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|---|---|
| **Study Title** | The effect of transcranial direct current stimulation on complex treadmill walking and cortical activity: A pilot study |
| **Study Design** | Observational study involving human participants |
| **Study Participants** | 20 Healthy young adults<br>20 Health older adults |
| **Planned sample size** | 30 |
| **Follow up duration** | N/A |
| **Planned Study Period** | 12 months |
| **Research Question(s)** | The aims of the research project are to:<br>1. Evaluate the effect of transcranial direct current stimulation on treadmill walking.<br>2. Investigate changes in dual task interference following transcranial direct current stimulation.<br>3. Determine the effect of transcranial direct current stimulation on cortical activity.<br>4. Examine the effect of ageing on responses to transcranial direct current stimulation. |

# CONTENTS

# 1. BACKGROUND

Daily real-world walking activities in the home and community environment generally involve performance of additional tasks, such as talking, obstacle avoidance and precision stepping (e.g. cued gait and stepping on target location). Compared to steady state walking (walking in the absence of additional tasks), complex walking places a heightened demand on visual, motor and cognitive resources [1]. Cognitive function is strongly associated with prefrontal cortical activity (PFC). Until recently, knowledge of cortical activity during locomotion was derived from functional magnetic resonance imaging (fMRI) studies involving tapping movements and gait imagery tasks [2]. However, advances in technology have led to assessment of cortical activity during walking, with the application of functional near infrared spectroscopy (fNIRS) or electroencephalography (EEG) devices.

fNIRS measures the amount of oxygenated haemoglobin (HbO2) and deoxygenated haemoglobin in the cortex which are related through neurovascular coupling, to cortical activity [3]. fNIRS offers the potential for mobile monitoring and as such have been applied during active movements [4] and steady-state walking [5]. Several studies have applied these devices during walking, especially in older adults [6] and patients with gait impairments [7, 8]. Although some controversial findings have been reported [9], most studies observed higher PFC activity during more complex walking tasks (e.g. walking while talking and negotiating obstacles) compared to regular walking [8, 10-12]. Also, young adults have been reported to show greater increase in HbO2 levels in PFC compared with older adults during attention-demanding locomotion tasks [10]. Recent comprehensive reviews on brain activity during walking concluded that cortical activity during walking is highly sensitive to task complexity, age and pathologies [3, 13].

Age-related walking impairments are more severe for complex walking tasks than for typical steady-state walking [14]. The decrease in gait function has been associated with age-related changes in the brain [9, 15, 16]. Cortical regions implicated in deterioration of gait control include frontal association areas such as the premotor cortex, supplementary motor area, and prefrontal cortex. Clinically, impaired gait is significant as it is an independent risk factor for falling [17]. Falls occur with higher frequency during complex walking tasks due to increased attentional and motor demands [18, 19]. The consequences of falls and fall-related injuries can negatively affect quality of life, with fear of falling resulting in greater inactivity [20, 21]. In addition, fall-related injuries and hospital admissions have been associated with substantial economic and public health costs [22]. There is therefore a critical need for development of an effective intervention that will optimise gait during complex walking.

An intervention, which has been applied to improve gait, is non-invasive transcranial direct current stimulation (tDCS) [23-25]. tDCS has been shown to facilitate motor learning [26] as a possible result of increasing cortico-spinal excitability [27] and/or modulation of reciprocal 1a spinal inhibition [28]. Kaski et al (2014) reported that application of tDCS combined with physical training increased gait velocity in people with Parkinson's disease [25]. The effects of tDCS on cortical activity and their relationship to subsequent changes in gait and cognition are however unknown [29].

### 1.1 AIMS

The aims of the research project are to:

1. Evaluate the effect of transcranial direct current stimulation on treadmill walking.
2. Investigate changes in dual task interference following transcranial direct current stimulation.
3. Determine the effect of transcranial direct current stimulation on cortical activity.
4. Examine the effect of ageing on responses to transcranial direct current stimulation.

## 2. METHODOLOGY

### 2.1 OVERVIEW

Participants (n=40) will be assigned to two groups; *healthy older adults* (HOA) (n=20) and *healthy younger adults* (HYA) (n=20), after an initial screening. An observational design will be employed with assessments performed during 1 session (as below) for both groups.

