Changes in prefrontal cortical activity and turning in response to dopaminergic and cholinergic therapy in Parkinson's disease: a randomized cross-over trial

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ABSTRACT

Introduction: Cholinergic dysfunction contributes to mobility deficits in Parkinson's disease (PD). People with PD rely on limited prefrontal executive-attentional resources for the control of locomotion, including turning. Cortical and behavioral responses to cholinergic augmentation during turning remains unclear. We examined prefrontal cortex (PFC) activity while turning-in-place and spatiotemporal measures of turns in response to usual dopaminergic medication and adjunct cholinergic augmentation. **Methods**: This study consisted of a single-site, randomized, double-blind crossover trial. Twenty PD participants were assessed in the levodopa-off state and then randomized to either levodopa + donepezil (5 mg) or levodopa + placebo treatments for two weeks followed by a 2-week washout before crossover. The primary outcome was change from off state in PFC activity while turning-in-place (assessed with functional near-infrared spectroscopy). Secondary outcomes were changes in spatiotemporal turning measures (assessed with body-worn inertial measurement units) and accuracy in the secondary task. **Results:** Nineteen participants completed the trial. While levodopa + placebo had no effect on PFC activity when turning-in-place with a dual-task, levodopa + donepezil led to a large reduction in PFC activity (effect size, -0.82). Spatiotemporal measures of turning improved with both treatments, with slightly greater effect sizes observed for levodopa + donepezil. Additionally, the accuracy in the concurrent cognitive task improved only with levodopa + donepezil (effect size, 0.63). **Conclusion**: The addition of cholinergic therapy with donepezil (5 mg/day for 2 weeks) to standard dopaminergic therapy reduced the burden on prefrontal executive-attentional resources while turning with a dual-task and improved secondary task accuracy and turning.

Keywords: fNIRS; cognition; prefrontal cortex; Parkinson's disease; locomotion

INTRODUCTION

Mobility deficits, including gait and turning impairments, are common in Parkinson's disease (PD) and lead to increased risk of falling and reduced quality of life [1, 2]. Mobility deficits only partially respond to dopaminergic medications [1], indicating a potential role for additional neurotransmitters. Specifically, a growing body of evidence support that cholinergic dysfunction is an important contributor to mobility deficits in PD [3]. Hence, the cholinergic system has been suggested as a complementary target for therapeutic interventions in PD, with mixed findings reported for gait: two studies found that cholinergic augmentation can improve gait in PD [4, 5], whereas another study found no changes in gait [6].

Turning is an often-overlooked mobility task in PD. Turning is slow, requires more steps, and it is performed with an “en-bloc” strategy in people with PD [2]. Development of complementary treatment for turning in PD is needed as dopaminergic medication does not restore turning to the level of healthy individuals [1] and falling during turning is 8 times more likely to lead to hip fracture than falls forward or backwards [7]. To our best knowledge, the effects of cholinergic augmentation on turning has not been investigated yet.

Motor control requires a balance between automatic and executive processes that is dependent upon each individual’s abilities and task demand. Due to degeneration in neural networks associated with movement automaticity, people with PD recruit additional prefrontal executive-attentional resources for the control of walking and turning [8, 9]. This may bring people with PD closer to the limit of executive-attentional resources available, which are reduced in PD [10]. Consequently, PD-related mobility deficits become

more pronounced during executive-attentional demanding tasks, such as walking or turning while performing a concurrent task [1]. However, little is known about the effects of cholinergic augmentation on motor control mechanisms in PD. Recently, our research group demonstrated that the addition of cholinergic augmentation with donepezil (5 mg/day) to the usual levodopa increased prefrontal cortex (PFC) activity while walking and improved gait and the accuracy of a concurrent dual-task to a greater extent than levodopa alone [4]. These findings suggest that cholinergic augmentation may have contributed to better allocation of the prefrontal executive-attentional resources available to compensate for impaired automaticity.

In this short communication, we present the analysis related to turning in the above-mentioned trial. We examined PFC activity while turning-in-place and spatiotemporal measures of turns (single and dual-task) to usual dopaminergic medication with and without cholinergic augmentation with donepezil. We hypothesized that, similar to the effects on gait we observed in the original study, cholinergic augmentation would improve turning and the dual-task performance by better allocating the prefrontal executive-attentional resources available.

