. Therefore, the primary aim of this project will address this lacuna by studying the effects of training in weight-shifting performance in older adults and its underlying neural imprint. As our previous study (unpublished) showed that adding an extra cognitive task in a so-called dual-task (DT) negatively affects weight-shifting performance, a secondary aim will be to test whether weight-shift training will enhance performance during such DT conditions. The results of this study might form a basis for future technology-based rehabilitation programs.

4 Study objectives

The effects of postural learning on cortical activity have not been identified yet in older adults. During non-postural tasks, older adults needed greater activity and recruited more brain areas during automatization compared to young adults. This is suggested to be the primary reason for impaired motor automaticity with age[16]. We will use fNIRS to examine postural learning in the upright position for the first time in older adults. More specifically, we will investigate:

1. Changes in brain activity in frontal, (pre-)motor, and parietal regions associated with the acquisition and consolidation of weight shifting in older adults. In addition, as moving the Centre of Mass (CoM) deliberately also loads sensorimotor function, we will include the parietal cortex as region of interest.
2. Changes in brain activity in frontal, (pre-)motor, and parietal regions associated with the acquisition and consolidation of weight shifting compared to no training (control group).
3. Changes in brain activity in frontal, (pre-)motor, and parietal regions associated with the transfer of single-task acquisition and consolidation of weight shifting to dual-task weight shifting performance.

5 Methodology of the research

5.1 Participants

In total, 40 subjects will be recruited aged 65+. Inclusion criterion include being able to independently stand upright > 5 min. Exclusion criteria are: (a) history of neurological disorders; (b) balance impairments (i.e. vestibular disorders); (c) cognitive impairment (Mini Mental State Exam (MMSE) < 24); (d) visual impairment precluding following of visual targets or colour-blindness as measured with the Ishihara test for color deficiency; (e) chronic musculoskeletal (e.g. osteoarthritis, osteoporosis), cardiovascular (e.g. hypertension, peripheral vascular disease) and respiratory (e.g. chronic obstructive pulmonary disease) disease, as well as diabetes related polyneuropathy.

For this study, 40 healthy older adults will be included. Our previous fNIRS study (unpublished) revealed that our primary outcome, weight-shifting speed, improved from 0,0668 ± 0,0255 m/s to 0,0916 ± 0,0350 m/s. Based on Caljouw et al.[17], we expect a training effect size of 20%, resulting in a weight-shifting speed of 0.1094 ± 0,0418 m/s. Applying a power of 80% and alpha of 0.05 for a repeated measures ANOVA with a within-between interaction design (within: pre vs post: between: training vs control) we calculated a total sample size of 40 participants (20 per group). Considering possible data exclusion due to fNIRS measurements, the collected fNIRS data will be monitored during recruitment, and recruit more participants if necessary.

5.2 Recruitment

Heathy older adults will be recruited based on the age-criterion, i.e. 65+ years. We will announce our study on websites and pin boards reaching older adults (e.g. seniorama, Universiteit Derde Leeftijd, gym clubs, etc.). When interested, potential participants will be provided with the information folders (either via e-mail or regular mail) to present the necessary information in writing. A follow-up conversation will follow, either via telephone or at the candidates' home if preferred. During this conversation the study goals and protocol of the study, as described in the informed consent forms, will be explained thoroughly to make sure everything is clear for the possible participant and allowing him/her to ask questions and make an informed decision. The researchers responsible for testing will execute this recruitment process. The flyers and information folders can be found in the respective files.

5.3 Experimental procedure

5.3.1 General procedures

Design

Participants will be randomly allocated to the training and control groups. The control group will not receive any form of training. Randomization will be computer-generated and blocked in groups of four to achieve optimal distribution in each training arm. The study will have a repeated measures design with two test sessions on two consecutive days.

Motor and cognitive screening

We will collect data on fall frequency, Mini-Balance Evaluation System (Mini-BESTest), and Falls Efficacy Scale. The cognitive assessment will consist of Montreal Cognitive Assessment and specific tests for visuospatial and attention.