All Groups (HOA, HYA) (up to 90 min)

- Screening, demographic and neuropsychological assessment (30min)
- Cortical activity measurement and sham or active tDCS applied during treadmill walking (60min)

**Table 1 - STUDY FLOW CHART**

| Milestones | Months | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | #1 | #2 | #3 | #4 | #5 | #6 | #7 | #8 | #9 | #10 | #11 | #12 |
| Training (equipment and procedures) | X | | | | | | | | | | | |
| Participant recruitment | X | X | X | X | X | X | X | X | | | | |
| Data collection | X | X | X | X | X | X | X | X | X | | | |
| Data analysis and interpretation | | X | X | X | X | X | X | X | X | X | | |
| Final scientific report | | | | | | | | | | X | X | X |
| Manuscript preparation/ submission | | | | | | | | | | X | X | X |

## 2.2 PARTICIPANTS

### 2.2.1 Eligibility Criteria

Subjects will be recruited if they meet the following screening criteria:

*Inclusion Criteria*

I. Able to walk unaided for 10 minutes.
II. HOA group aged ≥50
III. HYA group aged 18 – 40 years
IV. Stable medication for the past 1 month
V. Understand English language
VI. Adequate hearing and visual capabilities
VII. Community dwelling

*Exclusion Criteria*

I. History of alcohol and drug abuse
II. History of major gait abnormality
III. Chronic musculoskeletal (e.g. osteoarthritis, osteoporosis), cardiovascular (e.g. hypertension, peripheral vascular disease), respiratory (e.g. chronic obstructive pulmonary disease) disease affecting gait.
IV. History of an implanted metal device in the skull area
V. Psychiatric co-morbidity (e.g major depressive disorder) or other severe cognitive impairment
VI. Acute lower back or lower extremity pain
VII. Unstable medical condition including cardio-vascular instability in the past 6 months

### 2.2.2 Recruitment

Healthy young and older adult groups will be recruited via advertisement using posters, which will be placed within university notice boards, and word of mouth. The advertisement will also be sent via the university email system to staff and students at Newcastle University, the recipients will be advised to pass on the poster to potential interested parties (i.e. family or friends). Older adults will also be recruited through the Elders Council and Voice North.

Once healthy young or older adult subjects have expressed interest in the study, they will be sent a participant information sheet concerning the study and arrange a convenient time with the researchers to attend an assessment.at the Henry Wellcome Building. The researcher will explain the study to the potential participant and screen them for inclusion and exclusion factors. An informed

consent will then be obtained from the participant, if willing to participate and satisfying the criteria. The following procedures will then be followed.

## 2.3 PROCEDURE

### 2.3.1 Demographic and Neuropsychological Tests

1. Structured Interview; Each participant will be interviewed by a member of the study team. The interview will include questions regarding education level, falls history and activity levels.
2. Montreal cognitive assessment (MoCA). Cognitive function will be assessed using standardized neuropsychological tests such as the MoCA; a rapid screening instrument for global cognitive dysfunction [30]. Different cognitive domains are assessed (attention and concentration, executive functions, memory, language, visuo-constructional skills, conceptual thinking, calculations, and orientation). The MOCA was found to be a valid instrument for cognitive screening in MCI. In this study the MoCA will be used as a descriptive measure [30].
3. *Beck Depression Inventory (BDI).* The BDI will be used to evaluate subjects' depression. This involves 21 questions about the mood of the subjects and has been validated for both healthy subjects and subjects with PD [31, 32]. Scores of 1 to 10 are in the normal range, 17 to 20 indicate borderline clinical depression, and 31 to 40 indicate moderate to severe depression.
4. Falls efficacy scale – International (FES-I); Fear of falling will be measured using the falls efficacy scale – international version. This is a short and valid measure of fear of falling in older adults, which assesses basic and demanding activities (both physical and social) [33]. It consists of 16 scenarios (e.g. cleaning the house) and subjects must rate their fear of falling on a scale from 1 (Not at all concerned) to 4 (Very concerned).

### 2.3.2. Treadmill walking

*Initial Baseline Collection*

The participants (n=40) will be asked to stand still for 60 s with eyes open and then for a further 60 s with eyes closed. A 60 s period of rest will separate the two standing sessions.

*Treadmill Walking*

Participants (n=40) will be asked to walk on a treadmill while doing several tasks at different times. The comfortable walking velocity will be determined for each participant by adjusting the treadmill velocity until the participant is satisfied that it is like his or her normal walking velocity. The participant will walk on the treadmill for 2 minutes followed by 5 minutes of alternating 30 s bout of normal walking and dual task walking. Following a 5 minute rest the participant will repeat the 2 minutes of walking followed by 5 minutes of dual-task walking. The participant will then have a further rest period

of 5 minutes after which he / she will walk on the treadmill for a period of 10 minutes and will simultaneously have tDCS (either sham or active) applied. They will then rest for 5 minutes before repeating the two sets of 5 minute dual task walking preceded and ended with 1 minute of normal walking.

#### 2.3.3 Equipment

Cortical activity will be assessed using an fNIRS device (LABNIRS, Shimadzu, Kyoto, Japan). The fNIRS device is lightweight (approx. 0.2kg) and consists of up to 32 optodes which record data from the cortex of participants. The participants will also wear a small device (oximeter) over the index finger of their left hand to measure blood saturated oxygen (SpO2) levels and pulse rate as a systemic increase in blood O2 will increase the fNIRS signal.

