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Cognitively Challenging Agility Boot Camp Program for Freezing of Gait in Parkinson's Disease

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Abstract

Introduction: It is well documented that freezing of gait (FoG) episodes occur in situations that are mentally challenging, such as dual-tasks, consistent with less automatic control of gait in people with Parkinson disease (PD) and FoG. However, most physical rehabilitation does not include such challenges. The purpose was to determine 1) feasibility of a cognitively challenging Agility Boot Camp Program (ABC-C) and 2) effects of this intervention on FoG, dual-task cost, balance, executive function and functional connectivity.

Methods: Forty-six people with PD and FoG enrolled in this randomized cross-over trial. Each participant had 6 weeks of ABC-C and Education interventions. Outcome measures were: FoG - perceived and objective measures, dual-task cost on gait, balance, executive function, and right supplementary motor area (SMA) - pedunculopontine nucleus (PPN) functional connectivity. Effect sizes were calculated.

Results: ABC-C had high compliance (90%) with a 24% drop-out rate. Improvements after Exercise, revealed by moderate and large effect sizes, were observed for subject perception of FoG after exercise, dual-task cost on gait speed, balance, cognition (SCOPA-COG), and SMA-PPN connectivity.

Conclusions: The ABC-C for people with PD and FoG is a feasible exercise program that has potential to improve FoG, balance, dual-task cost, executive function and brain connectivity. The study provided effect sizes to help design future studies with more subjects and longer duration to fully determine the potential to improve FoG.

Conflict of Interest Statement: Dr. Horak has an equity interest in APDM, a company that may have a commercial interest in the results of this study. This potential conflict of interest has been reviewed and managed by the Research & Development Committee at the VA Portland Health Care System and Oregon Health & Science University. They have put in place a plan to help ensure that this research study is not affected by the financial interest.

Keywords

exercise; Parkinson's disease; brain imaging

Background

The majority of patients with Parkinson's disease (PD) eventually develop freezing of gait (FoG), an intermittent failure to initiate or maintain walking. Specifically, 26% of people with mild PD and 80% of those with severe PD are affected by FoG, and it is one of the most common reasons for falls and dependency^{1,2}. FoG leads to overall loss of mobility, increased social isolation, and decreased quality of life³. There is currently no consensus on the brain mechanism underlying FoG and no good treatment for this troubling feature of PD³.

There is no singular brain region associated with FoG. Cortical, subcortical, limbic and heteromodal systems (e.g., attention and default networks) have been associated with FOG^{4–6}. For example, studies have reported white matter loss associated with FoG that include both motor and non-motor regions such as striato-frontal tracts and connections of the cerebellum with the subthalamic nucleus and with the pedunculopontine nucleus (PPN)⁷. Abnormalities in functional connectivity between the PPN and frontal/visual cortices, cerebellum, corticopontine and pallidal-sensorimotor pathways in freezers compared to nonfreezers have also been reported^{7,8}.

Our group has previously demonstrated that people with PD and FoG have decreased structural connectivity and increased functional connectivity between the right PPN and the right supplementary motor cortex (SMA) and right subthalamic nucleus (STN) compared to people without FoG or age-matched control participants^{9,10}. In fact, the stronger the functional connectivity between the right SMA and PPN, the worse the FoG (quantitatively measured during a turning in place task), suggesting increased SMA-PPN connectivity may be a maladaptive compensation for loss of network structure⁹. This right-hemisphere pathway is part of both the cognitive inhibition network and the locomotor network, consistent with greater executive inhibition deficits in people with FoG compared to those without FoG^{9–13}.

People with PD and FoG also have increased pre-frontal cortex activity during walking and turning compared to people with PD without FoG, consistent with a loss of automaticity^{11,12}. FoG episodes occur in situations that are mentally challenging, such as dual-tasks¹³, also consistent with less automatic control of gait in PD with FoG¹⁴. For example, dual-task cost on gait speed and stride length as well as step initiation is larger in people who freeze¹⁵. Dual-task interference in people who freeze is related to: 1) larger right than left white matter structural connectivity of SMA-PPN and 2) executive inhibition impairments^{16–19}. Thus, dual-task cost in people who freeze has been linked to abnormalities in executive inhibition-locomotor brain networks, suggesting that interventions targeting dual-task cost may also improve FoG.

We adapted our original Agility Boot Camp (ABC) program to incorporate additional executive-function tasks during mobility challenges known to be challenging for people with PD, now called Agility Boot Camp-Cognitive (ABC-C)^{18,20,21}. We recently showed that rehabilitation using the ABC training for PD resulted in improvements in mobility such as turning, gait speed, and balance in people with PD^{21,22}. However, the original ABC and current physical therapy interventions might have limited success for people with FoG because the interventions do not directly address deficits related to executive function, specifically response inhibition, set-switching, and dual-task function. This is a sub-study focusing only on people with PD who have FoG; part of a larger clinical trial to improve balance, gait and cognitive function in people with mild to moderate PD²⁰.