Weight-shifting task

Before starting the weight-shifting task (WASP task), functional limits of stability (fLOS) will be assessed by asking the subject to move the Centre of Mass (CoM) as far as possible over its base of support (**Fig. 3A**) in eight different directions by pushing a virtual bar away from the center position. Mean CoM shifts will be calculated and used for personalized scaling of the WASP. Only weight-shifting in the ML direction will be tested and trained to avoid motion artefacts during fNIRS data collection, and because ML weight-shifting in particular has been linked to balance and falls[4, 5]. The WASP task (**Fig. 3B**) was developed and piloted to meet the requirements for balance training for older people in a PhD project under supervision of prof. S. Verschueren (De Vries A, 2018). Pilot data showed that the WASP is feasible for use in older adults and can capture fluency of motion as a learning outcome.

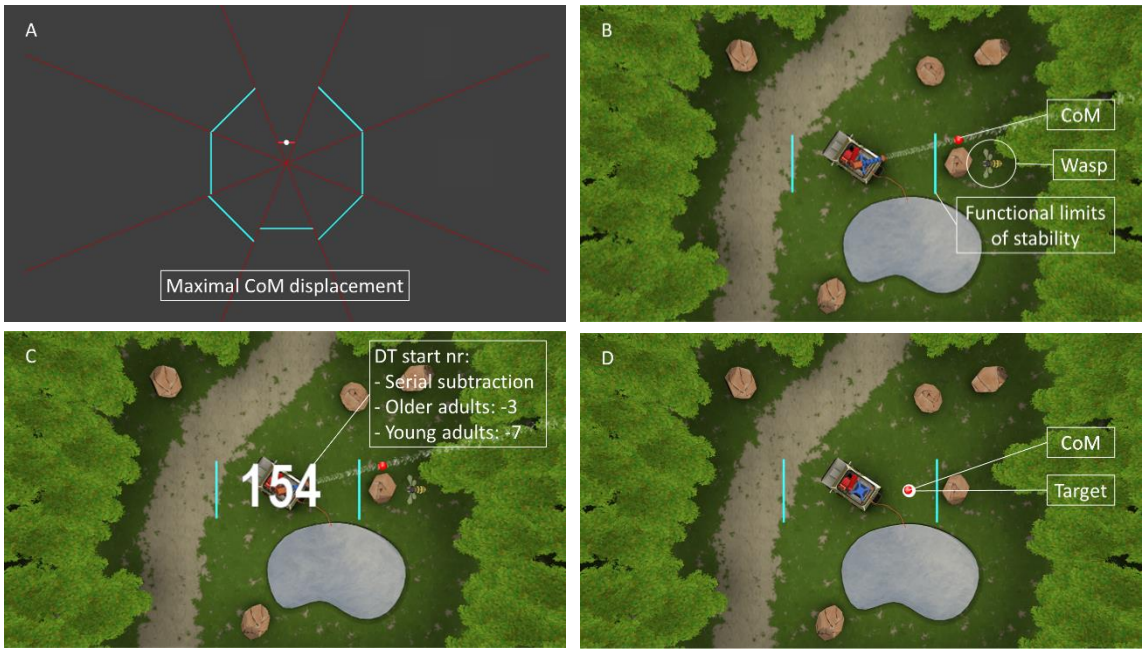

Figure 1: (A) Functional limits of stability; (B) Weight shifting task in ST. Red ball is CoM; (C) WASP + serial subtraction in DT; (D) ML tracking task

