Northumbria
University
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Abstract

Background and Purpose: Gait and turning impairments are common in Parkinson's disease (PD). Tactile cues delivered in open or closed-loop modalities may improve gait and turning in PD, but the underlying mechanisms are unclear. Evidence suggests attention stemming from the pre-frontal cortex (PFC) may play a role in cue response, but contributions to specific cue modalities are unclear. Examining how open and closed-loop cueing influences PFC activity during walking and turning in PD may allow greater understanding of the mechanisms involved in cue response, which could help develop effective therapeutics.

This pilot study examined PFC activity during walking and turning in response to open and closed-loop cueing in PD, and explored the relationships between PFC activity and behavioral measures.

Methods: A mobile functional near-infrared spectroscopy device measured PFC activity during walking and turning in 25 people with PD (n=13 freezers, n=12 non-freezers). Participants performed 180° and 360° turns while walking, and a two minute walk under single and dual-task (AX-CPT) with and without an open (metronome-like vibration) or closed-loop (bio-feedback vibration) tactile cue.

Results: PFC activity did not change when walking or turning in PD, which did not depend upon freezing status or task-demands. Dual-task cost of gait significantly improved, whereas turning slowed with both open and closed-loop cueing.

Discussion and Conclusions: Our preliminary results indicate that both open and closed-loop cueing can improve gait without additional burden to the PFC beyond usual walking. However, turning while walking slowed with cueing with no PFC activity change. Further investigations are necessary to establish these findings in a larger cohort (see Video, Supplemental Digital Content 1).

KEYWORDS: Parkinson's disease, freezing, cueing, rehabilitation, gait, turning

Introduction

Gait and turning impairments are common in people with Parkinson's disease (PD),[1,2] and are central to reduced mobility, independence, quality of life and increased falls risk. Gait impairments range from reduced speed and shortened step length, to more complex phenomenon such as Freezing of gait (FoG).[3] FoG develops in over half of people with PD and is a particularly debilitating issue that involves a transient period of being unable to continue forward progression of walking.[4] Similarly, laboratory studies show that people with PD turn with reduced speed, increased duration, increased number of steps, a narrower base of support and tend to turn "en-bloc" due to a lack of appropriate segmental co-ordination. Turning has also been shown to be one of the most provocative tasks for FoG, leading to instability.[5,6] To date, pharmacological treatment of mobility deficits has been unsatisfactory due to its refractory nature to dopaminergic treatments.[7] Indeed, our previous work has shown that mobility remains deficient in people with PD compared to controls regardless of medication use, however levodopa can improve pace-related gait measures, but other measures remain unresponsive.[7] Therefore, non-pharmacological therapeutic interventions, such as cues,[8-11] are used in clinical practice to alleviate PD-related deficits.

Sensory cueing modalities, such as auditory,[12] visual[13] or tactile[11] stimulus, have primarily been used to improve gait (i.e. increased step length, speed, reduced variability etc.) and reduce FoG episodes in people with PD.[14] Fewer studies have examined the influence of cues on turning in people with PD, but results have shown that turn speed increases,[15] festination improves[16] and FOG is reduced with cues.[17] Auditory and visual cues have received the most attention.[18-20] However, tactile cueing may be particularly useful for those who report FoG,[21,22] as there is growing evidence suggesting sensory integration and proprioceptive deficits accompany FoG.[23,24] In addition, for future use at home, tactile cues may be more unobtrusive compared to auditory or visual cue. Auditory, visual or tactile cues are predominantly used in clinical practice in an open-

loop (continuous rhythmic stimuli) rather than a closed-loop (intermittent stimuli based on individual movement) modality, likely due to limited availability (i.e. the majority of closed-loop systems are not marketed yet) and ease of application. Only recently have devices been engineered using wearable technologies to monitor gait and provide real-time biofeedback to improve performance.[25,26] Indeed, our recent work has shown that closed-loop tactile cueing can reduce FOG episodes in people with PD,[27] as well as improve turning performance to the same extent as open-loop cueing.[28] Although we showed similar behavioral results with open-loop and closed-loop cueing for turning,[28] the neural mechanisms to achieve a similar behavioral response may be very different. In addition, a greater understanding of cortical correlates of cueing may help develop effective and individualized strategies.

Current theories regarding open-loop cue response focus on: 1) attentional mechanisms that by-pass defective basal ganglia (BG) circuitry,[8,29-31] or 2) replacement of rhythmic BG output via external stimuli.[32-36] Similarly, closed-loop cues may replace defective internal and external feedback mechanisms by reinforcing or replacing weak or absent sensory signals required for adequate motor task performance.[20,37] The integration of closed-loop cues may require attentional resources to process multiple sources of simultaneous information (i.e. proprioception from feet but also simultaneously from cue) to ensure neural processes are not overburdened.[38] In general, gait leads to overactive conscious attentional activation in people with PD[39] stemming from the pre-frontal cortex (PFC)[40] to compensate for BG impairment that affects movement automaticity. The first open-loop cue response theory suggests that further attentional PFC activation during gait would be required to circumvent PD BG impairment. In line with this, tactile stimulus have been found to activate the PFC (fronto-striatal and fronto-parietal attentional pathways) in animal and human models,[41,42] which may be impacted by performing a secondary task (dual-task).[43] Alternatively, the second theory of open-loop cue response suggests that attentional activity at the PFC for gait control in people with PD would reduce by replacing faulty inconsistent BG output

with consistent external input. Indeed, rhythmic stimulation may facilitate BG and pre-motor cortex interactions,[44,45] as well as cerebello-thalamo-cortical projections.[46] Indeed, tactile cues may override the dominant visual proprioception[47] that occurs in people with PD[48] and allow faster subconscious processing of sensory information,[49,50] which would reduce PFC burden. To date however, these theories remain relatively unexplored, likely due to an inability to image the brain during walking.