The purpose of this proof-of-concept study was to determine: 1) feasibility of the ABC-C program and 2) the effects of this intervention on FoG, gait automaticity (dual-task cost), balance, executive function and functional connectivity between PPN and SMA.

Methods

Participants and study design.

Patients were eligible if they had mild to moderate severity of idiopathic PD (Hoehn and Yahr Levels II-III and FoG, defined as > 0 on the New Freezing of Gait Questionnaire, NFOGQ)²³. Additional inclusion criteria required that participants be: a) between ages 50–90 years old, b) without major musculoskeletal or peripheral or central nervous system disorders (other than PD) that could significantly affect their balance and gait, c) without recent changes in medication, excessive use of alcohol or recreational drugs, d) without history of structural brain disease, active epilepsy, stroke, or dementia that would interfere with ability to follow intervention and testing procedures, e) able to stand or walk for 2 min without an assistive device, f) without a medical condition that precludes exercise, g) without claustrophobia, severe tremor, or any health history (i.e., implanted devices, deep brain stimulation) that would put the subject at risk near the MRI scanner. Here, we considered only the participants with PD and FoG, who were part of two clinical trials registered at clinicaltrials.gov (NCT02236286 and NCT02231073²⁰). The Veterans Affairs Portland Health Care System (VAPORHCS) and Oregon Health & Science University (OHSU) ethics committees approved the study and it was compliant with the Declaration of Helsinki. The protocol was approved by the OHSU/VAPORHCS joint Institutional Review Board (IRB #8979 and IRB#4131).

This was a randomized, single-blinded, cross-over design, exercise trial. Each participant crossed-over to the 2nd intervention after 6 weeks of 1st intervention and midpoint assessment the following week (see Figure 1). Final assessment was completed the week following the 6 weeks of the 2nd intervention. Both interventions were designed to have the same quantity of intervention and were delivered by the same 2 trainers for all sessions. Participants completed the same battery of tests at baseline, midpoint and final assessments (Figure 1). All other non-study interventions (i.e., medication and other exercise) were kept as stable as possible and any changes monitored. The researchers who performed baseline, midpoint and final assessments remained blinded to group assignment throughout the duration of the study. Additionally, internal regulatory reliability assessments between raters

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were performed, all sessions are also videotaped and only experienced testers were used for the clinical ratings. Participants were randomly assigned, per a centralized database (REDCap) to either Education-first or Exercise-first after passing the phone screening procedure. Randomization was implemented by an independent statistician using a block size method. The certified exercise trainer, who was unblinded to group assignment, notified the participants of their group and schedule by phone. Participants were consented and enrolled immediately before baseline assessment.

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Exercise—People participated in 80-minute, group (2–6 per group) exercise sessions 3 days per week for 6 weeks. The exercise protocol is an adaptation of our ABC exercise program for PD published previously^{18,20,21}. Briefly, the exercises are designed as a circuit and challenge cognitive-mobility skills known to be impaired in PD. Stations included (1) gait training, (2) functional skill training²⁴ (3) agility obstacle course, (4) lunges, (5) boxing, and (6) adaptive tai chi.²⁵ Each activity was chosen for its inherent focus on multi-directional movements, dynamic postural transitions, axial mobility, big movements and whole-body, motor sequencing. Each activity was progressed with cognitive challenges (see Appendix 1 and Peterson et al.¹⁸). Participants engaged in each station for 10–20 minutes with rest periods in between stations, as needed.

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Each participant progressed from beginning to intermediate to advanced stages at each station at their own pace for both motor and cognitive challenges (Appendix 1). Since people with PD are known to have difficulty with self-initiated movements, we deliberately focused on movements without external cues. The exercise class structure and progressions were led by a trained and experienced exercise trainer with oversight from a licensed physical therapist. Trained research assistants stood nearby and assisted participants who self-reported frequent falls, or had observed instability during the first exercise session.

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Education—The Education program was a chronic disease education program developed by our research team to teach patients with PD how to live better with their chronic condition. Briefly, it included content and discussion of topics on: developing a care team, sleep, nutrition, mood, medication, and stress management. Classes consisted of the same group of people (2 to 6 per class) meeting with the same exercise trainer for 80-minute sessions, once a week for 6 weeks. In order to match the dose of the Education intervention with the Exercise intervention, participants were also given relaxation recordings to be used at home 5 days per week for 30 minutes for an overall Education dose of 240 minutes/week; similar to the Exercise dose.

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Compliance was recorded for both Exercise and Education at each session. Progression was tracked for each of the 6 stations with each progression accounting for a point (Appendix 1). Additionally, participants stated their level of perceived exertion (0–10 scale) after each exercise session. The level of self-reported exertion was recorded to determine the level of challenge of the program and to determine if people were progressively challenged during the exercise over time. We did not use this for analysis; only to determine if people with FOG could increase exertion in this type of exercise program. For Education, participants recorded compliance for the relaxation sessions in a logbook and the instructor record attendance at each weekly education session.

