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Altered prefrontal cortex responses in older adults with subjective memory complaints and dementia during dual-task gait: an fNIRS study

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ABBREVIATION LIST

DTG	- Dual-task gait
STG	- Single-task gait
SMC	- Subjective memory complaints
fNIRS	- Functional near-infrared spectroscopy
PFC	- Prefrontal cortex
MoCA	- Montreal cognitive assessment
MBLL	- Modified Beer-Lambert law
EEG	- Electroencephalography
HOMER2	- Haemodynamic optical measured evoked response 2
ANOVA	- Analysis of variance
O_2Hb	- Oxyhaemoglobin
HHb	- Deoxyhaemoglobin

ABSTRACT

People with cognitive impairments show deficits during physical performances such as gait, in particular during cognitively-challenging conditions (i.e. dual-task gait [DTG]). However it is unclear if people at risk of dementia, such as those with subjective memory complaints (SMC), also display gait and central deficits associated with DTG. In this study, we investigated the effects of single- and dual-task gait (STG and DTG), on left prefrontal cortex (PFC) activation in elderly people with subjective memory complaints (SMC) and Dementia. 58 older adults (aged 65-94 yrs; 26 Healthy; 23 SMC; 9 Dementia) were recruited. Gait spatiotemporal characteristics (i.e. stride velocity and length) were assessed using an instrumented walkway during STG and DTG. Single-channel functional near-infrared spectroscopy over the left PFC was used to measure changes in oxyhaemoglobin (O_2Hb) during gait. Stride velocity and length during STG (all $p<0.05$) and DTG (all $p<0.000$) were significantly impaired in people with Dementia compared to Healthy and SMC individuals. No differences were observed between Healthy and SMC. For STG, a greater increase in O_2Hb ($p<0.05$) was observed in those with Dementia compared to the Healthy and SMC, while no differences were observed between Healthy and SMC. A significant increase and decline in O_2Hb was observed during DTG in the SMC and Dementia groups respectively, compared to Healthy. Our findings indicate an altered pattern of cerebral haemodynamic response of the left PFC in DTG in people with SMC and Dementia, which may suggest that central changes precede functional impairments in people with SMC.

KEYWORDS

Gait kinematics; brain activation; neurodegeneration; cognitive demands; neuroimaging

INTRODUCTION

Ageing is associated with declines in cognitive functioning and is a significant risk factor for neurodegenerative conditions such as dementia. In the normal ageing process, it is expected that some cognitive declines would be apparent, typically exemplified by increased reaction time and reduced abilities related to attention and executive functioning (Salthouse, 2004). However, in dementia the trajectory of cognitive decline is magnified, significantly impairing activities of daily living and resulting in poorer quality of life. Considering the rapid increase in population ageing worldwide, there have been increased efforts to raise awareness, with an emphasis on lifestyle and dietary modifications, to mitigate the risks associated age-related cognitive declines and dementia (Simons *et al.*, 2006; Solfrizzi *et al.*, 2008; Di Marco *et al.*, 2014). However, identifying older individuals at greater risk of cognitive declines and dementia remains a challenge particularly in the prodromal stages, due to the absence of a clear clinical biomarker that would allow for early detection (Ahmed *et al.*, 2014).

The assessment of physical movement, such as gait, has gained interest as a simple method to test for cognitive-motor functioning particularly in older adults (Ijmker & Lamoth, 2012; Morris *et al.*, 2016; Tian *et al.*, 2017). The control of gait is typically thought to be autonomous that stems from both spinal and supraspinal centres of the central nervous system to maintain the continuous gait cycle during movement, and balance and postural control in relation to the environment in which the individual is walking (e.g. going up or down a hill) (Takakusaki, 2017). However there is a cognitive element to gait that involves attention and executive functioning resources to produce optimal gait (Montero-Odasso *et al.*, 2012).

To investigate the cognitive-motor processes associated with gait, single- and dual-task gait (STG and DTG) paradigms have been previously used. DTG uses a concurrent cognitive task (e.g. word association or counting backwards) during gait, to determine the level of deterioration of gait performance compared to STG (i.e. normal walking) (Howell *et al.*, 2016; Smith *et al.*, 2016; Li *et al.*, 2018). The reduction, or cost, in gait performance during DTG has been hypothesised to be caused by a reduction in attentional resources associated with performing two tasks concurrently (Boisgontier *et al.*, 2013; Nascimbeni *et al.*, 2015).