Recently, technological progression has allowed monitoring of cortical activity during real-time walking and turning in people with PD using functional near infrared spectroscopy (fNIRS) or electroencephalogy (EEG).[51] Changes in cortical activity with motor performance indicate that different mechanisms may underpin open and closed-loop cueing. For instance, closed-loop biofeedback can alter attentional processing in healthy adults, specifically enhancing beta (16-22Hz) and inhibiting high theta (4-8Hz) frequencies in EEG recordings at CPz-PCz channels,[52,53] which may support the attentional theory of cueing. Whereas, imaging studies have demonstrated that open-loop rhythmic cueing relates to premotor cortex and supplementary motor area activation,[44,45,54] which may support the BG output replacement theory of cueing. However, specific cortical contributions to open and closed-loop cueing are still unknown and warrant further investigation to inform the most effective strategy to alleviate gait deficit in people with PD.

This pilot study aimed to investigate changes in PFC activity in response to open (continuous metronome-like rhythmic stimuli) and closed-loop (intermittent stimuli based on individuals walking pattern) tactile cueing during walking and turning in people with PD. Our hypothesis was that cueing would alter PFC activation during walking and turning in people with PD, especially for those who report FoG. Specifically, we predicted that closed-loop cueing would increase PFC activity due to the attentional burden of integrating external sensory feedback into motor control. Whereas open-loop activity would reduce PFC activation due to replacing impaired BG output in people with PD.

Methods

Participants

Twenty-eight people with Parkinson's disease were consented and completed testing for this study. A total of 25 subjects (n=13 FOG+ and n=12 FOG-) were used within our data analysis. Inclusion criteria were; aged 55-90 years, able to stand or walk for two minutes without assistance, diagnosis of PD as defined by the UK Brain Bank criteria, Hoehn and Yahr score II-IV (OFF medication), taking anti-Parkinsonian medication. Exclusion criteria were; musculoskeletal, vestibular, visual or other medical condition that affected gait or balance. Self-reported FoG was based on the new Freezing of Gait Questionnaire (nFOGQ).[55] Participants were asked if they have freezing defined as: "Freezing is the feeling that your feet are transiently glued to the floor while trying to initiate walking, making a turn, or when walking through narrow spaces, or in crowded places; Sometimes it can be accompanied with trembling of the legs and small, shuffling steps." Subjects were categorized as "freezers" (FOG+) if they have experienced such a feeling or episode over the past month[55,56], or "non-freezers" (FOG-) if they had not. This study was by an independent research ethics board at Oregon Health and Science University.

Experimental Design

Protocol and Tasks

Participants underwent two sections of testing, 1) demographic, clinical, cognitive assessments, and 2) examination of PFC activity during walking and turning (OFF medication state; ~12hours withdrawal). Despite the majority of cueing studies examining participants while ON medication, here, we assessed individuals while OFF medication in an attempt to see a larger magnitude of change with cueing, which can be reduced when ON medication. In addition, testing in the OFF state may allow results to be generalized to people with more advanced PD. However, since

medication status could influence cueing response, future studies will test response to tactile cue in people with PD while ON their levodopa medication.

Participant age, sex, height, weight, education (years) and handedness were recorded. Standardized tests for depression (Geriatric Depression Scale),[57] fatigue (Multidimensional Fatigue Inventory)[58] and orthostatic hypotension (Orthostatic hypotension questionnaire)[59] were collected, as these features are known to influence PFC activity. Global cognition was measured with the Montreal Cognitive Assessment (MoCA)[60]. Executive function was examined using clock drawing (Royall's CLOX 1).[61] Attention was measured with the trail making test (TMT; parts A and B). Visuo-spatial ability was measured with clock copying (Royall's CLOX2).[61] Disease severity was measured using the unified Parkinson's disease rating scale (MDS-UPDRS-III, freezing-status was measured using the nFOGQ and levodopa equivalent daily dosage (LEDD) was calculated.

Gait, turning and PFC activity were assessed during four walking tasks: 1) an unanticipated 180° turn while walking over 9m, 2) an unanticipated 360° turn while walking over 9m, 3) usual walking back and forth over 9m for two minutes, and 4) walking back and forth over 9m while performing the a secondary cognitive task (dual-task) for two minutes. Participants performed randomized left and right 180° and 360° turns. Dual-tasking involved the Continuous Performance Task (AX-CPT); specifically, participants wore noise-cancelling headphones that played random letters and had to press a button (held in their least PD affected hand) every time the letter 'I' followed a letter 'A'. All tasks started and ended with 20seconds of quiet standing, with the instruction to not talk or move during this period. Researchers recorded observed FOG during turning trials.

Equipment

A mobile fNIRS system (Portamon, 50Hz, Artinis Netherlands), placed in the standard 10-20 EEG position, measured PFC activity. Distance from transmitter to detector was 3.5cm[62] and data was

collected and processed in line with previous studies.[51,63] Additionally, two short-separation reference channels (1.5cm; left and right PFC) were used to remove peripheral interference (i.e. blood flow in extra-cerebral layers) in other channels.