Procedures and Outcomes measures—The larger protocol and mobility assessment is described in the protocol publication of this clinical trial²⁰. All assessments were scored in the practical Off-levodopa state (12 hours withdrawal of anti-parkinson medication). Imaging and cognitive tests were assessed one day and clinical, patient-reported, and mobility outcomes assessed on a second day. Each participant wore 8 inertial sensors (APDM, Inc., Portland, OR, USA), worn over the sternum, lumbar spine, bilaterally on the wrists, shins, and feet while completing the walking, turning and mini Balance Evaluation System Test (mini-BESTest) trials. As part of the larger study, participants completed several other objective tests of balance, mobility and cognition²⁰ but were not analyzed as part of this smaller project.

The primary outcome measures for this study were: perceived FoG using the new FoG questionnaire (NFOG-Q)²³ and a quantitative FoG Ratio²⁶. The NFOG-Q is a self-assessment of a person's experience with FoG. The FoG Ratio is an objective measure of FoG severity extracted from the antero-posterior acceleration sensed by two inertial sensors on the shins while turning in place 360° to the right, then left, for 1-minute. The FoG Ratio was calculated as the square of the power in the 3- to 8-Hz band (trembling freeze band), divided by the square of the power in the 0.5- to 3-Hz band (stepping movement band)²⁶.

The dual-task cost on gait speed and stride length was calculated, as well as cognitive dual-task cost¹⁸. In both ST and DT conditions, participants were instructed to walk at a comfortable pace back and forth continuously between two lines 7.6 meters apart. In the DT condition, participants were instructed to walk while reciting every other letter of the alphabet. The ST condition was always completed before the DT condition and the ST condition was always completed after performing the cognitive test for one minute while seated. To evaluate the performance on the cognitive task, the number of responses and the number of errors were recorded for both the seated and DT walking conditions. Accuracy was calculated as the percentage difference (total-error) in the walking compared to sitting condition.

Balance impairments were measured with the (mini-BESTest), a sensitive measure of dynamic balance, commonly used to quantify balance impairments in people with PD²⁷. This is a 14-item clinical test (maximum score of 28) that measures four domains of balance with each item scored 0–2, with higher scores indicating better performance.

Measures of cognition included the Scales for Outcomes in Parkinson's disease-Cognition (SCOPA-COG) and tests targeting inhibition and set-shifting. The SCOPA-COG consists of 10 items divided into 4 domains: memory, attention, executive function, and visuospatial function²⁸. Scores range from 0–43, with higher scores reflecting better performance. The inhibition/set-shifting domain of executive function was assessed with the Trail Making Test (TMT Ratio B/A)²⁹, Flankers reaction time in incongruent/congruent conditions, and Stroop tests (ratio of naming colors/incongruent colors-words)³⁰.

A subset of 13 participants were measured at all three intervention timepoints with resting state functional magnetic resonance imaging (rsfMRI), an imaging method that evaluates regional brain area relationships that exist in a resting state^{6,8,9}. Using this method, we

measured right SMA-PPN connectivity. Our previous publication showed that the functional connectivity between SMA and PPN was abnormally high in people with PD with FoG compared to those without FoG or control participants, so we used the same regions of interest in the SMA and PPN to investigate whether resting state functional connectivity can be reduced by our ABC-C program⁹.

Briefly, a 10-mm sphere was created at the peak coordinates of the SMA on the midline ($x = 0$, $y = -7$, $z = 55$)³¹. A 6-mm sphere was created bilaterally for the PPN ($x = \pm 6$, $y = -30$, $z = -19$)^{10,32}. The mean time series from the SMA bold signal at rest was correlated with the mean time series from each of the PPN ROIs using Pearson's coefficient of correlation (r) for each participant. The procedures for the rsfMRI were previously described and details are in the Appendix 2^{9,40}.

Statistical analysis—Feasibility was assessed by drop-outs, adverse events, compliance and progression of this challenging agility program. We hypothesized that Exercise intervention would result in larger improvements in freezing, dual-task cost, balance, executive function, and brain connectivity than the placebo, control Education intervention. Since we had three observations for each participant (Baseline, Midpoint and Final (Figure 1)), we calculated the change due to the intervention as Midpoint-Baseline for the first intervention, and Final-Midpoint for the second intervention. The effect of Exercise and Education interventions were reported as the standardized response mean³³ (SRM) for each measure. The SRM was calculated as the mean change between before and after each intervention period divided by the standard deviation (SD) of the change³³ and the 95% confidence interval were reported³⁴. Generally, an SRM value of 0.20 represents a small, 0.50 a moderate, and 0.80 a large effect of the intervention³⁴. To assess whether the change in FoG measures was associated with baseline FoG ratio, we used Pearson correlation coefficient (in cases of skewness of the data, we used a log-transform).