In healthy older individuals and those with cognitive deficits, impaired DTG performance have been consistently reported (Hausdorff *et al.*, 2008; Taylor *et al.*, 2013). Portable functional

neuroimaging modalities such as functional near-infrared spectroscopy (fNIRS) have demonstrated that prefrontal cortex O_2Hb is increased, even in simple walking conditions, in older compared to younger adults (Mirelman *et al.*, 2017). During DT paradigms, increased cortical activity, particularly in the PFC (Beurskens *et al.*, 2014; Meester *et al.*, 2014), has been associated with increased attentional processing in older adults compared to young adults. Given the role of the PFC in attentional allocation, this evidence lends support to the hypothesis that DT activities which involve a walking component, lead to an increase in cognitive demand where more attentional resources or demands are necessary to maintain DT activities.

Preliminary evidence have suggested that DTG paradigms may be sensitive to detect changes in cognitive functioning, particularly when cognitive impairments are not yet apparent (Beauchet *et al.*, 2017). In this case, people with subjective memory complaints (SMC), those with reported memory impairments, but no clinical indication of memory deficits, may serve as an ideal population to determine if indeed DTG performance differ from age-matched controls with no memory complaints and individuals with a known memory impairment. Individuals with mild cognitive impairment have demonstrated increased PFC activation during DTG, associated with poorer executive function performance compared to age-matched controls (Doi *et al.*, 2013), but to date limited evidence on DTG performance exists in people with SMC. To the best of our knowledge, no neuroimaging evidence have been reported in relation to DTG performance in people with SMC.

In this pilot study, we compared spatiotemporal gait characteristics (i.e. stride length and velocity) of people with SMC, Dementia and healthy age-matched controls during STG and DTG conditions. We additionally compared the haemodynamic response of the left PFC during STG and DTG of all three groups. We hypothesized that people with SMC and Dementia would have impaired performance in gait outcomes compared to healthy age-matched controls during STG and DTG. We further hypothesized that the haemodynamic response of the left PFC would be greater in the SMC and Dementia groups compared to healthy controls during both gait conditions.

MATERIAL AND METHODS

Participants

In total 58 older participants (aged 65-94 yrs; 26 Healthy; 23 SMC; 9 Dementia) were recruited from the community and assisted living facilities within the Melbourne, Australia metropolitan area and surrounding regions. To be included in this study, all participants needed to be physically healthy and could walk at least 10m without assistance. Individuals with history of stroke, head trauma, alcohol or drug dependency, current clinical diagnosis of severe depression or anxiety were excluded. Participants with SMC were determined via verbal confirmation to the question "do you feel like your memory is becoming worse?" and had to provide three examples of day to day issues that have occurred regarding their memory. Additionally participants within the SMC group needed to score greater than 24 points on the Montreal Cognitive Assessment (MoCA) to rule out mild cognitive impairments (MCI). Participants with Dementia were required to have been provided with a diagnosis prior to inclusion in the study and have a MoCA score of less than 24. All participants or their carers gave written informed consent prior to participating in this study. This study was approved by the Deakin University Human Research Ethics Committee (DUHREC 2017-054) and conducted in accordance with the Helsinki Declaration.

Cognitive Assessment

The MoCA is a validated 30-point test system designed to screen for cognitive impairments (Larner, 2012). It assesses several cognitive domains that includes memory recall, visuospatial memory, language, attention, concentration and working memory. In this study, all participants assigned to the Dementia group attained a combined score for all cognitive domains of lower than 24 points.

Gait performance

Both STG and DTG performance was assessed on a 4.87m instrumented walkway (ZenoMetrics LLC, Peekskill, NY, USA, sampled at 120 Hz with a 0.5 cm spatial resolution). The instrumented walkway measured spatiotemporal gait characteristics, in particular stride length and velocity that was used as indices of gait performance in this study. All participants completed a total of 8 trials (8 passes away and back to the starting point) over the walkway using their preferred walking speed. All participants first completed 4 of the trials of STG, followed by 4 trials of DTG

(counting backwards taking off 7 from a pre-randomised list of 3-digit numbers). The 4 STG trials were completed first to avoid any influence on gait and haemodynamic responses of the DTG trials on STG trials. Prior to the STG, all participants were instructed to *"walk as you would normally walk"* across the instrumented walkway. Prior to the DTG, all participants were instructed to *"do your best to maintain your normal walking speed"* and *"to continue counting if you think you made a mistake"*. The number of counting responses during DTG was recorded. A schematic diagram of the setup is shown in Fig 1. All steps recorded under each condition were pooled for each participant and the mean of the pooled steps are reported as outcomes.