To measure gait and turning, 8 inertial measurement units (IMU; 128Hz, Opals, APDM, Inc., USA) were placed on the feet, shins, lumbar (L5), sternum and wrists.[64] The two systems were synchronized though a PortaSync (Artinis) device.

A tactile cueing device (VibroGait unit, Figure 2), described in detail elsewhere,[27] connected to the shank IMUs and was positioned on each foot sensor, with the vibrating tactor on each wrist. Briefly, the closed-loop setting consisted of a controller unit (Arduino microcontroller) that sensed when the foot was on the ground (stance phase) and activated the vibration, it then deactivated vibration when the foot was off the ground (swing phase). Alternatively, the open-loop setting provided a vibration every 750ms for 250ms. The tactors were C-2 tactors (Engineering Acustic, Inc) with a primary resonance of 200-300Hz, which provided vibration similar to that of a smartphone vibration. The method of gait intervention of this device has been detailed elsewhere.[27] Essentially the closed-loop setting of this device has the potential to detect online gait abnormalities and provide a tactile cue (i.e. vibration when the foot is on the ground, Figure 2),[27] whereas the open-loop setting provides rhythmic proprioceptive cues that have been shown to improve gait and step-synchronization in people with PD.[65,66]

<< Insert Figures 1 and 2 here >>

Data Analysis

A 3-dimensional digitizer (PATRIOT, Polhemus, VT, USA) provided locations for PFC regions relative to fNIRS channel scalp position. Digitized data was entered into NIRS-statistical package metric mapping (NIRS-SPM, http://www.nitrc.org/projects/nirs_spm),[67] which was implemented within MATLAB 2017a (Mathworks, MA, USA). NIRS-SPM allowed registration of fNIRS channel

data onto the Montreal Neurological Institute (MNI) standard brain space,[68] described in detail elsewhere.[69] HbO_2 changes were recorded bilaterally (left and right) within the PFC. Brodmann areas (BA) that corresponded to the PFC consisted of BA9 and BA10 for all participants.

The fNIRS data were median averaged and processed within custom-made MATLAB algorithms through the following steps:

1. **Data filtering**: after zeroing data to the initial time-point, a low-pass filter with a cut-off frequency of 0.14Hz, based on canonical hemodynamic response function, removed high-frequency noise.[70]
2. **Baseline correction:** removing the median of the initial 20seconds of baseline standing fNIRS signal from the entire trial (i.e. subtracted baseline period from the signal).
3. **Reference channel correction:** corrected signal distortions due to artefact caused by breathing, cardiac cycle, vasomotor or other error related to movement.[71,72] First, a scaling factor was determined by detecting the peaks (positive and negative) of the heart rate within the long and short-separation channel signals, then dividing them to produce the scaling factor. Detected noise was then removed from the fNIRS signal. The following formula describe the reference channel correction:

$$Scaling\ factor = \frac{Peak\ to\ peak\ difference\ in\ heart\ rate\ in\ long\ seperation\ channel}{Peak\ to\ peak\ difference\ in\ heart\ rate\ in\ short\ separation\ channel}$$

$$fNIRS\ signal = long\ separation\ channel\ signal - (short\ separation\ channel\ signal \times Scaling\ factor)$$

4. **Visual signal inspection:** all of the fNIRS signals were visually examined to ensure divergence between the HbO2 and HHb traces. This step excluded trials that had poor signal collection (n=3 participants were excluded), as a lack of divergence in HbO2 and HHb indicates noise interference.

5. **Averaging across fNIRS channels:** in line with previous research,[51] bilateral signals from fNIRS optodes over the PFC were median averaged for further analysis.

The primary outcome measure was relative change in HbO_2 concentration (a proxy for cortical activation). Relative changes from baseline standing in HbO_2 concentrations were reported to account for individual physiological variations;[63] see below calculations. HbO_2 rather than HHb was used due to its sensitivity to walking and cognitive tasks.[73,74] IMU data determined gait characteristics (speed, stride length, foot strike angle, and stride time variability) from foot sensors and turn characteristics (duration and peak velocity) with occurrence (onset and end of each turn) and timing periods (6seconds Prior-to vs During Turn) were calculated using angular velocity of the L5 sensor.[64] Dual-task cost was calculated as; 100*(single-task - dual-task score)/single-task.

Walking and turning periods;

1. Prior-to Turn = 6seconds before a turn – initial standing period (20seconds)
2. During Turn = during turn – initial standing period (20seconds)
3. Early Walk = first 40seconds of walking – initial standing period (20seconds)
4. Late Walk = second 40seconds of walking – initial standing period (20seconds)

Statistical Analysis

Data were analyzed using SPSS (v22, IBM, Chicago, Il., USA). Data normality was assessed using Kolmogorov-Smirnov tests and parametric or non-parametric analysis was conducted based on distributions. Descriptive characteristics were assessed with independent t-tests comparing groups (FOG+, FOG-), unless otherwise stated. PFC activity was not significantly different between left and right turns (e.g. baseline during 180° turn p=0.183 and during 360° turn p=0.544), therefore data were collapsed into single 180° and 360° turn outcomes. Separate linear mixed effects models (LMEM) examined whether PFC activity changed during turning and walking with closed-loop or open-loop cueing. For turning, main effects of Group (FOG+, FOG-), Turn

(180, 360), Period (Prior-to, During) and Condition (Baseline, Open-loop, Closed-loop) were reported. For gait, main effects of Group (FOG+, FOG-), Task (Single, Dual), Period (Early, Late) and Condition (Baseline, Open-loop, Closed-loop) were reported. Each LMEM included a random intercept for each subject to account for repeated measurements. Wilcoxon signed rank tests examined trends in PFC activation data. The same LMEMs examined change in gait and turning metrics with cueing. Spearman's rank correlations explored relationships between behavioral measures of gait and turning with PFC activity. As this was a pilot study we did not correct for multiple comparisons and $p<0.05$ was considered significant.