Lastly, as exploratory analysis (see Appendix 4), we used a linear mixed-model design that included an indicator of intervention effects (Education versus Exercise), order effects (Exercise or Education first), and period effects (sequence, Education-Exercise or Exercise-Education, differences) to determine whether the “difference in change” differed between Exercise and Education (significance threshold of 0.05). The intervention term reflected the main focus of the study, to determine whether the effects of Exercise differed from the effects of Education. A random effects term was included for participants. All statistical analysis was performed in MATLAB R2018b (The Mathworks Inc., Natick MA, USA) using the Statistics and Machine Learning Toolbox.

Results

Feasibility of ABC-C

A total of 108 potential people with PD and FoG were screened (Figure 2). Sixty-two were not included for the following reasons: 37 had exclusions - comorbidities (28), deep brain stimulation (8), recent medication change (1) and 25 declined to participate. We enrolled 46 participants with FoG with 25 randomly assigned to the Exercise first group and 21 to the Education first group (Figure 2). Clinical characteristics did not differ between randomized

groups, except for a higher MoCA in the Exercise first group ($p=0.04$, Table 1). The subset of 13 people with MRI were on average 69.3 ± 9.5 years old with MD-SUPDRS Part III 50.6 ± 17.6 ; PIDG 8.1 ± 4.0 ; Hoehn & Yahr 2.7 ± 0.09 and MoCA 25.5 ± 4.4 . Drop outs during interventions included people who discontinued intervention (7) or were lost to follow up (1, Figure 2). Overall, 17% of people dropped out over the course of the study. Specifically, 24% dropped out during the Exercise portion while 9% dropped out during the Education session. Subjects dropped out for the following reasons: 2 sustained injuries outside of classes (low-back injury and sciatica), 1 had a heart attack outside of classes, 1 had a medical procedure, and one had a urinary tract infection. One participant fell during their 4th exercise class resulting in a hip fracture and one participant didn't want to commute to classes anymore. In addition, one subject was lost to follow up and could not be contacted. The only serious adverse event was the fall with hip fracture. This adverse event occurred during the gait station when emphasis was placed on taking long strides. The participant was spotted by a research assistant but fell while making a turn. There were also 4 minor adverse events that did not result in drop-outs: 3 fell during the exercise class (no medical intervention required) and one fell getting out of their car. No subjects reported medication changes or major life, health or activity changes. We asked all participants to come to testing in the practical OFF state, at least 12 hours since their last dosage of medications. Only 2 people came in for testing after taking their medications that morning so they were sent home and rescheduled for another day that week.

The Exercise session compliance was 90%, while the Education session compliance was 80%, including both group class attendance and home relaxation practice (94% and 66%, respectively). Progression in mobility challenge, as documented by the exercise trainer, with a starting average of 34% maximal difficulty the first week and incrementally increased to 67% of the possible points for progression. Cognitive progressions averaged from 33% to 85% possible difficulty level between the first and final week. For the perceived exertion scale of 0–10, participants increased from on average from 4.3 to 6.9 over 6 weeks. No recorded changes in medications or exercise routines were reported during the study.

Freezing of Gait severity

The NFOG-Q showed a moderate effect size after exercise ($SRM_{\text{Exercise}}=0.42$ and $SRM_{\text{Education}}=-0.12$, for p-value see Appendix 4), Figure 3A and Table 2. The FoG Ratio showed small effect size ($SRM_{\text{Exercise}}=0.04$ and $SRM_{\text{Education}}=0.23$). However, the change of FoG Ratio was significantly associated with the baseline FoG Ratio. Higher (worse) FoG Ratios at baseline were associated with larger improvements with Exercise ($r=-0.41$, $p=0.01$) but not with Education (see Appendix 3 for regression figures).

Dual-task cost on gait

The dual-task cost on gait speed showed a large effect size after Exercise, but not after Education; ($SRM_{\text{Exercise}}=-0.73$ and $SRM_{\text{Education}}=0.23$), see Figure 3C. The dual-task cost on stride length showed a moderate effect size after Exercise ($SRM_{\text{Exercise}}=0.49$ and $SRM_{\text{Education}}=-0.03$). Lastly, the effect sizes on the accuracy of the cognitive task while walking were small, details Table 2.

Balance Impairments

The overall mini-BESTest showed a moderate effect size after exercise, but not after education ($SRM_{\text{Exercise}}=-0.45$ and $SRM_{\text{Education}}=0.05$), details in Table 2.

Executive inhibition function

The SCOPA-COG showed a moderate effect size after Exercise ($SRM_{\text{Exercise}}=-0.45$ and $SRM_{\text{Education}}=0.28$), while the TMT (B/A), the Stroop interference score, and the Flankers only showed small effect sizes after Exercise as well as after Education, details in Table 2.

Right SMA-PPN connectivity

The right SMA-PPN showed a large effect size after only after exercise ($SRM_{\text{Exercise}}=0.97$ and $SRM_{\text{Education}}=0.24$), see Figure 3D. Specifically, after exercise, but not after education, the connectivity between right SMA and PPN was reduced in the 13 participants who had imaging. The left SMA-PPN showed very small effect sizes with the interventions, Figure 3D and Table 2.