Left PFC measures

A portable single-channel fNIRS device (Portalite, Artinis Medical Systems, The Netherlands) was placed over the left PFC that corresponded approximately to the F3 region (based on 10-20 EEG system). The portable fNIRS device emits NIR light at two wavelengths (760 and 850nm) to detect changes in oxygenated (O_2Hb) and deoxygenated (HHb) haemoglobin separately. Based on the assumption that NIR light is permeable to bodily tissue, the modified Beer-Lambert law (MBLL) was used to determine the attenuation of NIR light in proportion to the regional change in cerebral O_2Hb and HHb. The MBLL describes the attenuation and scattering of NIR light as it passes through biological tissue, which underpins the concept of fNIRS (Delpy *et al.*, 1988). Prior to each trial, all participants stood quietly in an unassisted upright position with hands by the side and looking straight ahead for 30s to establish a baseline haemodynamic response. After 30s of baseline measurement, participants were instructed to walk towards the "X" on the other end of the instrumented walkway, walk around the "X", and back towards the start line. In total 4 trials were performed for each gait condition, with each participant randomly assigned to start with either STG or DTG.

RESULTS AND STATISTICAL ANALYSES

Data processing and statistical analysis

For all fNIRS measures, raw O_2Hb and HHb signals were collected using the proprietary software provided with the Portalite (Oxysoft 3.2.51.4 x64, Artinis Medical Systems, The Netherlands) and

processed using HOMER2 (MATLAB-based optical imaging toolbox). Prior to pre-processing, all raw fNIRS data were visually inspected for motion artefacts between 10 and 40s time-window follow commencement of the gait tasks. This time window corresponds to the peak fNIRS response which was used for further analysis. Following visual inspection, the raw data was pre-processed using a motion artefact detection and correction algorithm (i.e. principal component analysis [PCA]) (Brigadoi *et al.*, 2014), and the averaged peak change in O_2Hb and HHb (as defined by highest O_2Hb and lowest HHb value for each trial less pre-gait baseline values) over a 30s time window was used to compare between GROUPS (Controls vs SMC vs Dementia) and GAIT conditions (STG vs DTG). The pre-processing pipeline in HOMER2 for fNIRS signals is shown in Fig 2.

A one-way analysis of variance (ANOVA) was used to determine significant differences in participant demographic data and total number of counting responses during DTG. Additionally a repeated measures ANOVA was used to compare within-group (GAIT - STG vs DTG) and between-group (GROUP - Controls vs SMC vs Dementia) factors in step length and velocity and cerebral haemodynamic responses (O_2Hb and HHb). Post-hoc analysis was done using Tukey's honest significant difference (Tukey's HSD). An alpha level of $P<0.05$ was set as the level of significance between comparisons. All data analyses were conducted using Statistical Package for the Social Sciences v25 (SPSS, IBM Inc, USA). All results are presented as Mean ± Standard Deviation (SD) and scatter plot of individual data points.

Participant demographics

All Participant's demographic details are shown in Table 1. One-way ANOVA showed that participants in the Dementia group were significantly older ($P < .001$) and had significantly lower MoCA scores ($P < .001$) compared to both Controls and SMC groups. No significant differences were observed between Dementia and Controls or SMC groups for, height, weight and education level.

Step length and velocity

The comparisons of step length and velocity during STG and DTG, and number of counting responses between groups are shown in Fig 3. Repeated measures ANOVA showed significant main effects for GAIT conditions ($F_{1, 55} = 10.13$, $P = .002$) and GROUPS ($F_{2, 55} = 63.53$, $P < .001$) for step length, and similarly for step velocity (GAIT - $F_{1, 55} = 19.00$, $P < .001$; GROUP - $F_{2, 55} = 44.36$, $P < .001$).

Post-hoc analyses revealed a significantly lower step length (Fig 3A) and velocity (Fig 3B) for STG in the Dementia group (STG step length 47.1 ± 13.1 cm; velocity 70.8 ± 15.6 cm/s, both $P < .001$) compared to Controls (STG step length 75.6 ± 7.5 cm; velocity 122.8 ± 18.9 cm/s) and SMC (STG step length 71.2.4 ± 8.9 cm; velocity 118.9 ± 16.7 cm/s) groups. This was similar in DTG with the Dementia group showing significantly lower step length (45.3 ± 11.3 cm, $P < .001$) and velocity (73.6 ± 11.7 cm/s, $P < .001$) compared to Controls (DTG step length 67.3 ± 6.9 cm; velocity 96.7 ± 14.9 cm/sec) and SMC (DTG step length 63.1 ± 7.2 cm; velocity 96.7 ± 11.2 cm/sec) groups.