Results

Participants

Three participants had poor data upon visual inspection and they were removed before further statistical testing, which left twenty-five participants for full data analysis. Two participants were also unable to complete all of the testing conditions (baseline, open or closed-loop), but their collected data was included for analysis. Table 1 displays the demographic, cognitive, sensory and clinical data from the participants. FOG+ and FOG- participants were well matched for most characteristics, with the only significant difference seen in executive function (TMT B score) and as expected on nFOGQ that was used to classify the groups. The majority of participants were right handed and there was a relatively even split of participants who had symptoms onset on left or right side. Dual-task performance was also similar between the FOG groups across the cued conditions (Table 1).

<< Insert Table 1 here >>

PFC activity did not change with open or closed-loop tactile cues compared to baseline during walking and turning

After controlling for covariates (turn duration and gait speed) PFC activation was similar in FOG+ and FOG- participants during walking (p=0.836) and turning (p=0.652) (Table 2). Although, Figure 3 shows that under dual-task walking conditions FOG+ had non-significantly higher PFC activation than FOG- during Baseline (p=0.443) and open-loop cueing (p=0.928), but there was a reduction in PFC activation with closed-loop cueing in FOG- (p=0.037, Figure 3). The only significant differences in PFC activity were found between periods of a walk or turn (early walking vs late walking and before turn vs during turn), but not with different turns (180 vs 360, p=0.410) or task demands (single or dual, p=0.975). Specifically, PFC activity was higher during turning compared to 6seconds prior-to turning in people with PD (p<0.001). Similarly, PFC activity was higher within the first 40seconds (early period) of walking and significantly reduced in the second 40seconds (late period) of walking in people with PD (p<0.001).

Following control for covariates, there were no differences in PFC activity from baseline with open or closed-loop cueing (Table 2). Despite this, Figure 3 shows that there were non-significant trends in group differences in PFC activity. For example, FOG+ non-significantly reduced PFC activity from baseline during a 180° turn with closed-loop cueing (p=0.450), whereas the opposite trend occurred for FOG- participants (p=0.010). Similarly, there was a trend toward a reduction from baseline in PFC activity during the early-phase of walking under dual-task with closed-loop cueing for FOG- (p=0.084), whereas the opposite trend occurred for FOG+ (p=0.110, Figure 3).

<< Insert Table 2 and Figure 3 here >>

Behavioral measures of walking and turning improved with cueing

Dual-task gait was significantly slower, with shorter strides and reduced foot strike angle compared to single-task gait (all p<0.001, Table 3), regardless of cueing condition and freezing

status. Similarly, 360° turns were significantly slower and longer than 180° turns in each condition (p<0.001). There were significant improvements in dual-task cost of stride length and foot strike angle with both open (p=0.003 and p=0.014, respectively) and closed-loop cueing (p<0.001 and p=0.031, respectively). There were also several trends for improvement with the cueing conditions in other gait characteristics (Table 3).

Turn duration was significantly longer with open-loop cueing in people with PD (p=0.019). Participants tended to reduce velocity and increase durations of turns with both cueing conditions, but particularly with open-loop cueing (Table 3).

The number of FOG episodes with open or closed-loop cueing was similar to baseline (Table 4). There were no consistent relationships between behavioral measures and PFC activation during any of the conditions (Supplementary Table 1). However, better executive function (CLOX 1 and TMT A) and sensory function (touch processing) consistently related to greater PFC activation during baseline turning and walking (Supplementary Table 2).

<< Insert Table 3 and 4 here >>

Discussion

This study investigated PFC activation response to open and closed-loop tactile cueing during walking and turning in people with PD. In contrast to our hypothesis, we found that PFC activity while walking or turning did not significantly change from baseline with the application of open or closed-loop tactile cueing. This was consistent across FOG+ and FOG- participants. Despite this, there were significant improvements in gait with cueing, with significant reduction in dual-task cost. Turning characteristics (turning while walking) also significantly changed with open-loop cueing, although participants tended to slow down during turning with both cue modalities. These novel preliminary findings suggest that tactile cueing can modify walking behavior in people with PD, which does not occur at the cost of over-burdening PFC activity.

PFC activation when walking and turning in Parkinson's

Without cueing, PFC activity was greater in the early period (first 40seconds) compared to the late period (last 40seconds) of walking in people with PD, which is similar to previous older adult[75] and PD studies.[40] PFC activity also increased beyond usual walking during a turn in people with PD (irrespective of freezing status), which has only previously been reported in FOG+ subjects.[40,62] Therefore, beginning to walk and throughout turning executive-attentional resources may be required to compensate for underlying motor deficits, with return to more automatic walking after the initial period or when task demands reduce. However, due to the robust methodology we employed and novelty of our cueing device direct result comparisons to previous studies are limited. For example, unlike the current study previous studies[62] have only used subjective manual video observation rather than objective IMUs to determine turning periods. Similarly, other fNIRS studies[40,62,73] have not used short-separation channels to remove peripheral noise, which may affect data quality.

