WALKING AND THINKING - BRAIN ACTIVITY DURING COMPLEX WALKING IN AGING AND PARKINSON'S DISEASE

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Development of a protocol for assessment of brain activity during complex walking in aging and neurological disease

AIMS

The *overarching aim* of this research is to develop and test a state-of-the-art protocol for assessment of motor-cognitive performance during complex walking (e.g. navigation and dual-tasking) by integrating non-invasive measures of brain activity; functional near infrared spectroscopy (fNIRS), and objective assessment of motor behavior in young, older healthy adults and persons with neurological diseases (Parkinson's disease (PD), Multiple sclerosis (MS) and stroke).

Specific aims are to:

1) To explore the feasibility regarding data sampling and management of fNIRS measures of cortical activity and objective assessment of motor behavior during complex walking in young, older healthy adults and persons with PD, MS and stroke.
2) To investigate construct (known-group) and convergent validity of fNIRS measures of cortical activity and objective assessment of motor behavior during complex walking in young, older adults, people with PD, MS and stroke.
3) To describe and compare cognitive-motor performance during complex walking with regards to cortical activity and motor behavior in young, older healthy adults and people with PD, MS and stroke.
4) To examine personal, functioning and contextual factors associated with motor-cognitive performance during complex walking in young, older healthy adults and people with PD, MS and stroke.

BACKGROUND

Every-day life means being part of a complex environment, and performing complex tasks usually combining motor and cognitive skills. However, the process of aging or the sequelae of neurological diseases compromises motor-cognitive interaction necessary for an independent lifestyle. The challenge of improving the treatment of motor-cognitive difficulties is daunting and the first step in this process is arriving at a method that accurately portrays these impairments in an ecological valid state. This project focuses on establishing a protocol addressing two critical and overlapping hallmarks of healthy walking; that is gait automaticity and gait adaptability.

Gait automaticity. Safe and independent walking is controlled by a balance between automaticity, i.e. movements controlled without the attention by the individual, and executive control processes, i.e. movements requiring attention [1]. In healthy individuals, walking is considered to be a highly automated skill since minimal use of executive control is needed to coordinate the walking pattern [1]. The automatic control of walking is critical for safe ambulation, since executive control may then be allocated to other important aspects of the environment (e.g. an approaching obstacle) or to other tasks (e.g. reading items on a shopping list). The most widely used approach to assess walking automaticity is with dual-tasking (DT), i.e. the simultaneous

performance of two tasks with different goals in which one could be referred to as the primary and the other as the secondary task [1]. In the DT paradigm, the primary task is performed as a single-task (e.g. walking) as well as a DT (e.g. walking while performing a cognitive task). The DT performance is often expressed as the DT-cost: i.e. the difference between single-task (e.g. walking alone) and DT (e.g. performing a cognitive task while walking) [2]. The extent of the DT-cost provides an indication of the automaticity of the primary task. Thus, a higher DT-cost is expected when walking requires heightened executive control whereas lower DT-cost is expected when walking is automatically controlled [3].

Gait adaptability during complex walking. Human walking is remarkable adaptable in the face of changing environmental demands such as transition from walking on a hard surface road to a soft sandy beach or changing the direction in response to unexpected objects. Adapting gait in response to changes in the environment is a key aspect for efficient and safe ambulation [4, 5]. In fact, up to 50% of the steps executed each day incorporate more complex walking conditions (e.g. turning, acceleration/deacceleration, obstacle crossing or descending stairs) where we are required to adapt and walk with an asymmetric step ratio [6]. Complex walking is an essential element of daily living relying on sensory integration (somatosensory, visual and vestibular information) to inform us about the body position and any external object with which the body could interact [7]. In contrast, problems integrating sensory information not only interfere with the ability to respond to changes in the environment (e.g. negotiating obstacles) but also planning of movements.