Within-group comparisons showed no significant differences between STG and DTG step length and velocity in the Dementia group. However, a significant reduction in step length (STG vs DTG, Control 75.6 ± 7.5 vs 67.3 ± 6.9 cm, $P < .001$; SMC 71.2 ± 8.9 vs 63.1 ± 7.2 cm, $P < .001$) and velocity (STG vs DTG, Control 122.8 ± 18.9 vs 96.7 ± 14.9 cm/s, $P < .001$; SMC 118.3 ± 16.7 vs 96.7 ± 11.3 cm/s, $P < .001$) between STG and DTG in both Control and SMC groups were observed.

Fig 3C shows the total number of counting responses for all DTG trials in each group. One-way ANOVA showed a significant between-group difference ($F_{2,57} = 4.49$, $P = 0.16$) with the Dementia group (21.2 ± 12.4 total responses) having significantly lower responses compared to Controls (39.5 ± 21.9, $P < .001$) and SMC (43.9 ± 19.4, $P < .001$) groups. No significant difference was observed between Controls and SMC groups.

Change in O_2Hb and HHb

Fig 4 shows the change in O_2Hb and HHb of the left PFC during STG and DTG in all groups. Repeated measures ANOVA showed significant main effects for GAIT conditions ($F_{1, 55} = 23.3$, P

< .001) and GROUP ($F_{2, 53}$ = 25.6, P < .001) for O_2Hb, however for a signifi $F_{1, 53}$ = 3.87, P = .04; GROUP - $F_{2, 53}$ = 4.59, P = .04).

For measures of O_2Hb, post-hoc analyses showed a significant increase in O_2Hb during DTG in the Control (0.41 ± 0.12 Δμmol, P < .001) and SMC (0.91 ± 0.40 Δμmol, P < .001) groups compared to STG (Controls 0.25 ± 0.07 Δμmol; SMC 0.23 ± 0.05 Δμmol). Between-group comparisons further indicate that the SMC group (0.90 ± 0.40 Δμmol, P < .001) showed a greater increase in O_2Hb during the DTG task compared to Controls (0.41 ± 0.15 Δμmol). For the Dementia group, an increase in O_2Hb was observed in STG (0.51 ± 0.11 Δμmol, P < .001) compared to Control and SMC groups (Controls 0.25 ± 0.07 Δμmol; SMC 0.23 ± 0.05 Δμmol), however a significant reduction in O_2Hb was observed during DTG (0.23 ± 0.08 Δμmol, P < .001) compared to Control and SMC groups (Controls 0.41 ± 0.15 Δμmol; SMC 0.91 ± 0.40 Δμmol).

For measures of HHb, post-hoc analysis showed a significant decrease in HHb in the SMC group (-0.08 ± 0.04 Δμmol, P < .001) in the DTG condition compared to STG (-0.03 ± 0.02 Δμmol). Between-group comparisons further showed a significant reduction in HHb during DTG in the SMC group (-0.08 ± 0.04 Δμmol, P < .001) compared to Controls (-0.02 ± 0.01 Δμmol) and Dementia groups (-0.03 ± 0.01 Δμmol).

DISCUSSION

This study aimed to determine if (1) people with SMC and Dementia would have impaired STG and DTG performance as measured by changes in step length and velocity, and (2) cerebral haemodynamic responses associated with STG and DTG would differ between SMC and Dementia, compared to healthy age-matched controls. In partial support of our first hypothesis, that gait kinematics would be impaired in people with SMC and Dementia, our results showed impaired step length and velocity in people with Dementia for STG and DTG compared to healthy control and SMC groups. In terms of our second hypothesis, individuals with SMC and Dementia displayed a differential response in left PFC to DTG. Those with SMC demonstrated a significant increase in left PFC activation during DTG, whist people with dementia showed an increase and decrease in left PFC activation during STG and DTG respectively.

Gait performance during STG and DTG and total counting responses

Dual-tasking paradigms such as DTG have increasingly been used to investigate the cognitive-motor relationship in various neurodegenerative conditions such as Huntington's disease (Purcell *et al.*, 2020; Radovanovic *et al.*, 2020), Parkinson's disease (Fok *et al.*, 2010; Rochester *et al.*, 2014) and Dementia (Muir *et al.*, 2012; Montero-Odasso *et al.*, 2017). The premise of DTG is such that doing 2 tasks simultaneously (i.e. a cognitive and gait task) will result in greater utilization of cognitive resources than either tasks performed alone (Ebersbach *et al.*, 1995). In line with previous studies, we showed that the Dementia group had poorer gait performances in the STG and DTG conditions compared to healthy control and SMC groups (Muir *et al.*, 2012; Montero-Odasso *et al.*, 2017). It is now fairly well-established that changes in gait parameters such as stride length, frequency and variability are key motor changes that occur alongside changes with cognitive deficits. Additionally, longitudinal studies have suggested that these changes in gait parameters are predictive of cognitive declines that may have clinical utility in early diagnosis of dementia (Cedervall *et al.*, 2014; Montero-Odasso *et al.*, 2017). Although, participants with dementia performed worse compared to the other groups, it should be note that there were no differences in gait spatiotemporal parameters between the STG and DTG tasks in participants with dementia. While it is unclear as to why this may be the case, a likely reason was that the participants with dementia strategized performing only the gait task, rather than devoting equal attention to both cognitive and gait tasks simultaneously.