Discussion

The main finding from this study was that a small-group, agility exercise intervention with cognitive challenges, ABC-C, is a feasible rehabilitation intervention for people with PD who have FoG. The study has provided effect sizes for FoG, dual-task cost, balance, executive inhibition, and right SMA-PPN connectivity, that can be used to power future clinical trials.

Freezing of Gait

This is the first exercise study to examine if an objective measure of FoG could be improved. We found some improvement in perceived FoG, but no change in the objective measure of FoG. Although a strength of the study was assessing people with PD Off their dopaminergic medication, the perception of FoG severity may come from the recollection of On periods at home. Similarly, a recent paper showed that cognitive training, 2x/week for 7 weeks, was effective in improving the NFOG-Q but only when assessed in the On state³⁵. Additionally, we found that those with the most severe FoG, measured objectively, improved with the ABC-C exercise (Appendix 3). Specifically, the worse the FoG Ratio was at baseline, the larger the improvement in FoG Ratio after Exercise, but not after Education. However, we cannot identify the number of subjects who improved since we do not have a threshold severity for the objective measure. Future studies should determine the clinically important difference for both the NFOG-Q and the FOG Ratio in the same subjects.

Previously a handful of small rehabilitation studies focused on improving FoG have had mixed results. A study of a bike-walking device reported reduced FoG in some, but not all, people with FoG³⁶. Likewise, a study of 20 people with PD practicing dual-tasking on a virtual-reality device while stepping in place on a balance platform reported some improvements in dual-task cognitive and gait measures in people with FoG, but not with the FoG-Q³⁷. Of note, these studies did not have a placebo or control intervention group. Though some positive results have been shown for the effects of dance versus no

intervention on balance in people with FoG^{38,39}, a change in FoG, itself, was not significant in two recent meta analyses on the topic⁴⁰. A recent review⁴¹ on robot assisted gait training for FoG detailed four studies showing beneficial results on FoG but the studies were primarily of low quality.

Dual-task Gait

The effect of ABC-C on dual-task cost on gait speed showed a large effect size (-0.73). The improvement in dual-task cost on gait in people with FoG in our study is consistent with a growing body of evidence that dual-task function can be improved with training and practice in people with PD, as well as healthy elderly control subjects^{42–44}. A short (non-systematic) review recently highlighted the importance of training, rather than avoiding, dual-task situations and recommended the need for larger controlled trials⁴⁵. Subsequently, a large, well-controlled trial assessed the effects of dual-task training in a group of 121 people with PD and found that regardless of how the dual-task training was administered, people with PD improved in other, unique, dual-task situations, thereby suggesting that dual-task performance can be transferred to daily life situations⁴⁵. In this large study however, the subgroup of people with FoG also improved in dual-task cost on gait measures after training but the improvements were not retained as they were in those without FoG⁴⁵.

Balance Impairments

The mini-BESTest score improved a small to moderate amount ($\text{SRM} = -0.45$) with exercise compared to the control education intervention. This improvement was primarily related to improvement in the anticipatory postural adjustment (APA) items in the mini-BESTest ($\text{SRM} = -0.45$), which may be expected since subjects focused on increasing the size and speed of mobility but did not practice postural responses nor standing balance. APAs are known to be more abnormal in people with PD who have FoG compared to nonfreezers, especially under dual-task conditions⁴⁶.

Executive Function

Apart from a moderate effect size in the general SCOPA-COG test, the other executive tests (TMT, Flankers and Stroop) only showed small effect size. It is unclear whether potential improvements did not transfer to the paper/computer cognitive tests or because the tests were not sensitive enough to detect small changes over 6 weeks of practice. In fact, subjects were able to progress in the difficulty of their cognitive challenges during the agility training as detailed in Appendix I. Two earlier systematic reviews on the topic of exercise reducing cognitive dysfunction in PD^{47,48} reported a handful of studies suggesting improved cognition after exercise, but reported evidence of reporting and selection bias; variability on dosing, timing and intensity of the exercise; and overall varying quality of studies. However, both of these systematic reviews suggested that while the evidence was not strong, there were positive trends worth future trials given the impact of cognitive dysfunction on people with PD, their caregivers and the costs of care⁴⁹.

Brain Connectivity

The change in neural connectivity between SMA and PPN, although with only 13 people, showed the largest SRM at 0.97. A power analysis showed that we would achieve 80% power to detect this difference in a similar, cross-over trial with 34 participants (17 in each group), and 90% power with 46 participants. Here, we focused specifically on two regions of interest because our previous studies demonstrated reduced structural connections as well as increased functional connectivity between right SMA and PPN in freezers compared to non-freezers or control subjects^{9,10}. Our a priori hypothesis was that the abnormally increased functional connectivity between right-sided SMA and PPN in people with FoG was maladaptive and could be reduced with exercise, associated with a reduction in FoG. A larger study should determine whether these changes in connectivity between specific brain regions is associated with extent of FoG reduction or improvement of dual-task cost.