PFC activation during walking and turning did not change with tactile cueing

Despite being able to modify behavioral outcomes, open and closed-loop tactile cueing did not change PFC activation during walking or turning in people with PD. This was consistent between FOG+ and FOG- groups and under different attentional demands (dual-task). Our findings are similar to previous research in people with PD that has shown no significant differences in EEG measured cortical activity with or without visual cues for motor (postural response) performance.[76] However, results also contrast with previous auditory cueing studies during treadmill walking in healthy adults, which have shown increased PFC and motor-region activation with cues.[73,77]

Lack of change in PFC activity with tactile cueing may relate to inflexibility or over-burdening (i.e. ceiling effect) of executive-attentional resources for gait or turning in people with PD, which may not allow further increased activity. For example, during gait the processing of environmentally

salient stimuli rather than motor task performance may pre-occupy executive-attentional resources in people with PD,[78] whereas cueing may change resource allocation. Measuring only PFC activation provides limited understanding of specific resource application. Therefore, rather than increased use of PFC executive-attentional resources, tactile cues may prompt more appropriate focus of resources for application to particular task or movement elements (e.g. selection, sequencing, timing or amplitude of movements) that may involve PFC projections to alternative brain regions.

Different brain regions may play a larger role in tactile cue response than the PFC. Previous research suggests that with age and pathology additional cortical regions are recruited to manage the increased demands of a given task,[79] such as walking. Similarly, selective activation of specific cortical regions (i.e. PFC) is reduced with age[79] and further with pathology.[80] Consequently, our PD participants likely recruited diffuse brain regions, such as pre-motor, supplementary motor or parietal regions to compensate for additional demands of cueing. Another factor is that PFC activation represents conscious (voluntary, top-down) attention, however improved motor performance in people with PD may relate to automatic (bottom-up) attentional integration of heightened sensory information that does not heavily involve the PFC.[81]

Clinical Implications

Gait metrics similarly improved with both cues, but PFC activation during walking did not change in people with PD in response to open or closed-loop tactile cueing. This was consistent under attentional distraction (dual-task) and between freezers and non-freezers. In line with previous research,[82,83] these preliminary findings suggest that both open and closed-loop tactile cues can improve gait in people with PD, which occurs without further burdening executive-attentional resources beyond usual walking. However, findings are only applicable to the immediate use of cueing, while further studies would need to examine the effects of longer bouts of training with

cues to investigate whether cueing response differs over-time, and whether they lead to different learning strategies in people with PD.

Turning was slower particularly with open-loop cueing, while PFC activity was similar in all conditions. Turning performance in people with PD is generally impaired compared to controls, typically having more steps, being slower and taking longer. Previous open-loop auditory cueing studies have reported reduced turn duration, increased turn velocity and reduced FOG episodes in people with PD.[82] However, other auditory cueing studies have shown increased number of steps required to turn and no change in FOG episodes.[17] The tactile cues used in this study did not influence FOG episodes, and made turning longer and slower than without cues. However, we cannot be certain that the cues made turning "worse" per se, as fast turning in people with PD has been found to be less stable compared to slower turn[84]. Therefore, slower turning possibly indicates a more conservative strategy with cueing compared to without. Further analysis on turning stability may be able to explain whether a slower turn is safer with cueing.

Study Limitations

There were several limitations of this study. First, testing was only conducted OFF dopaminergic medication in a relatively small cohort. Post-hoc power analysis demonstrated that this pilot study had sufficient power to detect PFC activation differences between conditions during walking (Effect Size f^2=0.52, Power [1-β]=0.92), but may have been slightly under-powered for turning (Effect Size f^2=0.28, Power [1-β]=0.71), therefore future studies in a larger cohort are required to examine this feature. Second, we were unable to adapt the open-loop cue to individual walking patterns (e.g. 20% above usual cadence). Third, although our hypothesis focused on PFC activation with cueing, we may have found activation in other cortical regions with cueing by using a full-cap fNIRS system. Lastly, turns were repeated once, whereas continuous repetitions of 360° turns may elicit more impairments in people with PD.

Conclusions

Our preliminary observations suggest that providing heightened somatosensory information with open or closed-loop tactile cueing may improve gait characteristics in people with PD, which does not burden PFC activity beyond usual walking. However, results on turning are less clear, in fact turning was longer with cueing compared to baseline. Future studies, with larger sample size, are required to assess contributions of various brain regions during open and closed-loop cueing to provide a robust understanding of the underlying mechanisms involved.