Fig. 3B shows that the player is in the middle of an area infested by wasps. By moving the CoM (displayed by the red dot) towards a pre-defined 80% of the fLOS, a water stream will come on to hit the wasp. The number of wasps hit, weight-shifting accuracy, comprising the CoM traject and target deviation, and speed are used as outcomes. The WASP-ST involves hitting wasps in the ML direction by shifting weight. **Fig. 3C** illustrates the WASP-DT. Participants have to perform a serial subtraction task as the secondary task, whereby the red ball (representing the CoM) will change color from red to white and white to red within a random interval between 2-5 seconds. A starting number will appear on the screen for 1.5 sec at the beginning of each trial. Every time the ball changes its color, subtractions have to be made in threes. Subjects will indicate the correct number afterwards, so as not to disturb the fNIRS recording. To standardizing weight-shifting speed, a ML tracking task has been implemented in the WASP game (**Fig. 3D**). Participants have to track a white target which is moving in the ML direction at a constant speed. With this task, we will be able to investigate whether the fNIRS brain response is different between groups and/or after training when performance is similar.

5.3.2 Study specific procedures

On day 1, subjects in the training group will receive the WASP-training, consisting of 10 blocks of 2.5 minutes. Training will be adjusted to the individual fLOS targeting at least 80%. Before and after training, weight shifting ability will be assessed using the WASP-tests with and without serial subtractions as well as the tracking task. We will measure cortical activity with fNIRS during weight-shifting following recent guidelines[11]. We propose a block design distinguishing periods of quite stance from weight shifting. Participants will undergo three blocks offered in a fixed order: I) tracking task; II) WASP-ST; III) WASP-DT. Each block has a duration of 6m40s, starting with 20s quiet stance~~,~~ followed by 20s weight-shifting, alternating in ten trials. This block design allows for the 4s-7s delay in the hemodynamic peak response by having sufficiently long periods of task exposure. Subjects are not allowed to speak, so as not to disturb the fNIRS signal. In the DT-condition, subjects will be asked to focus on the primary and secondary tasks equally. Subjects in the control group will not receive any form of training. Retention tests will occur on day 2 (24 hr). Also, simultaneous fNIRS measurements will be carried out. On day 1, only the optodes will be removed to avoid cap removal. fNIRS was found to have adequate test-retest reliability[18]. Cap placement will be marked to facilitate accurate placement on day 2.

5.4 Equipment

Postural outcomes will be measured on the Computer Assisted Rehab Environment (CAREN) (Motek Medical BV, Amsterdam) with integrated force plates. Spherical reflective markers placed bilaterally on anatomical landmarks will allow 3D-kinematic analysis with 7 MX-T20 optoelectronical cameras (Vicon, Oxford Metrics, UK), which will be done both online with D-Flow software (Motek Medical BV, Amsterdam) as offline. Changes in the brain hemoglobin concentrations will be registered with a wireless 16-16 fNIRS system (NirXsports 2), which has the required resolution and coverage to meet the study objectives. Sixteen optodes per hemisphere will be placed over the prefrontal, posterior parietal and premotor, SMA and M1 regions with an inter-optode distance of 35 mm, placed on an EEG-cap using the 10-20/10-10/10-5 EEG system.

6 Statistics, data handling and data management

6.1 Data storage

Part of the data that are obtained on paper will be stored on paper (e.g. questionnaires, informed consent forms), as well as in an excel file. The data obtained by computerized measures will all be stored in the original digital files, and the main variables will be stored in excel data files. All digital files will be saved on protected server file storages of the KU Leuven (automatic back-up). Anonymized data files will be shared after publications of the results and upon request with the PI.

6.2 Data analysis and statistics

Calculation of the CoM data will be processed using Nexus 2.4 and customized Matlab scripts. Body movement during postural control, comprising CoM displacement, deviation of trajectory and target, and speed will be calculated. To account for motion artefacts during fNIRS measurements, we will perform visual checks and signal processing techniques, including filtering and noise removal. A mixed model ANOVA will analyze learning effects with training group as between-subject and pre-post as within subject factor. Similar analyses will be adopted for consolidation.