METHODS

Participants and study design

This study consisted of a randomized, double-blinded (participants and researchers), cross-over trial in 20 people with PD who were at least 50 years old and able to walk independently. Full methodological details are available at clinical trials.gov (NCT03599726) and

our previous paper [4]. The study was approved by a Research Ethics Committee at Oregon Health and Science University (eIRB #17805) and all participants provided written informed consent. Participants were eligible to participate if they: (i) had a diagnosis of idiopathic PD with response to levodopa and off-medication Hoehn & Yahr (H&Y) scores of II-IV; (ii) were able to stand unassisted for one minute and to walk continuously for 2 minutes without assistance or assistive devices; (iii) were taking levodopa, and not already taking donepezil; (iv) were able to cooperate with testing and be compliant with taking the experimental medications. Exclusion criteria were: (i) other factors affecting gait, uncorrected vision or vestibular problem; (ii) major depression, hallucinations or other psychiatric disturbances, (iii) medical problems that might be worsened by donepezil, including tachycardia, bradycardia, arrhythmias, and peptic ulcer disease; (iv) use of anticholinergics for Parkinsonism, bladder antispasmodics for urinary urgency or tricyclic antidepressants for depression.

Protocol

Participants completed three visits to the laboratory (see Supplemental Figure 1). Visit 1 involved screening, clinical, cognitive and turning assessments while “Off” Parkinsonian medications (>12-hour withdrawal overnight). Visits 2 and 3 were conducted following the two-week period of medication intervention, and involved repeating the turning assessment that was done in visit 1. Prior to visit 1, participants were randomized in a 1:1 ratio to start with either donepezil (i.e., levodopa + donepezil) or a placebo (i.e., levodopa + placebo). After visit 2, there was a two-week washout prior to crossing-over to the other treatment. Donepezil was taken at 5mg per

day (in the evening, just prior bedtime) for two weeks and participants were assessed while “On” their regular dopaminergic medications in visits 2 and 3.

The Research Pharmacy at OHSU was responsible for creating the blinded capsules, randomizing to maintain blinding, dispensing medication and checking compliance by returned capsule counts. Adverse events were reported on a weekly basis.

Demographics

Participant characteristics of age, sex, height, weight, disease duration and years of formal education were recorded. The following clinical and cognitive assessments were applied: the Movement Disorders Society revised Unified Parkinson’s disease Rating Scale (MDS-UPDRS) motor sub-section, the H&Y and the Montreal Cognitive Assessment (MoCA).

Turning assessment

Turning execution was quantified with eight body-worn inertial sensors (Opal, APDM, Portland, Oregon, USA) located at the sternum and pelvis levels, on the wrists, shanks and both feet of participants. They recorded tri-axial acceleration, angular velocity and magnetic field. Details on processing of the turning task are described elsewhere [11].

Participants performed a turning-in-place task at self-selected pace. The task started with a 20-s quiet standing period while looking forward. After, participants turned in place for 80s, alternating 360° turns to the right and left. Two conditions were tested (with a single trial per condition): single- and dual-task. The dual-task condition consisted of executing the turning-in-place task while performing a concurrent cognitive task (auditory Modified AX-Continuous Performance Test), which involved listening to a series of letters being read out and pressing a hand-held button when participants heard 'A' followed by the letter 'I'.

fNIRS to measure cortical activity

PFC activity (i.e., changes in oxygenated hemoglobin (HbO_2) levels) while turning-in-place was measured using an 8-channel mobile fNIRS system (Octamon, Artinis, Netherlands), with two reference channels used to remove the components of superficial interference (i.e., peripheral blood flow changes in extra-cerebral layers of the head). Cortical areas assessed included BA9 and BA10 (bilaterally). Our previously reported custom-made MATLAB algorithms[9] analyzed the fNIRS raw signals, which involved data filtering, baseline correction (relative to standing still), reference channel correction, visual signal inspection and averaging across channels.

Outcomes measures

The primary outcome measure was the relative HbO_2 levels (turning – standing) within the PFC, which is a proxy for cortical activation. Secondary outcomes included turn peak velocity, turn duration, and the response time and accuracy of the concurrent cognitive task.