Our results further indicated that participants with SMC did not show any difference in gait performance of the STG and DTG tasks compared to the healthy controls. As SMC has been previously shown to predict conversion from normal cognitive functioning to dementia (St John & Montgomery, 2002; Wang *et al.*, 2004), the ability to use functional or behavioral tests that is strongly associated with SMC remains inconclusive. While there is some evidence to show associations between gait parameters (i.e. gait variability) and SMC (Beauchet *et al.*, 2017), other studies showed no associations between gait measures, but rather an association between the fear of falling and SMC (Sakurai *et al.*, 2017). It therefore remains to be seen if more robust associations can be made based on functional or behavioral tests in people with SMC. At least in our sample, spatiotemporal gait parameters and MoCA scores of the SMC group were comparable with healthy controls that precludes us from making any conclusions of gait deficiencies in people with SMC.

Left PFC activation during STG and DTG

While we did not find any differences in gait measures of STG and DTG between SMC and healthy controls, we did observe a significant increase in left PFC activation during the DTG but not the STG task between SMC and healthy controls. To the best of our knowledge, this is the first study to demonstrate such a novel finding. In people with Dementia, there is strong evidence to suggest that atrophy and reduction in left PFC function leads to memory decline and increased care-giver burden (Maillet & Rajah, 2013; Matsuoka *et al.*, 2018). Additionally gait studies further implicate the role of the left PFC in gait control and balance (Harada *et al.*, 2009; Meester *et al.*, 2014). In our age-matched healthy controls, an increase in left PFC activation during DTG compared to STG was expected and indicates an increased utilization of attentional resources to cope with the demands of performing two tasks simultaneously. A recent study by Wagshul *et al.* (2019) suggested that the increase in PFC activation is likely to stem from neural inefficiency (i.e. increase PFC activation with no concomitant increase in functional performance) that was associated with reduced grey matter volume of the PFC with ageing. This effect has been consistently shown in healthy older adults during DTG (Doi *et al.*, 2013; Ohsugi *et al.*, 2013; Mirelman *et al.*, 2017) or balance (Lin *et al.*, 2017; Teo *et al.*, 2018) tasks that require increased attentional demands. What was therefore surprising was that people with SMC displayed a higher level of left PFC activation, significantly greater than that of healthy controls, despite no differences in age or MoCA scores between both groups. We postulate that the increase in left PFC activity in people with SMC may indicate some form of neural compensation, as proposed by the compensation-related utilization of neural circuits hypothesis (CRUNCH) (Reuter-Lorenz & Cappell, 2008), where additional cognitive resources are needed to maintain DTG performance. If this is indeed the case, then perhaps this pattern of increased neural activity of the left PFC in people with SMC may represent very early central changes in cognitive processing that precedes any observable change in motor function or behavior.

In the Dementia group, we observed two key findings that lend further support to our observations in the SMC group. Firstly, during STG performance, left PFC activation was significantly greater, concomitant with poorer gait performance in the Dementia group compared to healthy control and SMC groups. Similarly, this is in line with the CRUNCH framework whereby compensational and/or additional resources may be required to perform basic tasks, when cognitive abilities are

compromised. Secondly, we further observed that under DTG conditions, left PFC activity in the Dementia group was reduced compared to healthy controls or SMC. This likely indicates a failure to utilize attentional resources in situations whereby cognitive demands of the task becomes increasingly overwhelming. A recent systematic review of fNIRS studies in people with mild cognitive impairment or dementia showed decreased resting state and task-related oxyhaemoglobin response (Yeung & Chan, 2020), supporting our hypothesis of reduced prefrontal cortex activation when executive function is challenged.