Previous studies have also shown changes in brain functional connectivity and functional imaging with exercise in people with PD^{50–54}, but not specifically in people with FoG and not in the brain circuitry we investigated here. For example, forced-rate, lower-extremity pedaling over eight-week showed significantly increased functional connectivity between the primary motor cortex and the ipsilateral thalamus that was retained for four weeks after exercise in people with PD^{50,55}. This change in functional connectivity was correlated with change in pedaling rate, providing a plausible mechanism for efficacy of high-rate exercise for bradykinesia. Results of our mobility-cognitive agility training program also agree with other studies in people with PD looking at the effects of dual-task training on brain activity. A study comparing treadmill training versus treadmill training while using virtual reality to avoid obstacles, considered to be a dual-task condition, showed different effects on brain activity after each intervention. Specifically, brain activity using fMRI mental imagery showed that only the group who practiced walking with virtual reality showed lower activation in frontal brain regions after training⁵³, consistent with more automatic, less cortical control. However, this study did not measure functional network connectivity or consider FoG or cognitive changes.

The current study has several limitations. The small sample size, specifically, only 13 subjects with rsfMRI before and after both interventions. Although we consider it a strength that we tested in the Off levodopa state to better reflect FoG, future studies should consider testing participants both Off and On levodopa. Another limitation is measuring FoG with a questionnaire and a turning task in the laboratory. Since FoG is very context-dependent, quantifying FoG under natural, daily living situations with continuous monitoring may provide more sensitive measures of change. Heterogeneous group exercise classes may not be as effective as grouping people with PD according to disease severity or freezing status. Although an effort was made to match the ABC-C Exercise and control Education groups in minutes per week of intervention, some of the education protocol involved relaxation practice at home, so while the dose might match between conditions, the overall contact time with staff was not equal and compliance was lower with the meditation at home. Exercise required 3 in-person visits per week while Education required just 1 visit per week which may have contributed to the higher dropouts during exercise. The lack of a washout period may have been a limitation and this may have influenced the variability of the results.

However, we did not expect a strong after-effect after such a short intervention. A 6-week intervention for complex gait and balance disorders in a chronic disease may be too short. In fact, reduction of falls with exercise in PD appears to require at least 6 months of exercise⁵⁶. Finally, while our overall dropout rate was 17%, most of the drop outs occurred during the exercise portion of the study. While the Exercise first group had lower MoCA scores than the Education first, we did not find any relationship regarding lower cognition relating to higher drop outs. Specifically, the 2 that dropped out from Exercise first had a mean MOCA score of 27.5 and the 6 that dropped out from the Education first group had a mean MoCA score of 25.2. The mean of the people who did not drop out was very similar; Exercise first = 26.5 and Education first = 23.9.

In conclusion, the ABC-C for people with PD and FoG is a practical, feasible group exercise program that has potential to improve balance, dual-task cost, and brain connectivity. Whether the ABC-C is effective for FoG in particular is still not clear, and perhaps a longer trial (i.e., six-month) and/or added cueing-based exercise^{57,58} is needed. Overall, more work with longer, larger trials is needed to determine the potential for rehabilitation to improve FoG in Parkinson's disease.

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Appendix 1:: Progression of ABC-C Exercise Intervention

Exercises are divided into three levels to provide an incremental progression of various activity tasks, with increasing levels of motor or cognitive challenge. Each activity was systematically progressed from beginning to intermediate to advanced levels by challenging with: a) dual-tasking by divided attention with secondary cognitive tasks, b) response inhibition such as go-no go commands and switching commands quickly, c) limiting visual cues with focus on self-initiated movements, (d) increasing the length, complexity, and novelty of whole body movement sequences, and (e) increasing repetitions, speed, amplitude, resistance, or balance requirements.

Station 1: Gait

Task: Walk over-ground in long hallway with emphasis on big steps and big arm swing				
	Support	Speed	Focus on big steps	Cognitive task
Level 1	Poles	Comfortable pace	Verbal cues	None
Level 2	Poles	Increase by 5%	1 lb ankle weights	Dual-task*

Task: Walk over-ground in long hallway with emphasis on big steps and big arm swing				
Support	Speed	Focus on big steps		Cognitive task
Level 3	No Poles	Increase by 5%	2 lb ankle weights	Switching (alter attentional focus)

Station 2: Functional skill training

Task: Therapeutic modules of PWR!Moves®: A functional skill training program				
*Basic 4 Skills: Antigravity extension (PWR! Up), weight shifting (PWR! Rock), axial mobility (PWR! Twist), transitions (PWR! Step)				
Goal	Positions	*Basic 4 Skills	Repetitions (reps)	
Level 1	<ul style="list-style-type: none"> Activate / High effort for bradykinesia 	<ul style="list-style-type: none"> Prone / All 4's / Standing 	<ul style="list-style-type: none"> All four skills <u>repeated</u> in each position 	<ul style="list-style-type: none"> 10–20 reps each skill per position Max 190 reps
Level 2	<ul style="list-style-type: none"> Position Flows for incoordination and balance 	<ul style="list-style-type: none"> Prone / All 4's / Standing 	<ul style="list-style-type: none"> All four skills <u>linked</u> together in each position 	<ul style="list-style-type: none"> 10 reps per flow per position Max 120 reps
Level 3	<ul style="list-style-type: none"> Vertical Flows for floor to stand (task-switching) 	<ul style="list-style-type: none"> Prone / All 4's / Standing 	<ul style="list-style-type: none"> All three <u>positions</u> <u>linked</u> together for each skill 	<ul style="list-style-type: none"> 10 reps per skill per position Max 120 reps