Statistical analysis

The standardized response mean (SRM) was calculated to compare changes from the Off medication and levodopa + placebo or levodopa + donepezil, which were interpreted as follows: trivial (<0.2), small (>0.2 and <0.5), moderate (>0.5 and <0.8), and large (>0.8). Linear mixed-effects models (LMEMs) were used to determine whether the effect of levodopa + donepezil differs from levodopa + placebo; thus, the corresponding deltas (i.e., changes relative to baseline Off medication) were entered in the models. LMEMs were run with the Restricted Maximum Likelihood Estimation selection in MATLAB R2019b. Researchers were blinded to study intervention or placebo until following the further analysis of all outcomes.

RESULTS

One participant had adverse side effects (gastrointestinal side effect and worsening of depression) and did not complete the study. Thus, results are based on 19 participants. Overall, participants (age=72.7±7.58 years; 14 men/6 women) had moderate disease

severity (off-MDS-UPDRS-III=41.9±10.54; levodopa + placebo=38.16±11.01; levodopa + donepezil=37.11±12.13) and were not severely cognitively impaired (MoCA=25.9±2.99). Additional participants' characteristics are presented in Supplemental table 1.

PFC activity while turning-in-place with a dual-task decreased with levodopa + donepezil, but not with levodopa alone

In the dual task condition there was a large reduction in PFC activity when turning-in-place from Off medication to levodopa + donepezil (SRM=-0.82), but no change from Off medication to levodopa + placebo (SRM=-0.17, Table 1 and Figure 1). In addition, the LMEM confirmed a significant difference between treatments (p=0.035, Table 1).

In the single-task condition, there was a small reduction in PFC activity when turning-in-place from Off medication to levodopa + donepezil (SRM=-0.26), but no change from Off medication to levodopa + placebo (SRM=0.01, Table 2 and Figure 1). The LMEM revealed no significant difference between treatments (p=0.262, Table 1).

Turning and performance of the concurrent cognitive task were slightly better with levodopa + donepezil

Some of the secondary outcomes had greater effects with levodopa + donepezil compared to levodopa + placebo (e.g., accuracy of the concurrent cognitive task: moderate effect with levodopa + donepezil (SRM=0.63), but no effect with levodopa + placebo (SRM=0.13); Table1). However, the LMEMs revealed no significant difference between treatments (Table 1); a trend for difference

between treatments (p=0.066) was observed for turning duration in the dual-task condition, with slightly greater reduction in turn duration with levodopa + donepezil (Table 1). Specifically, turning improved with both treatments (Table 1).

DISCUSSION

This is the first pilot study to examine the cortical and behavioral responses to levodopa and cholinergic augmentation during turning in PD. While levodopa alone had no effect on PFC activity when turning-in-place with a dual-task, the addition of donepezil (i.e., levodopa + donepezil) led to a large reduction in PFC activity. Turning improved with both treatments, with slightly greater effect sizes observed for levodopa + donepezil. Additionally, the accuracy in the concurrent cognitive task improved only with levodopa + donepezil. Overall, current findings suggest that the addition of cholinergic augmentation to standard dopaminergic therapy reduced the burden on prefrontal executive-attentional resources while turning with a dual-task and led to slightly greater behavioral improvements (i.e., turning and accuracy in the concurrent cognitive task) compared to levodopa alone. Thus, this study corroborates previous studies reporting benefits to gait in PD with anticholinesterase inhibitors [4, 5] and points out potential contributions of donepezil to treat turning impairments. Since turning is an essential part of functional mobility and PD-related turning impairments increase the risk of falls [1, 2], cholinergic augmentation has potential to increase independence levels and reduce the risk of falls in PD.