Limitations and future directions

To this end, there are several limitations that we need to acknowledge. Firstly, as we only used a single-channel fNIRS system, our study lacked the spatial resolution to measure from other key brain regions, such as the right PFC, to validate other known ageing models such as the HAROLD (hemispheric asymmetry reduction in older adults) model, which could help explain the pattern of left PFC activity that we observed. Secondly, our study may have lacked the statistical power to detect differences in STG and DTG gait performances between SMC and healthy control groups. Thirdly, our study did not include single task performance for the cognitive task nor did we record the number of correct responses during DTG, which may provide an estimate of cognitive interference. However, considering that the focus was in people with SMC, and that both STG and DTG performance and total counting responses were similar between Controls and SMC, we suggest that cognitive interference (if any) is likely to be similar. Thus, the increase in fNIRS responses during the DTG in SMC is therefore likely to represent higher dual-task demand associated with SMC. Fourthly, our Dementia group has significantly less participants, and were older in age compared to the SMC and healthy control groups. It is also likely that the secondary task alone, during DTG, may have been perceived as more difficult to perform in the dementia group, which may be additional to the need to concurrently perform a motor and cognitive task. Finally, the lack of differences in gait parameters between Controls and SMC could be due to the lack in sensitivity of stride length and velocity in detecting specific cognitive changes. Recent evidence from a longitudinal population-based study suggests that double support time was predictive of memory decline in a large sample of older adults compared to other gait parameters (Jayakody *et al.*, 2019). We acknowledge that these limitations may potentially bias our findings. Future studies should consider using a montage sufficient to measure from both left and right PFC

and with other brain regions (e.g. sensorimotor and premotor areas) to provide a more comprehensive understanding of brain activation during STG and DTG tasks.

Conclusion

In conclusion, our results indicate that while participants with SMC do not exhibit functional gait deficits in STG and DTG tasks, an increase in activity of the left PFC during DTG may be indicative of additional recruitment of attentional resources to maintain DTG performance that is comparable to healthy controls. In addition, a reduction in left PFC activation during DTG observed with the Dementia group may be indicative of failure to utilize attentional resources during tasks that have a higher cognitive load. Overall, our findings suggest that central changes may precede functional impairments in SMC, and that fNIRS during DTG may be able to detect early attentional changes, which may lead to detriments in gait seen in people with Dementia.

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Data Availability Statement

Data pertaining to this study may be made available by contacting the corresponding author.

Competing Interests

The authors declare no actual or potential conflict of interest.

Author Contribution

WPT, TR and HM conceptualized the research design and secured funding from AADRF to conduct this study. NN and LV were involved in the data collection and supported WPT, TR and HM in the data analyses. All co-authors were involved in the write-up of this manuscript.

Figure Captions

Fig 1. A diagram of the study setup for the STG and DTG. A trial consists of a participant beginning at the start line, walking towards an "X" marked on the floor (1st pass), walking around the "X", and walking back towards the start line (2nd pass). All participants performed 8 trials (4x STG; 4x DTG) that consisted of a total of 16 passes one way.

Fig 2. The processing pipeline used to process O_2Hb and HHb signals. Firstly, all raw signals were converted to changes in Optical Density (OD). A motion artefact detection algorithm was applied to identify potential motion artefacts, by identifying parts of the signal within each trial that exceeded the pre-specified thresholds. After identification of a motion artefact, a principal component analysis (PCA) filter was used to correct any potential motion artefacts identified. A bandpass filter was then applied to filter out any low and high frequency noise. Once filtered, the OD signal was converted into concentration changes using the MBLL and the concentration change was averaged over the 4 trials in each gait condition. *note that as each participant had a different completion time for each trial, the average time of the 4 trials for each gait condition was used to set the end time range.

Fig 3. Comparisons between (A) Step Length, (B) Step Velocity for STG and DTG between groups and (C) total number of counting responses over 4 DTG trials. Between-group comparisons as indicated by (*, $P < .001$) showed significantly lower step length and velocity in both STG and DTG in Dementia compared to both Controls and SMC groups. Within-group comparison further showed a significantly (#, $P < .05$) lower step length and velocity between STG and DTG only in the Controls and SMC groups, but not Dementia group. Total number of counting responses were significantly ($P<0.01$) lower in the Dementia group compared to Control or SMC groups.

Fig 4. Comparisons of (A) O_2Hb and (B) HHb response to STG and DTG between Controls, SMC and Dementia groups. The peak O_2Hb response for STG for each group occurred at 21.3 ± 6.5s (Control), 25.3 ± 8.2s (SMC) and 23.6 ± 6.7s (Dementia), while for DTG the peak O_2Hb response occurred at 17.6 ± 5.5s (Control), 18.9 ± 4.6s (SMC) and 20.4 ± 5.5s (Dementia). Within-group comparisons (STG vs DTG) indicate a significant increase ($P < .001$) in O_2Hb of the left PFC during DTG in both Control and SMC groups, but a significant decrease ($P <.001$) in O_2Hb in the Dementia group. Between-group comparisons (Control vs SMC vs Dementia) showed a significant increase ($P < .001$) in O_2Hb in the left PFC during STG in Dementia compared to Controls and SMC. However, during DTG, a significant increase in O_2Hb in the left PFC was observed in the SMC group, while a significant decrease ($P < .001$) in O_2Hb in the Dementia group was observed. Only the DTG condition performed by the SMC group elicited a significant reduction ($P < .001$) in HHb (as indicated by a greater negative value) when compared between- and within-groups. (#) indicates within-group (STG vs DTG) significance of $P < .001$, while (*) indicates between-group significance of $P < .001$ with other two groups.