7 Safety

There are no permanent risks involved for the subjects participating in this study. All experiments are painless and harmless for participants. A safe and existing test infrastructure will be used and experienced researchers will conduct the experiments. Participants will be informed about the procedure and possible risks of the tests before the start of the experiment. Some of the participants may feel some fatigue during the weight shifting trials. To prevent excessive fatigue, participants will be encouraged to take breaks as needed in-between all trials. The fNIRS head cap will be cleaned/washed after each participant to ensure appropriate adherence to infection control policies. Based on a recent PhD thesis on the development and validity of the WASP task [de Vries, A (PhD thesis, March 2018)] we do not anticipate that any risks will be involved in the use of this WASP task.

For all subjects, a safety screening will be executed for the MRI protocol before informed consent will be obtained. Participants will be encouraged to ask questions about the study protocol and possible risks at any time of the experiment, as well as during the inclusion session. In between trials, sufficient rest periods will be inserted to avoid fatigue. During the MRI scan sessions, the aim is to minimize the potential discomfort of the participants. All subjects will be informed thoroughly about MRI technology and the setup in UZ Leuven Hospital. In addition, participants will be prepared for the real scanning session by including a practice session in a dummy MRI scanner. During the MRI scan session at the UZ Leuven Hospital, the researcher will be in contact (verbally) with the subject to assess his / her condition. An easily accessible panic button will be provided to all subjects and the function of this button will be explained in detail. The MRI scan sessions will be conducted by the researchers involved and will have no diagnostic purpose. Through the consent form, participants will be informed that the images will go through standard checks by a radiologist. Possible abnormalities can always be missed. If any deviations are detected, this will be reported to the Radiology Department of the UZ Leuven hospital, supervised by Prof. Stefan Sunaert and appropriate information will be delivered to the general practitioner involved.

7.1 Adverse event reporting

7.1.1 Definitions

- Adverse event (AE): any untoward medical occurrence in a patient or subject during an experiment, and which does not necessarily have a causal relationship with this treatment. An AE can be any unfavorable and unintended sign (including an abnormality on an MRI scan), symptom or disease temporally associated with the intervention, whether or not considered related to the intervention. Any worsening (i.e., any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be considered an AE.
- Adverse Reaction (AR): any untoward and unintended responses to an investigational medicinal product or to an experiment and, when an investigational product is concerned, related to any dose administered.
- Serious adverse event (SAE): any untoward medical occurrence that results in any of the following:
    - Death
    - A life-threatening experience, i.e. in which the subject was at risk of death at the time of the event
    - In-patient hospitalization
    - A persistent or significant disability or incapacity
    - Important medical events that may be considered an SAE when, based on appropriate medical judgement, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the above outcomes
- Suspected Unexpected Serious Adverse Reaction (SUSAR): an adverse reaction, the nature or severity of which is not consistent with the information on the experiment, and, when a clinical trial is concerned, with the applicable product information (e.g. investigator's brochure for an unauthorised investigational product or the patient leaflet joined to the summary of product characteristics for an authorised product).

7.1.2 Adverse events that do not require reporting

- Pre-existing conditions related to the symptomatology and medical treatment of Parkinson's disease, e.g. tremor, rigidity, balance impairments, freezing, orthostatic hypotension, etc.
- Pre-planned hospitalizations, unless the condition for which the hospitalization was planned has worsened from the first trial-related activity after the subject has signed the informed consent

7.1.3 Recording and reporting of adverse events

The investigators will seek information on AEs during each patient contact after the start of the intervention, i.e. at the end of day 1 and on day 2, by means of a safety assessment. All events, whether reported by the patient or noted by the trial staff, will be recorded within a reasonable time after becoming aware.