Cholinergic augmentation may ameliorate the efficiency of the so-called “executive locomotor network”. Specifically, locomotor signals originated in the PFC are then transmitted through the basal ganglia before reaching the spinal cord [12]. In PD, the executive locomotor network is activated as a compensatory mechanism to reduced automaticity. However, due to a limited pool of executive-attentional resources in PD [10], the executive locomotor network is not effective in maintaining mobility levels comparable to healthy individuals [1, 8]. The cholinergic augmentation may expand or better allocate the executive-attentional resources to the control of walking and turning. In our previous study, the addition of cholinergic augmentation to the usual levodopa improved gait and accuracy in the concurrent dual-task to a greater extent compared with levodopa alone [4]. In the current study, we observed slightly greater effects sizes on turning and accuracy in the dual-task with levodopa + donepezil. Additionally, the reduction in PFC activity while turning-in-place observed with levodopa + donepezil may indicate that the PFC became more efficient: similar to slightly greater behavioral benefits were achieved with a reduced burden on executive-attentional resources.

Limitations and future directions. The present findings should be interpreted cautiously. Our study involved a small cohort and is limited by assessing the PFC only. Future studies should assess multiple cortical areas for a more complete understanding of the effects of cholinergic augmentation on cortical control mechanisms in PD. Further studies on larger sample sizes are required to identify predictors of response to cholinergic augmentation.

In conclusion, this double-blind, randomized crossover trial suggests that the addition of cholinergic augmentation, with donepezil at 5 mg/day for 2 weeks, to standard dopaminergic therapy reduced the burden on prefrontal executive-attentional resources while turning with a dual-task and led to slightly greater turning improvements than dopaminergic therapy alone.

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Figure 1. Mean and SEM of primary and secondary outcome measures across the three time-points.

Supplemental figure 1. Study CONSORT diagram.

Table 1. Summary of findings. Means and standard deviations (SDs) of outcome measures at baseline and changes related to treatments.

Outcome	**Condition**	**Baseline Off medication**	**Change after 2 weeks levodopa + placebo $\Delta_{placebo}$**		**Change after 2 weeks levodopa + donepezil $\Delta_{donepezil}$**		**Linear-mixed effects model (treatment) $\Delta_{placebo}$ X $\Delta_{donepezil}$**			
		mean (SD)	**mean (SD)**	**SRM**	**mean (SD)**	**SRM**	**Estimate**	**SE**	**t**	**p**
Primary										
Relative HbO_2 (µmol/L)	Single-task	-0.075 (0.190)	0.003 (0.253)	0.01	-0.072 (0.284)	-0.26	-0.076	0.067	-1.143	0.262
	Dual-task	-0.103 (0.193)	-0.051 (0.305)	-0.17	-0.260 (0.316)	-0.82^{L}	-0.218	0.099	-2.209	**0.035***
Secondary (turn)										
Turn peak velocity (degrees/s)	Single-task	99.52 (31.33)	14.96 (21.20)	0.70^{M}	14.93 (22.41)	0.67^{M}	-0.414	4.205	-0.098	0.922
	Dual-task	99.65 (29.38)	11.59 (25.08)	0.46	17.41 (24.52)	0.71^{M}	4.208	4.051	1.038	0.307
Turn duration (s)	Single-task	8.13 (4.69)	-1.24 (1.89)	-0.66^{M}	-1.31 (2.02)	-0.65^{M}	0.060	0.293	0.204	0.840
	Dual-task	8.22 (4.49)	-0.80 (4.31)	-0.19	-1.84 (3.27)	-0.56^{M}	-1.076	0.565	-1.904	0.066
Secondary (AX-CPT)										
Response time (s)	Dual-task	0.53 (0.09)	0.01 (0.10)	-0.13	0.00 (0.08)	-0.03	0.009	0.018	0.489	0.630
Accuracy (-)	Dual-task	0.88 (0.11)	0.02 (0.13)	0.13	0.08 (0.12)	0.63^{M}	0.050	0.030	1.682	0.107