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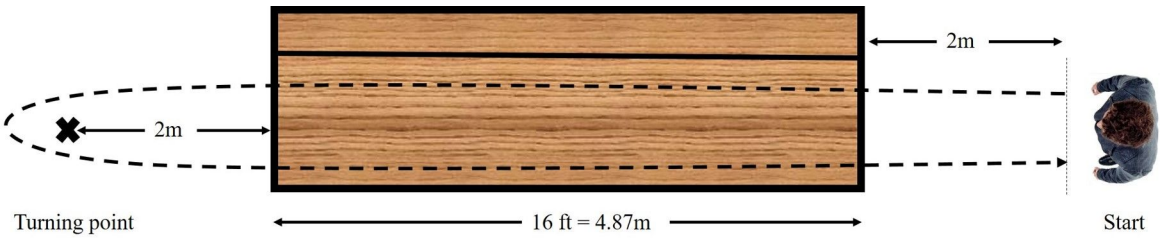
Table 1. Demographic data for each group presented as Mean ± SD

	Controls	SMC	Dementia	F, P values
Sample (n)	26	23	9	-
Age (yrs)	71.1 ± 4.2*	73.5 ± 6.7*	86.1 ± 7.3	$F_{2,56} = 20.82$, $P < .001$
Gender (M/F)	14M 12F	10M 13F	5M 4F	-
Height (cm)	164.7 ± 8.3	164.4 ± 6.5	163.5 ± 12.0	$F_{2,56} = .84$, $P = .483$
Weight (kg)	77.3 ± 19.0	74.5 ± 13.8	77.3 ± 12.3	$F_{2,56} = .69$, $P = .515$
Education level (yrs)	14.5 ± 4.3	14.6 ± 3.5	12.5 ± 3.0	$F_{2,56} = .98$, $P = .383$
MoCA score (/30)	28.1 ± 1.6*	27.8 ± 1.9*	20.3 ± 3.5	$F_{2,56} = 38.17$, $P < .001$

(*) Indicates significance of P<.001 from Dementia group



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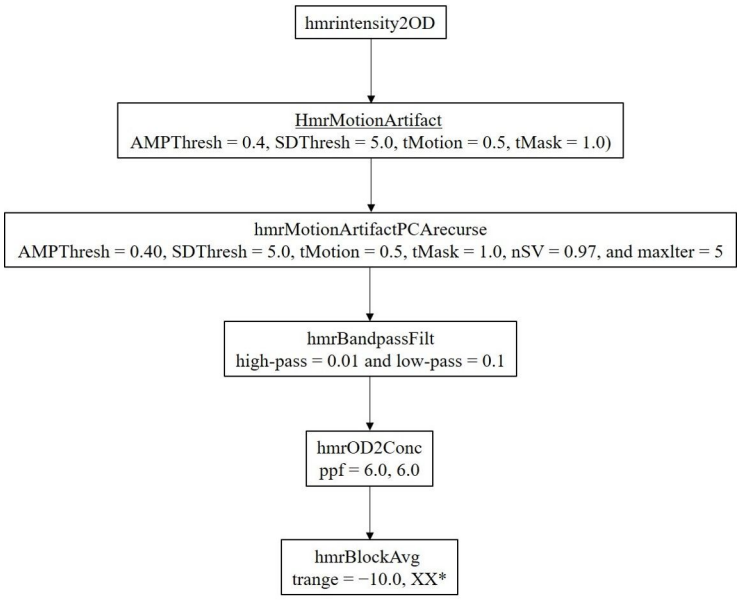