All AEs will be evaluated by an investigator as to:

- Seriousness: whether the AE is an SAE or SUSAR, see above for criteria
- Severity

    - Mild: no or transient symptoms, no interference with the subject's daily activities
    - Moderate: marked symptoms, moderate interference with the subject's daily activities
    - Severe: considerable interference with the subject's daily activities, unacceptable
- Causality
    - None: An AE which is not related to the study-related interventions
    - Unlikely: An AE for which an alternative explanation is more likely (e.g. concomitant medication(s), concomitant disease(s)), and/or the relationship in time suggests that a causal relationship is unlikely
    - Possible: An AE which might be due to the study-related interventions. An alternative explanation is inconclusive. The relationship in time is reasonable; therefore the causal relationship cannot be ruled out.
    - Probable: An AE which might be due to the study-related intervention. The relationship in time is suggestive (e.g. confirmed by dechallenge). An alternative explanation is less likely.
    - Definitely: An AE which is known as a possible adverse reaction and cannot be reasonably explained by an alternative explanation. The relationship in time is very suggestive (e.g. it is confirmed by dechallenge and rechallenge).

After informed consent has been obtained and after initiation of study-related interventions, all AEs, ARs, SAEs and SUSARs causally related to a study-related intervention will be reported until 30 days after the last study-related intervention or until last follow-up visit (whichever occurs first). All SAEs or SUSARs will be reported to the treating physician and ethical committee within 24 hours of the trial staff becoming aware of the event. Further study participation will be discussed with the treating physician. The immediate report shall be followed by detailed, written reports.

SAEs and SUSARs will be followed up until the outcome of the event and any related queries are resolved. Non-serious AEs and ARs will be followed up until the participants last study visit, and until all related queries have been resolved.

If the investigator becomes aware of an SAE with suspected causal relationship to the study-related interventions after the subject has ended the trial, the investigator will report this SAE within the same timelines as for SAEs during the trial.

7.1.4 Annual reporting

The sponsor has the obligation to, once a year throughout the clinical trial (or on request), submit a progress report to the ethical committee containing an overview of all serious adverse reactions that occurred during the reporting period and taking into account all new available safety information received during the reporting period.

8 Costs

Full reimbursement of travel expenses for the people with Parkinson's disease and age-matched controls (i.e. the healthy elderly) will be covered by the project. There will be no additional reimbursement.

9 Ethics

The protocol is submitted for review to the local Ethics Committee of KU Leuven (Commissie Medische Ethiek UZ Leuven, Herestraat 49, 3000 Leuven). The study will be performed in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) and the principles of GCP. Any subsequent protocol amendments will be submitted to the Ethics Committee and Regulary Authorities for approval.

After complete explanation of the study protocol, written informed consent will be obtained from all participants prior to participation in the experiment.

The investigators will treat all information and data relating to the study confidential. If data are shared on the internet upon publications of the results, obligations with regard to protection of the results, confidentiality, security and the obligations to protect personal data will be guaranteed. Critical or sensitive data will be pseudonymized to ensure that re-identification by combining pseudonymized data with other population data is impossible. The key to the pseudonymized data will be stored on KU Leuven network drives, with no access from outside.

The collection, processing and disclosure of personal data, such as patient health and medical information is subject to compliance with applicable personal data protection and the processing of personal data (Directive 95/46/EC and Belgian law of December 8, 1992 on the Protection of the Privacy in relation to the Processing of Personal Data).

It is possible that pseudonomized data will be shared with other partners in the Keep Control network, to further improve and cross-validate algorithms. This network consists of 12 European Principal Investigators and fellows, respectively, all focusing on the improvement of motion-based algorithms for the detection and description of neurological movement disorders and age-associated movement deficits. Transmission of information will only be performed with encrypted data files. The cooperation partners are not entitled to pass on the data to third parties. Anyone with access to the data, including the investigator, is subject to professional secrecy during and after the project.

10 Insurance

In accordance with the Belgian Law relating to experiments on human persons dated May 7, 2004, Sponsor shall assume, even without fault, the responsibility of any damages incurred by a Study Patient and linked directly or indirectly to the participation to the Study, and shall provide compensation therefore through its insurance.

The study is insured by KU Leuven.

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