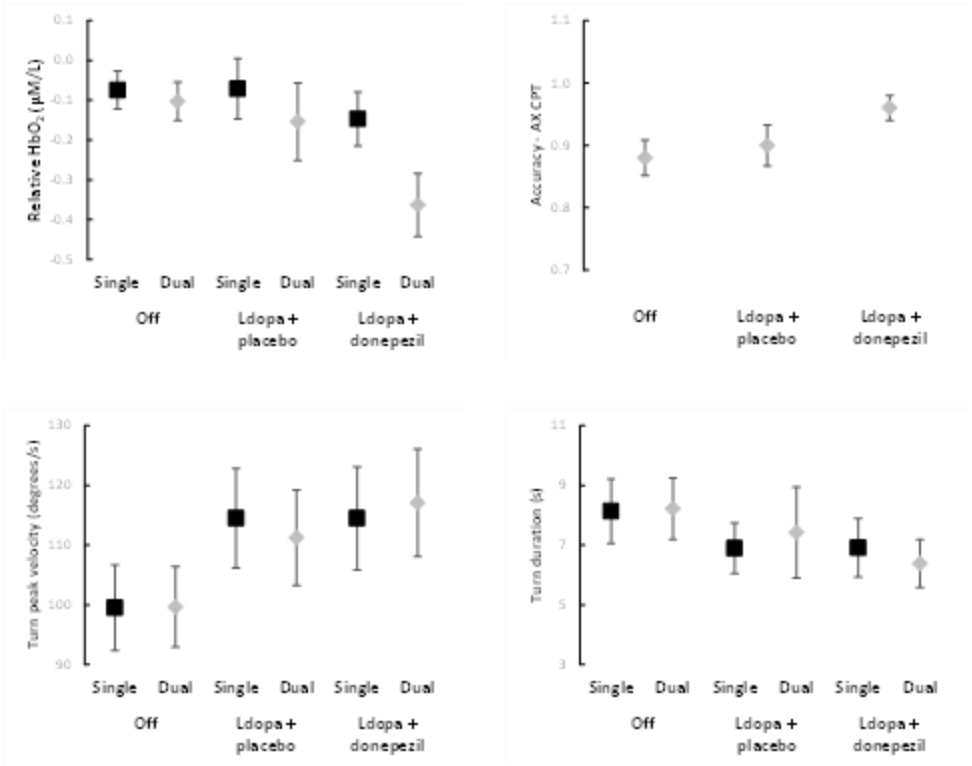
AX-CPT: auditory Modified AX-Continuous Performance Test; SE: standard error; SRM: standardized response mean. ^{M} indicates a moderate effect size; ^{L} indicates a large effect size; * indicates a significant difference between treatments

Supplemental table 1. Participant's characteristics

Measure	Baseline Off medication mean (SD)	Levodopa + placebo mean (SD)	Levodopa + donepezil mean (SD)
Age (years)	72.68 (7.58)	-	-
Sex	M (14)/F (6)	-	-
Years of education	17.00 (3.37)	-	-
Height (cm)	175.82 (8.30)	-	-
Weight (lb)	190.21 (50.47)	-	-
Disease duration (years)	7.63 (4.78)	-	-
MoCA	25.95 (2.99)	-	-
FOGQ	5.32 (6.51)	-	-
LED (mg/day)	717.95 (263.76)	-	-
MDS-UPDRS-III	41.90 (10.54)	38.16 (11.01)	37.11 (12.13)
MDS-UPDRS-III UE	17.2 (4.5)	16.0 (5.2)	15.7 (4.7)
Hoehn & Yahr stage	II (13)/III (7)	II (18)/III (1)	II (18)/III (1)
Presence of dyskinesias	yes (0)/no (19)	yes (4)/no (15)	yes (2)/no (17)

FOGQ: Freezing-of-Gait Questionnaire; LED: Levodopa-equivalent daily dosage; MDS-UPDRS-III: Movement Disorders Society Unified Parkinson's Disease Rating Scale – motor section; MoCA: Montreal Cognitive Assessment; SD: standard deviation. UE: upper extremity

Figure 1.


Relative HbO_2 (μM/L)
0.1
0.0
-0.1
-0.2
-0.3
-0.4
-0.5
Single Dual Single Dual Single Dual
Off
Ldopa + placebo
Ldopa + donepezil
Accuracy - AX CPT
1.1
1.0
0.9
0.8
0.7
Off
Ldopa + placebo
Ldopa + donepezil
Turn peak velocity (degrees/s)
130
120
110
100
90
Single Dual Single Dual Single Dual
Off
Ldopa + placebo
Ldopa + donepezil
Turn duration (s)
11
9
7
5
3
Single Dual Single Dual Single Dual
Off
Ldopa + placebo
Ldopa + donepezil

Supplemental Figure 1.