Walking impairments and falls are common in older adults and in people with neurological diseases with devastating consequences on health; including serious injuries, activity limitations, social isolation and mortality [8-11]. While studies have shown that walking is often slow and variable in these population, gait impairments become more pronounced during DT [12-15] or complex walking conditions [16, 17]. For instance, walking is often less automatic in people with neurological disease as demonstrated by DT-cost on walking velocity up to 30% in these populations [12, 13] compared to only 5-10% in healthy individuals [1]. These findings suggest that movements in people with neurological disease are more under executive than automatic control (i.e. attention is required to “how” the body is moved). Similarly, as we age, walking becomes more affected by divided attention (DT) [18, 19], likely contributing to an increased risk of falling in this population [9, 20]. The ability to efficiently and safely adapt the gait pattern is often impaired in people with neurological disease; such as PD [21], MS [22] and stroke [23]. Walking and turning ability, in particular, are vital aspects of mobility that deteriorate with age and are further impaired in people with neurological diseases. Such deficits have been linked with reduction in automatic control of movement and the need for compensatory cognitive cortical control via the pre-frontal cortex (PFC) [24-26], however the underlying neural mechanisms remain unclear. Establishing robust methodology to examine cortical activity during DT and complex walking conditions may aid in the understanding of mobility deficits and support the development of appropriate interventions for older adults and people with neurological diseases.

Functional near infrared spectroscopy (fNIRS) is a non-invasive medical device which utilizes the optical properties of neuronal activity to measure changes in the concentration of oxyhemoglobin and deoxyhemoglobin in cortical regions [27]. This device could be used to measure cortical activity during a variety of different motor tasks, from static postural tasks (e.g. sitting or standing) to more dynamic mobility tasks, such as walking during different conditions [27]. fNIRS has several advantages such as lightweight, easy to use, robustness to head movement and the ability to measure cortical activity at high spatial resolution during walking [27, 28]. Previous studies that have examined PFC using fNIRS during dynamic mobility tasks have generally shown increased PFC activity in older adults, and even higher activity in people with PD, MS and stroke [28, 29]. Although previous studies have provided significant information about PFC activity during walking, there are important limitations to the existing body of research. Firstly, the majority of previous studies have examined relatively homogenous and small cohorts (N < 15) of healthy young or older adults [28-30], with few previous studies in people with neurological diseases. Secondly, previous studies have used different protocols with methodological differences regarding data sampling and processing which makes generalization of results difficult [30]. For instance, most previous have not used short-separation reference channels to remove peripheral hemodynamic response (i.e., increased skin or superficial blood flow due to physical activity) from the recordings of cortical activity [31, 32].

METHODS AND MATERIALS

Study design & sample size

This project includes a cross-sectional study with a test-retest design including the following subgroups: adults, older adults, and persons with a clinical diagnosis of PD, MS or stroke. A total of 250 participants will be included (50 participants per subgroup). The sample size, deemed representative for the target study populations, is based on previous studies which have explored the reliability of assessment of cognitive-motor performance using fNIRS in older adults and people with neurological disease [29].

Study participants and recruitment

Inclusion criteria for adults (18-50 years) and older adults (≥60 years of age) are free from cognitive impairments or any medical conditions that could affect their daily ambulation. Recruitment will take place through advertisements and senior organizations.
Inclusion criteria for the groups with neurological disease are: >18 years of age, a clinical diagnosis ≥6 months prior to enrolment according to clinical guidelines; PD according to Queens Square Brain Bank criteria [33], MS according to McDonald criteria [34] and ischemic stroke according to World Health Organization [35], with the ability to walk with or without a mobility device for ≥5 minutes continuously. People with speech difficulties (e.g. aphasia) or cognitive difficulties affecting the ability to understand and/or follow verbal/written instructions, severe perceptual problems (e.g. spatial neglect) or severe freezing of gait will be excluded. People with PD, MS and stroke will be recruited through advertisement, patient organizations and our

established collaboration with clinical sites in Stockholm (e.g. Karolinska University Hospital, Stockholms Sjukhem and Stora Sköndal Rehabilitation Center).

Information and consent
Individuals meeting the inclusion criteria will receive oral and written information about the aim and procedure of this study before starting data collection. Written informed consent will be obtained from all participants by the test leader.

Testing procedure
The project comprises three parts. 1) All study participants will attend one test session which comprise structured interviews, clinical tests of cognition and balance/gait, laboratory assessment of cortical activity and movements during postural tasks and walking. The session will be conducted at the uMOVE core facility, Karolinska University Hospital, Solna (Stockholm). 2) After this test session, participants will be equipped with wearable sensors for measurement of physical activity in their daily life. 3) Subsequently, half of the study participants in each subgroup (i.e. n=25/group, total n= 125) will be invited to a second test session at the uMOVE core facility and will conduct the same laboratory assessment of cortical activity and movements during postural tasks and walking in order to explore test-retest reliability of these measures. The procedures and measures for part 1-3 are detailed bellow.