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Figure 1 – Representative raw HbO_2 data during the two-minute walking task [grey dashed line is zero point of HbO_2 concentration]

Figure 2 – (A) Vibro-Gait cueing device and placement, and (B) depiction of closed-loop cue method

Figure 3 – Changes in HbO_2 concentration in PD

Table 1 - Demographic, cognitive, sensory and clinical outcomes

	PD (n=25) Mean (SD)	FOG+ (n=13) Mean (SD)	FOG- (n=12) Mean (SD)	*p*
Demographic				
Age	69.20 (3.99)	69.69 (4.21)	68.67 (3.85)	0.532
Gender	M (17) / F (8)	M (8) / F (5)	M (9) / F (3)	0.471
Height	1.62 (0.13)	1.61 (0.12)	1.63 (0.14)	0.210†
Weight	169.78 (31.84)	163.74 (23.23)	176.33 (39.15)	0.334
Education (yrs)	17.88 (2.88)	18.39 (3.07)	17.33 (2.67)	0.373
MFI	51.16 (11.99)	53.77 (13.25)	48.33 (10.27)	0.266
OHQ	10.68 (13.18)	11.46 (14.16)	9.83 (12.59)	0.765
GDS	5.76 (3.78)	6.46 (3.99)	5.00 (3.54)	0.345
Handedness	L (2) / R (23)	L (1) / R (12)	L (1) / R (11)	0.953
Cognitive				
MoCA	27.12 (3.83)	26.08 (3.62)	28.25 (3.62)	0.161
FAB	14.48 (3.04)	14.08 (3.23)	14.92 (2.91)	0.502
TMT A	51.48 (57.10)	65.25 (21.16)	36.56 (17.14)	0.056†
TMT B	98.35 (51.74)	123.55 (57.31)	71.04 (26.31)	**0.008***
TMT B-A	46.87 (35.57)	58.30 (42.66)	34.48 (21.29)	0.095
CLOX 1	11.76 (2.32)	12.08 (1.38)	11.42 (3.06)	0.488
CLOX 2	13.44 (1.66)	12.92 (2.02)	14.00 (0.95)	0.106
Sensory (AASP)				
Taste/Smell	21.38 (3.56)	21.75 (2.80)	21.00 (4.29)	0.617
Movement Processing	22.63 (3.92)	21.83 (4.71)	23.42 (2.94)	0.334
Visual Processing	23.00 (4.60)	23.67 (6.23)	22.33 (2.10)	0.490
Touch Processing	29.21 (5.12)	28.83 (6.48)	29.58 (3.55)	0.728
Activity Level	27.00 (3.89)	27.33 (4.46)	26.67 (3.39)	0.684
Auditory Processing	25.92 (5.99)	26.42 (6.22)	25.42 (5.98)	0.692
Clinical				
Disease duration (yrs)	10.00 (6.27)	12.08 (6.18)	7.75 (5.77)	0.084
UPDRS III	36.40 (11.67)	40.00 (14.01)	32.50 (7.15)	0.110
H&Y	I (0) / II (22) / III (3)	I (0) / II (10) / III (3)	I (0) / II (12) / III (0)	0.076
LEDD	883.89 (501.40)	924.92 (609.37)	839.44 (373.20)	0.679
FOGQ	7.12 (8.51)	13.69 (6.89)	0.00 (0.00)	**<0.001***
Side initial symptoms	L (11) / R (12) / Both (2)	L (7) / R (4) / Both (2)	L (4) / R (8) / Both (0)	0.128
Dual-task Performance				
Baseline				
Accuracy (%)	65 (37)	59 (41)	70 (35)	0.505
Reaction Time (s)	0.53 (0.32)	0.43 (0.14)	0.59 (0.40)	0.298
Closed-loop				
Accuracy (%)	70 (36)	69 (36)	71 (37)	0.876
Reaction Time (s)	0.41 (0.16)	0.47 (0.16)	0.36 (0.16)	0.127
Open-loop				
Accuracy (%)	74 (36)	69 (41)	78 (34)	0.543
Reaction Time (s)	0.36 (0.13)	0.32 (0.16)	0.38 (0.11)	0.443

*[*significance level p<0.05, † = Mann-Whitney U Test. MFI = modified fatigue inventory, OHQ = orthostatic hypotension questionnaire, GDS = geriatric depression scale, MoCA = Montreal cognitive assessment]*

Table 2 – Fixed Effects of Relative Change in HbO2 during Turning while walking and Two minute walk tasks

	Estimate	SE	t	DF	*p*
180° and 360° turns while walking[#]					
Group (FOG+ vs FOG-)	-0.01	0.04	-0.21	277	.836
Turn (180 vs 360)	0.02	0.03	0.83	277	.410
Period (Prior-to vs During)	0.08	0.02	4.02	277	**<.001***
Closed-loop cue	0.02	0.03	0.86	277	.392
Open-loop cue	-0.00	0.03	-0.08	277	.934
Two minute walking[†]					
Group (FOG+ vs FOG-)	-0.06	0.13	-0.45	273	.652
Task (Single vs Dual)	0.00	0.05	0.03	273	.975
Period (Early vs Late)	-0.22	0.05	-4.70	273	**<.001***
Closed-loop cue	-0.01	0.06	-0.25	273	.805
Open-loop cue	-0.07	0.06	-1.14	273	.258

[*significance level p<0.05, [#]Adjusted for turn duration, [†]Adjusted for gait speed]

Table 3 - Gait characteristic, Dual-task cost (%) and turning characteristic change with cueing