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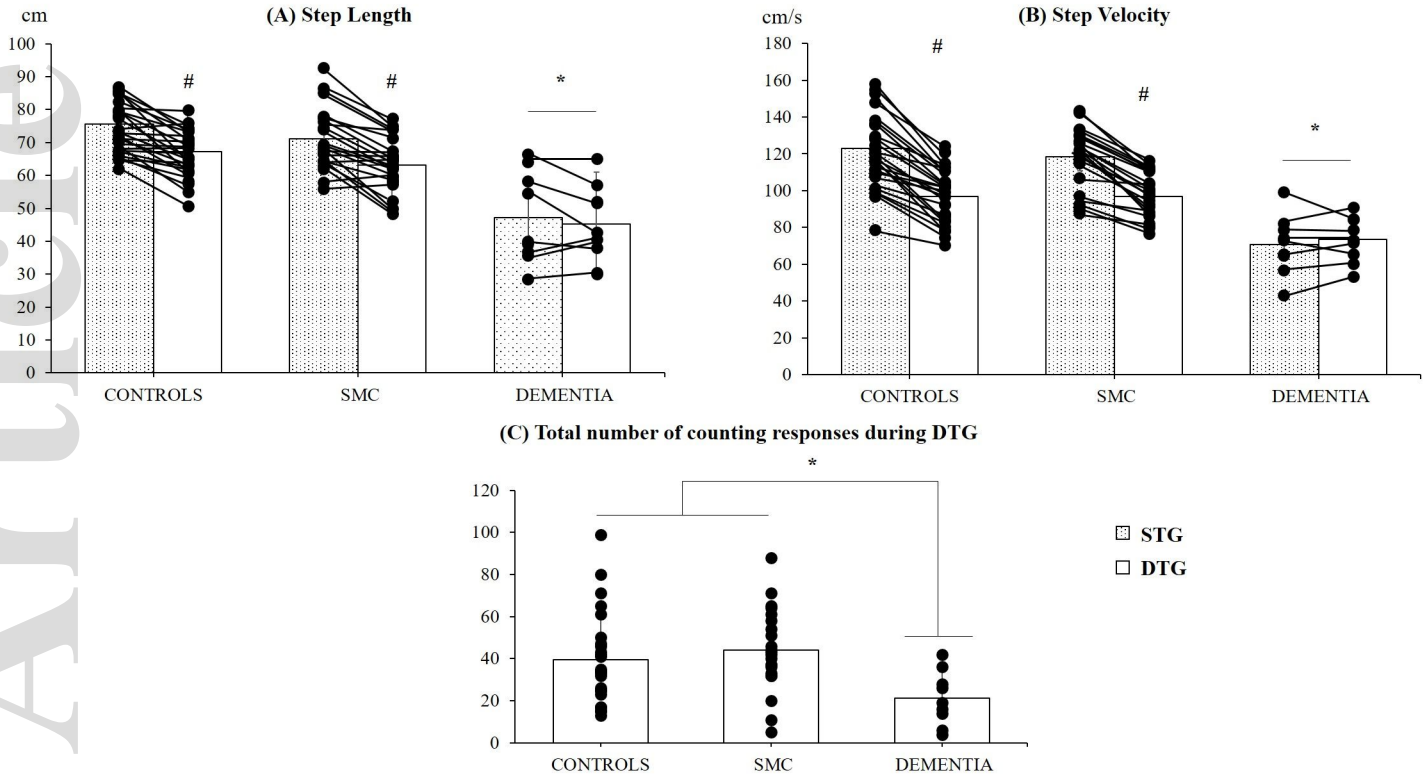

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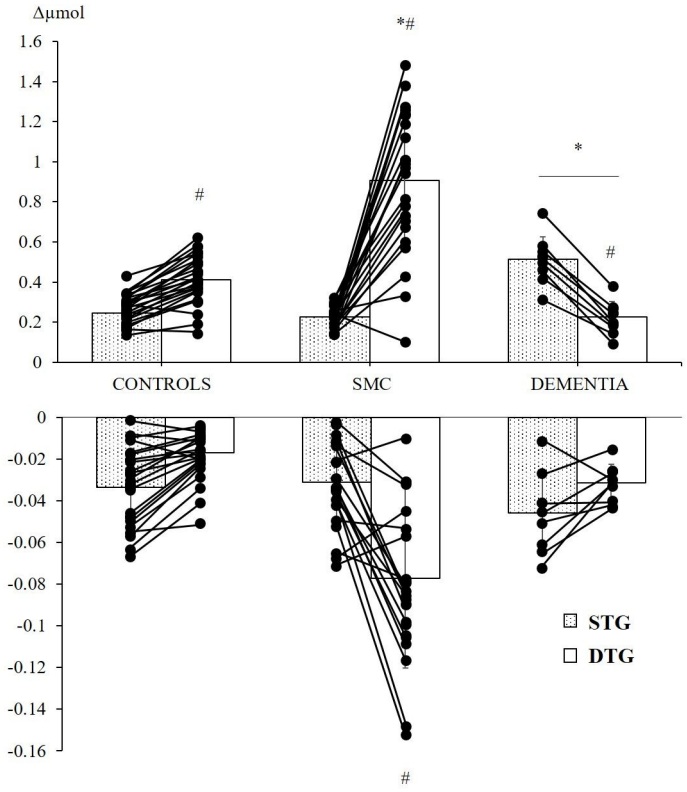

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