Lab-based assessment of cortical activity and movements during postural tasks and walking (part 1)
Standardized interviews will be used to collect information on personal factors (e.g. gender, age, length, weight, diseases, educational level, medical history, chronic diseases and fall history) and environmental factors (e.g. living situation, education, employment status, support resource in daily life and use of assistive devices). For study participants with PD, MS and stroke, the interview will also include questions on disease duration and prevalence of motor (e.g. weakness, coordination deficiency) and non-motor symptoms (e.g. fatigue, sleep and concentration).
Clinical tests and questionnaires. The following disease specific clinical tests of neurological symptoms/function will be conducted; Unified Parkinson's Disease Rating Scale motor score (UPDRS-motor) [36], Expanded Disability Status Scale (EDSS) [37] and National Institute of Health Stroke Scale (NIHSS) [38] for people with PD, MS and stroke, respectively. All clinical tests and questionnaires included in this study are validated or commonly used in research and/or clinical practice for the different age groups and people with neurological diseases. The data level of the questionnaires is ordinal, and the result will be reported as a sum score.

Instruments. Gait parameters (such as cadence, velocity, step time and trunk/arm movements) during different types of complex walking will be measured using wireless inertial sensors (Opal, APDM Inc) positioned on trunk, low back, left and right wrist and ankle. These sensors are light-weighted; similar to a regular watch, and continuously streams data to a computer with Mobility LabTM software. Cortical brain activity will be assessed using a mobile fNIRS system (NirSport 2). fNIRS is a non-invasive technic assessing the brain's hemodynamic response by optical

properties of light. During testing, study participant is wearing a tight cap fitted to the head and a controller box attached as a light back-pack (approx. 800 g). The recipient box is connected to the cap with a bundle of cables organized on the back of study participants trunk and neck. fNIRS collecting data from the cortex up to 2-3cm deep, it is well suited to study cortical involvement in cognitive processes. The wireless fNIRS system records (50 Hz) changes in oxygenated hemoglobin (HbO2) and deoxygenated hemoglobin (HHb) including 8 Source-receiver pairs allowing for 64-data channels. Distance from each sources to detector is 3 cm [39] and data will be collected in line with previous studies [30, 40]. To allow for removal of peripheral interference (i.e., from blood flow changes in the extra-cerebral layers of the head), this system also includes short-separation reference channels spread on the left and one right hemisphere which enable measurement of extra-cerebral blood flow [31, 32].

Test procedure. All testing will be conducted by a healthcare professional or a researcher in the project group with experience of balance and gait assessment, and patients with neurology diseases. The participants will perform different postural tasks and walking tests requiring different level of motor-cognitive performance. The conditions will include;

1. standing quite (reference conditions)
2. walking straight in a self-selected and brisk walking speed
3. continuously turning task, walking turns in a self-selected speed where participants follow a predefined track directed by cones placed on floor

The duration of these test conditions will range between 1 to 6 minutes. All test conditions will be performed as a single-task; participants are instructed to focus only on the postural/motor task, and as a dual-task; with concomitant cognitive tasks, such as the Auditory Stroop test, n-back, Stroop Color and Word Test. Condition order will be randomized, with breaks between tasks if needed.

Data management and analysis. Gait parameters will be processed using the Mobility Lab™ Software and outcomes will be average and variability metrics (e.g. SD) of temporal and gait parameters for each gait condition. Cortical activity will be processed and analyzed using Aurora fNIRS (NIRSport 2 acquisition) software and programming software's, such as MATLAB (Mathworks, MA, USA). Analysis of fNIRS data includes the following steps: data filtering (i.e. removing high frequency noise), baseline correction (i.e. removing the mean/median of the initial a standing reference trial), reference channel correction (i.e. correcting from artefacts, e.g. caused by breathing, cardiac cycle and vasomotor). The outcomes will be change in oxygenated hemoglobin (HbO2) from baseline standing to the walking conditions, which is a proxy for cortical activation. HbO2 will be used as a primary outcome due to its sensitivity to walking and cognitive tasks [41]. For both gait and cortical activity outcomes, we will calculate the potential change between less complex postural tasks (e.g. sitting and standing) and more complex motor tasks (e.g. continuously turning task and obstacle crossing). Dual-task interference will also be calculated as the absolute and relative change (percentage) between single-task and dual-task performance.