WALKING	**Baseline**				**Closed-loop**				**Open-loop**				**Group**	**Task**	**Closed-loop**	**Open-loop**
	Single		**Dual**		**Single**		**Dual**		**Single**		**Dual**					
	FOG+	FOG-	FOG+	FOG-	FOG+	FOG-	FOG+	FOG-	FOG+	FOG-	FOG+	FOG-	*p*	*p*	*p*	*p*
Gait Speed (m/s)	0.90 (0.20)	0.94 (0.15)	0.85 (0.22)	0.88 (0.15)	0.89 (0.21)	0.94 (0.16)	0.88 (0.23)	0.92 (0.17)	0.91 (0.20)	0.94 (0.17)	0.89 (0.23)	0.92 (0.19)	0.694	**<0.001***	0.059	0.052
Stride Length (m)	0.95 (0.20)	1.03 (0.14)	0.89 (0.22)	0.98 (0.16)	0.95 (0.20)	1.03 (0.16)	0.92 (0.23)	1.00 (0.16)	0.95 (0.19)	1.03 (0.16)	0.91 (0.23)	1.01 (0.18)	0.267	**<0.001***	0.170	0.219
Foot Strike Angle (°)	12.25 (5.68)	9.48 (0.57)	10.35 (6.00)	8.21 (6.22)	11.54 (5.23)	9.53 (5.05)	10.84 (5.08)	8.51 (5.16)	11.73 (4.85)	10.11 (4.58)	11.33 (5.17)	9.01 (4.55)	0.253	**<0.001***	0.998	0.959
Stride Time Var (CV)	3.76 (2.52)	2.70 (1.00)	3.46 (2.07)	2.96 (1.02)	3.31 (2.83)	3.03 (1.35)	4.14 (4.06)	2.67 (0.87)	3.64 (2.97)	2.87 (1.72)	3.42 (1.81)	2.93 (1.11)	0.370	0.825	0.864	0.934
	Baseline Dual-Task Cost (%)				**Closed-loop Dual-Task Cost (%)**				**Open-loop Dual-Task Cost (%)**				**Group**	**Task**	**Closed-loop**	**Open-loop**
	FOG+		FOG-		FOG+		FOG-		FOG+		FOG-		*p*	*p*	*p*	*p*
Gait Speed (m/s)	-7.43 (8.61)		-5.83 (6.85)		-3.80 (10.29)		-2.38 (4.99)		-4.40 (10.70)		-2.25 (4.35)		0.716	-	0.665	**0.050***
Stride Length (m)	-8.45 (8.63)		-5.45 (5.21)		-5.02 (10.32)		-3.34 (3.25)		-5.76 (10.49)		-2.80 (3.95)		0.417	-	**0.003**[#]	**<0.001**[#]
Foot Strike Angle (°)	-20.79 (-25.95,-7.46)		-17.85 (-21.64, 1.18)		-5.01 (-10.35, -3.71)		-7.90 (-16.74, -2.03)		-2.71 (-8.86, 2.88)		-11.00 (-27.61, -2.79)		0.225	-	**0.014***	**0.031***
Stride Time Var (CV)	-2.71 (24.76)		13.31 (27.84)		22.20 (30.92)		-6.86 (24.54)		7.27 (58.61)		11.66 (32.50)		0.256	-	0.784	0.069
TURNING		**Baseline**			**Closed-loop**				**Open-loop**				**Group**	**Turn**	**Closed-loop**	**Open-loop**
		FOG+		FOG-	FOG+		FOG-		FOG+		FOG-		*p*	*p*	*p*	*p*
Duration (s)	180°	2.37 (0.49)		2.38 (0.74)	2.39 (0.51)		2.33 (0.63)		2.45 (0.44)		2.25 (0.63)		0.449	**<0.001***	0.402	**0.019***
	360°	4.38 (0.91)		4.34 (1.32)	4.92 (1.71)		4.78 (2.12)		6.93 (7.11)		4.71 (1.77)					
Velocity (°/s)	180°	115.58 (28.35)		115.62 (32.41)	123.56 (30.48)		115.24 (30.48)		117.39 (28.15)		109.26 (34.34)		0.970	**<0.001***	0.653	0.059
	360°	127.05 (31.66)		129.98 (36.94)	122.23 (31.63)		124.80 (33.63)		121.76 (29.56)		123.90 (35.80)					

*[*significance level p<0.05, Mean (Standard Deviation) reported]*

Table 4 - Number of freezing episodes observed during turning and walking

		FOG episodes (n)	*p**
Baseline	180 turn	1	-
	360 turn	6	-
	Single task gait	3	-
	Dual task gait	3	-
Closed-loop	180 turn	1	1.000
	360 turn	6	0.180
	Single task gait	1	0.157
	Dual task gait	3	1.000
Open-loop	180 turn	1	1.000
	360 turn	5	0.083
	Single task gait	2	0.564
	Dual task gait	3	1.000

*[FOG = freezing of gait, *Wilcoxon signed rank test for difference between baseline and cued conditions]*

Supplementary Table 2 - Relationship between pre-frontal cortex activation and behavioral measures