Video recording and body worn monitors (e.g. accelerometers) will record individuals' movement during walking. Video data is obtained to check the veracity of the data and identify causes for potentially anomalous results (such as the participant stopping). Accelerometers are a valid and reliable method of assessing the spatiotemporal parameters of gait in healthy adults [34]. For example; stride-to-stride fluctuations (swing time, stride time and step width) will be described using the following formula: Coefficient of Variation - CV (%) = (Standard Deviation/Mean)*100. Within each trial, data will be averaged across repeated samples and stride pooled for estimation of stride-to-stride fluctuations in gait. Electromyography (EMG) may record muscle activity of the legs using surface electrodes placed on the skin overlying the muscles.

Direct current will be applied to the cortex via transcranial direct current stimulation (tDCS). A direct current rectangular stimulating (anodal) electrode (3 cm x 3 cm) will be placed on the scalp overlying an area of the frontal cortex [25, 35-37]. The cathode will be placed on the contralateral supraorbital region of the skull [36, 38]. Prior to placement, both electrodes will be soaked with saline solution. The magnitude of current will be 2mA and duration of application will be ten minutes [25, 35].

### 2.4. OUTCOME MEASURES

*Cortical Activity*

The fNIRS device will record changes in cerebral oxy-haemoglobin (HbO2), deoxy-haemoglobin (HHb), and total haemoglobin concentrations. Data analysis will be carried out according to previously described procedures for measuring cortical activity using fNIRS [6, 7]. Mean changes in haemoglobin levels will be the main measure for cortical activity.

*Gait Characteristics*

Spatiotemporal gait characteristics will be derived from body worn monitor data and video recordings. Characteristics include velocity, step /stride length, step / stride time and gait variability recorded during different walking conditions.

*Muscle activity*

Muscle activity will be recorded using EMG. Mean amplitude, duration and patterns of muscle activity will be analysed.

# 3. SAFETY CONSIDERATIONS

All measurements are non-invasive and place the subject at no risk other than those that may normally occur during walking. Participants may feel tired during the 10-minute walking trials, although all walking trials are conducted at the participant's comfortable walking velocity. Rests will be provided between walking bouts. There is a small falls risk, although all participants in this study are healthy adults who are able to walk unassisted for a minimum time of 10 minutes. Participants will have a safety cord attached to them which will cause the machine to stop immediately if the cord is being pulled away. The fNIRS head cap will be cleaned or washed after each participant, to ensure appropriate adherence to infection control policies.

# 4. DATA ANALYSIS

## 4.1 SAMPLE SIZE

The sample size for this pilot study is 40 which should provide sufficient power to find differences between groups based on previous fNIRS studies in HYA and HOA [6, 7, 9, 10, 39-44] participants.

## 4.2 STATISTICAL ANALYSIS

Processing of fNIRS signals will follow current recommendations when possible [3]. The data will be analysed using the software NIRS-SPM and processed in MATLAB. The difference in haemoglobin levels will be analysed to determine the effect of tDCS on cortical activity. Gait parameters will be extracted from the accelerometer data according to published methods developed by our research group and described in detail in previous publications [45,46]. Gait variables included: step time, swing time, step length and gait variability (i.e. step time, stance time, swing time, step length and step velocity).

Demographic characteristics and baseline data will be summarized using descriptive statistics, including means, standard deviations, median, minimum, maximum and inter-quartile ranges for continuous or ordinal data and percentages for categorical data. The descriptive statistics will be

tabulated and presented graphically for clarity. The assessments recorded at pre-testing will be taken as baseline values. Differences in the levels of haemoglobin between groups (i.e., young vs. older adults), tasks (i.e., usual walking vs. DTW and trials (i.e., 1, 2, 3, 4 and 5) will be analysed using linear mixed models in SPSS (v21, IBM, Chicago, Il., USA), $P< 0.05$, while controlling for treadmill speed. Bonferroni corrections for multiple comparisons (p-value / number of comparisons) will be applied to the post hoc analyses. Gait measures will also be analysed using the linear mixed model approach. Non-normally distributed continuous variables will be log-transformed for statistical analysis. The association between cortical activation and cognitive or gait measures will be explored using Spearman and Pearson correlation coefficients (according to data type and distribution).

## 5. PROJECT MANAGEMENT

The study will be run by the Brain and Movement (BAM) Research Group at Newcastle University, led by Principal Investigator Annette Pantall. The BAM team will be responsible for ensuring progress of the study in relation to administrative, clinical and academic issues. All published output from the study will acknowledge this study group.

## 6. STUDY SETTING

The study is a single centre study and all data will be collected at the Institute of Neuroscience, Newcastle University. The baseline assessment will take place in the EEG room, the first floor of Henry Wellcome Building. The Institute of Neuroscience is dedicated to the investigation of neurological (e.g. neuro-physiology) issues in older people linking with the research themes of the Biomedical Research Centre/Unit in Ageing.

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