Assessment of physical activity behavior (part 2)

Instruments and procedure. After completing part 1, the participants will be equipped with one accelerometer (Actigraph GT3X+) [42] and a GPS (i-gotU GT-600) in order to assess the participants physical activity in the community. Both the accelerometer and GPS sensors are lightweight (about 20 gram each) and will be attached to an elastic belt around the hip. The participants will be asked to wear the devices in their daily life during all woke hours for 7 consecutive days and to fill in the diary of the times the device was worn. After the 7-day measurement period, participants will return the device to the research coordinator using a pre-paid mail service. The participants will also receive instruction on how to attach, wear and remove the device as well as brief written information about this procedure.

Data management and analysis. Accelerometry data are stored in the units of gravity (g) and is subsequently transformed into an arbitrary unit (*i.e.* activity counts) in either axes or as a combined vector magnitude [42]. Physical activity data will be sampled at 30 Hz and processed using the ActiLife 6 software (ActiGraph, Pensacola, FL). The GT3X+ has been proven reliable and valid in assessing energy expenditure in healthy adults [43]. The primary outcomes for physical activity will be steps per day, total vector magnitude counts, and the time spent in different physical activity intensities (e.g. sedentary, light and moderate-to-vigorous physical activity). The latitude and longitude GPS data and its corresponding time stamp will be synchronized with the acceleration data. The physical activity and the GPS data will be interpolated to create a heat map and geographical information system layers will be added for spatial representation. This approach allow us to describe where and how physical activity take place in relation to the home, neighborhood, residential and regional areas, and the characteristics of the environment (e.g. city, parks and forest).

ETHICAL CONSIDERATIONS

The testing procedure will not include any additional risks compared to regular clinical assessments as a majority of the clinical tests and questionnaires included in this proposal are part of regular clinical assessments of the targeted groups.

While testing of complex walking conditions (e.g. dual-tasking and navigation tasks) in populations with impaired balance (e.g. PD, MS and stroke) or older adults there is always a risk of instability and falls. Therefore, participants will not be asked to walk faster than they are comfortable, and the test leader will be positioned close to the participants during all testing to prevent them from falling in case of a trip or slip. If needed, participants with more severe balance impairments will be equipped with a safety belt to further ensure safety. Consideration for fatigue during testing has been made and breaks in the protocol have been set up.

fNIRS is a new technology assessing the brain's hemodynamic response by optical properties of light. fNIRS collecting data from the cortex up to 2-3cm deep, it is well suited to study cortical involvement in cognition. It is quiet, portable, and does not require being still in a narrow tube which for example is the case for magnetic resonance imaging. There are no known associated risks of measuring cortical activity with fNIRS, only wearing a tight cap fitted to the head might

result in temporary discomfort or headache. Testing of cognitive functions might be perceived as stigmatizing and therefore a neuropsychologist will be part of the research team.

The instruments used to measure physical activity (accelerometer and GPS) are non-invasive methods without any documented associated risks for the individual. Furthermore, the size of the accelerometer and GPS is similar to a normal wristwatch and will not interfere with the ability of the participant to perform daily activities. We are aware of the potential confidentiality risk associated with using GPS data of spatial position. To date, there is no universal standard for "adequate confidentiality protection", however we have an established procedure of geomask the data (masking geographic identifiers) to preserve confidentiality.

All data will be analyzed on a group level to protect individual's anonymity and the code key to connect individual with data will be kept secured and encrypted Only authorized researchers will have access to the data. Data will be pseudonymized and stored as paper and digitally in accordance with regulations of public authority archives and the General Data Protection Regulation. The code key and coded data will be stored separately. To reduce any bias, assessors and researchers will be blinded through all stages of data collection and analysis. The generated/analyzed datasets will not be publicly available due to Swedish and EU personal data legislation. They will be available upon reasonable request and sharing will be regulated via a data transfer/user agreement.

SIGNIFICANCE

While motor-cognitive performance has been identified as an important goal for sustained health across different clinical populations, little is known about corresponding brain activity leading to these difficulties and how to best target these motor-cognitive difficulties in the context of rehabilitation. The goal of this project is to develop and test a state-of-the-art protocol for assessment of motor-cognitive performance using fNIRS in both healthy and disease populations. The proposed studies has great potential to increase the knowledge of motor-cognitive difficulties in older adults and people with neurological diseases which in turn will inform fall prevention strategies for these populations. Increased knowledge can lead to targeted interventions and better care, development of rehabilitation programs and thereby decreasing the risk of secondary complications, reducing costs for society and increasing quality of life for older adults and people with neurological diseases.

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