Spearman's rho (p)				Turn Duration	Turn Velocity	Gait Speed	Stride Length	Foot Strike Angle	Stride Time Variability
BASELINE	**Turning**	**180° turn**	**Prior**	-.058 (.782)	.111 (.596)				
			During	.083 (.693)	-.188 (.367)				
		360° turn	**Prior**	.160 (.455)	-.265 (.211)				
			During	-.092 (.669)	-.060 (.779)				
	Walking	**Single**	**Early**			.104 (.628)	.015 (.946)	-.042 (.847)	.001 (.994)
			Late			.094 (.661)	.039 (.855)	-.223 (.294)	-.034 (.876)
		Dual	**Early**			-.109 (.613)	-.079 (.715)	-.047 (.827)	.003 (.989)
			Late			-.098 (.648)	.031 (.887)	-.123 (.565)	.003 (.991)
CLOSED-LOOP	**Turning**	**180° turn**	**Prior**	.107 (.618)	.062 (.773)				
			During	.205 (.336)	-.100 (.640)				
		360° turn	**Prior**	.382 (.072)	-.219 (.316)				
			During	-.282 (.193)	.227 (.297)				
	Walking	**Single**	**Early**			.386 (.069)	.362 (.090)	.239 (.272)	**-.652 (.001)**
			Late			-.093 (.674)	-.038 (.864)	.252 (.247)	.188 (.390)
		Dual	**Early**			.024 (.915)	.030 (.892)	.114 (.603)	-.013 (.953)
			Late			-.045 (.839)	-.088 (.691)	.134 (.543)	.067 (.762)
OPEN-LOOP	**Turning**	**180° turn**	**Prior**	.123 (.576)	.123 (.576)				
			During	.230 (.290)	.134 (.543)				
		360° turn	**Prior**	.089 (.692)	-.317 (.150)				
			During	-.421 (.051)	.385 (.077)				
	Walking	**Single**	**Early**			-.131 (.552)	-.257 (.237)	.128 (.561)	.179 (.414)
			Late			-.063 (.775)	-.098 (.656)	.165 (.452)	-.131 (.551)
		Dual	**Early**			-.025 (.911)	-.074 (.737)	.170 (.439)	.075 (.734)
			Late			-.067 (.760)	-.093 (.672)	.066 (.765)	.027 (.901)

Supplementary Table 2 – Relationships between baseline PFC activation, demographic, cognitive and sensory outcomes in PD

		180° turn		360° turn		Two minute walk			
						Single		Dual	
		Prior	During	Prior	During	Early	Late	Early	Late
Demographics	Age	-.125 (.552)	.054 (.796)	.058 (.789)	.228 (.284)	.003 (.989)	.101 (.637)	-.042 (.846)	-.055 (.800)
	UPDRS III	-.371 (.068)	-.092 (.663)	-.092 (.669)	-.088 (.683)	-.072 (.738)	-.370 (.075)	-.039 (.857)	-.291 (.168)
	nFOG	.035 (.868)	.371 (.068)	.245 (.249)	.131 (.540)	.023 (.916)	-.080 (.709)	-.303 (.150)	-.155 (.470)
	GDI	-.024 (.909)	-.115 (.583)	-.117 (.587)	-.086 (.689)	-.092 (.669)	.123 (.565)	-.055 (.797)	-.195 (.361)
	MFI	-.330 (.108)	-.105 (.617)	-.193 (.367)	***-.420 (.041)***	-.056 (.796)	-.401 (.052)	-.170 (.427)	-.299 (.156)
	OHQ	-.257 (.214)	.014 (.948)	-.182 (.395)	-.300 (.154)	.036 (.868)	-.293 (.165)	-.247 (.244)	-.263 (.215)
Cognition	MoCA	-.243 (.242)	-.321 (.118)	-.061 (.776)	-.190 (.374)	.057 (.790)	-.020 (.927)	.228 (.284)	-.094 (.663)
	FAB	.187 (.372)	.139 (.509)	-.226 (.288)	-.093 (.665)	.223 (.295)	.236 (.267)	.203 (.342)	.371 (.074)
	CLOX 1	***.473 (.017)***	.384 (.058)	.220 (.302)	.234 (.272)	***.557 (.005)***	.327 (.119)	-.020 (.927)	.341 (.103)
	CLOX 2	.334 (.103)	.094 (.655)	.383 (.065)	.047 (.826)	.303 (.150)	.196 (.359)	.050 (.817)	.101 (.639)
	TMT A	***-.521 (.008)***	-.285 (.167)	-.122 (.570)	-.048 (.823)	-.293 (.165)	-.105 (.626)	-.022 (.920)	-.139 (.516)
	TMT B	-.341 (.095)	-.004 (.984)	-.039 (.856)	-.069 (.748)	-.046 (.831)	-.088 (.683)	-.231 (.278)	.044 (.840)
Sensory	Taste/Smell	-.121 (.572)	-.097 (.651)	.045 (.840)	.192 (.381)	.230 (.291)	.147 (.503)	-.235 (.280)	.113 (.607)
	Movement Processing	-.103 (.633)	-.324 (.123)	-.367 (.085)	-.166 (.450)	-.112 (.609)	-.089 (.685)	-.084 (.702)	.028 (.901)
	Visual Processing	-.388 (.061)	-.128 (.551)	-.162 (.459)	.017 (.940)	.031 (.887)	-.225 (.301)	-.161 (.462)	-.183 (.403)
	Touch Processing	***-.599 (.002)***	-.304 (.149)	-.369 (.083)	-.110 (.616)	-.208 (.340)	***-.474 (.022)***	-.052 (.812)	-.233 (.285)
	Activity Level	-.309 (.142)	-.074 (.729)	-.239 (.271)	-.339 (.113)	-.222 (.308)	-.312 (.147)	-.151 (.492)	-.034 (.878)
	Auditory Processing	-.377 (.069)	-.184 (.390)	-.007 (.975)	-.273 (.207)	-.320 (.137)	-.302 (.162)	-.381 (.073)	-.251 (.247)

[Spearman's rho (p) correlations displayed. Significant p<0.05 correlations in Bold and italics]