Station 3: Lunges

Task: Perform multidirectional lunges with good form. Focus on large steps, multi-directional, clock stepping lunges. Always prioritize form over size of step.				
	Sequence	Visual Cues	Support	Cognitive task
Level 1	Clockwise (with Go/No-Go)	Rubber disc	Chair	None
Level 2	Random callout (with Go/No-Go)	No cues	Pole	Dual-task*
Level 3	Incongruent <ul style="list-style-type: none"> Opposite Response STROOP board 	No-body glasses	None	Switching (alter attentional focus)

Station 4: Agility

Task: Move through a determined agility course with memorized sequences, turns, narrow spaces, lateral stepping over obstacles, and changing directions.		
	Speed	Cognitive Task
Level 1	Comfortable	None
Level 2	Timed	Dual-Task*
Level 3	Faster and timed (while safe)	Switching (Alter attentional focus)

Station 5: Boxing

Task: Perform basic punches with emphasis on power of punch and trunk rotation. This activity is done in pairs.			
	Response Inhibition	Hand weights	Plane of movement
Level 1	Random 'stop'	None	Stationary
Level 2	Opposite arm than called	1 lb	Forward, lateral and backward stepping
Level 3	Conflict Resolution (visual cue vs. auditory cue)	2 lb	Circle Backwards

Station 6: Adaptive Tai Chi

Task: Therapeutic modules of the Tai Ji Quan: Moving for Better Balance program.		
	Activity	
Level 1	<ul style="list-style-type: none"> Ankle sway Pelvic rotation Stepping with an imaginary ball motion Sit-to-stand, stand-to-sit 	
Level 2	<ul style="list-style-type: none"> Ankle sway with "Butterfly" movement patterns Mirror image push-pull Sit-to-stand, stand-to-sit Multidirectional stepping exercises 	
Level 3	<ul style="list-style-type: none"> From ankle sway, to pelvic rotation, to stepping (Forward "Part Wild Horse's Mane") Multidirectional stepping exercises Stepping with forms around a chair (Sideways "Part Wild Horse's Mane", "Repulse Monkey") Reactive balance recovery exercises 	

* Dual-task, choose from:

- Conversing with neighbor/instructor
- Counting backward or forward by 1's, 3's, 7's
- Listing as many states and/or capitals as possible
- Counting number of steps in a given distance and reduce

- Listing girls/boys names starting with a letter of the alphabet
- Listing as many fruits/veggies as you can
- Simple arithmetic problems, answer > or < 10

Appendix 2.: Resting State Functional Connectivity Methods

Imaging data were acquired using a 3.0 T Siemens Magnetom Tim Trio scanner with a 12-channel head coil. We acquired two 10-minutes runs, providing a total of 20 minutes of resting state data for each subject in the study. Participants were instructed to lie still and keep their eyes open. The rsfMRI scan used a gradient-echo echo-planar imaging sequence (TR = 2500 ms, TE = 30 ms, FA = 90°, 3.8 mm³ voxels, 36 slices with interleaved acquisition, FOV = 240 × 240 mm).

All functional images were preprocessed in an identical method to best alleviate known types of artifacts^{35,36,37}. Connectivity preprocessing followed prior methods³⁸. These steps included 1a) a temporal band-pass filtering (0.009 Hz < f < 0.08 Hz) and, 1b) spatial smoothing (6 mm full width at half maximum). All data were computed with and without smoothing; unless otherwise stated, all results reported were drawn from the no smoothing condition, 2) regression of six parameters obtained by rigid body head motion correction, 3) regression of the whole brain signal averaged over the whole brain, 4) regression of ventricular signal averaged from ventricular region of interest (ROI), and 5) regression of white matter signal averaged from white matter ROI. Regressions of the first order derivatives from steps 3–5 were also included in the correlation preprocessing. These preprocessing steps are thought to best reduce variance that is unlikely to reflect neuronal activity³⁹. In an effort to account for inter-acquisition subject motion that could potentially be problematic for correlation analysis, an additional motion correction step was implemented⁴⁰.

Motion Correction.

In an effort to account for inter-acquisition subject motion, an additional motion correction step was implemented as described by Power and colleagues. This method, titled framewise displacement (FD), calculates a time series of volume-to-volume motion from the movement measures created by the aforementioned rigid body motion correction. This is calculated for all six parameters by the equation $FD_i = |d_{ix}| + |d_{iy}| + |d_{iz}| + |\alpha_i| + |\beta_i| + |\gamma_i|$, where $d_{ix} = d_{(i-1)x} - d_{ix}$, (the same holds true for the other five parameters $[d_{ix} d_{iy} d_{iz} \alpha_i \beta_i \gamma_i]$). Essentially, this formula sums the absolute values of the volume-to-volume changes in six directions. The rotational measures were first converted to millimeters by calculating surface displacement on a sphere of radius 50mm, which is the approximate distance from the cerebral cortex to the center of the head. This method ‘scrubs’ the data by removing any volume that exceeds a set threshold (in this case 0.5mm) from the time series. The correlation analysis was performed on the remaining concatenated volumes. If greater than 50% of the functional volumes (>150 out of 300) exceeded the threshold, participants were excluded from analysis. Of twenty people who underwent imaging, 7 were excluded due to poor data quality.

Appendix

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Appendix 3 Figure:

Association between FoG Ratio at baseline and delta for the Education (A) and ABC-C (B) interventions.

Appendix

Appendix 4:

Mean and SD of the delta for each outcome measures. Treatment (exercise or education), order (Exercise and education, or education and exercise), and period (Exercise or education first) effects are reported.

Measurement	Baseline		After Education		After Exercise		Treatment		Order		Period	
	Mean	SD	Mean	SD	Mean	SD	t	p	t	p	t	p
<i>Freezing</i>												
NFOGQ	11.98	6.94	11.46	7.66	11.49	8.01	2.20	0.03	1.43	0.16	0.61	0.54
FOG ratio (%)	1.93	1.99	1.71	1.95	1.54	1.69	0.73	0.47	0.29	0.78	0.45	0.65
<i>Perceived</i>												
PDQ-39 Total	20.08	11.55	19.82	9.60	20.05	11.25	0.58	0.57	1.32	0.19	1.30	0.20
ABC scale	74.90	16.99	75.44	19.57	73.19	16.74	0.90	0.37	0.39	0.70	0.25	0.81
MDS-UPDRS Part II	17.03	7.40	16.30	6.54	16.54	8.10	1.01	0.32	0.70	0.49	2.24	0.03
<i>Clinical</i>												
MDS-UPDRS Part III	46.36	12.97	45.90	11.83	45.16	11.36	0.29	0.77	1.54	0.13	0.72	0.48
PIGD	6.38	2.98	5.55	3.16	5.32	3.47	0.70	0.49	1.13	0.26	0.35	0.73
Mini-BESTest Total	17.21	5.43	18.33	6.16	18.51	5.41	1.97	0.05	0.69	0.49	1.97	0.05
<i>Gait objective</i>												

Measurement	Baseline		After Education		After Exercise		Treatment		Order		Period	
	Mean	SD	Mean	SD	Mean	SD	t	p	t	p	t	p
<i>DT Gait speed (%)</i>	-18.43	12.37	-14.90	10.58	-9.73	10.13	4.32	0.00005	0.24	0.81	0.40	0.69
DT Stride length (%)	-13.55	7.67	-10.93	12.67	-8.01	9.99	1.65	0.10	0.67	0.50	0.07	0.94
DT Cognitive accuracy (%)	-6.86	12.36	-0.35	26.34	-0.76	14.74	1.30	0.20	0.62	0.54	1.40	0.17
<i>Cognitive</i>												
SCOPA-COG	26.95	5.49	29.00	6.49	28.73	6.13	0.10	0.92	0.91	0.37	1.47	0.15
Stroop Interference	3.03	0.94	2.75	1.12	2.70	0.73	0.19	0.85	0.67	0.51	1.90	0.06
TMT B/A	1.77	0.92	1.52	0.53	1.67	0.89	1.24	0.22	1.28	0.20	1.22	0.22
Flankers	8.02	0.84	8.09	0.92	8.06	0.97	0.71	0.48	0.37	0.71	0.54	0.59
<i>rsfMRI</i>												
<i>R SMA-PPN</i>	0.037	0.207	-0.051	0.143	-0.148	0.173	1.82	0.08	1.1	0.29	0.09	0.93
<i>L SMA-PPN</i>	-0.070	0.181	-0.057	0.118	-0.038	0.161	0.85	0.85	0.43	0.67	0.48	0.64

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Figure 1:
Study design

Figure 2:
Consort diagram

Figure 3: Mean (and SEM) over the three time-point in the 2 groups (exercise first and education first) and bar graphs (Mean±SEM) of the delta for: A) NFOG-Q, B) FoG Ratio, C) Dual-task cost on gait speed, and D) SMA-PPN Connectivity.

Table 1:

Subjects characteristics

Characteristic	Exercise first				Education first			
	Enrolled (N=25)		Completed (N=23)		Enrolled (N=21)		Completed (N=19)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
<i>Height</i>	173.8	11.2	174.7	10.2	176.2	8.4	176.7	8.5
<i>Weight</i>	80.0	15.5	81.5	15.1	79.9	14.1	80.3	13.0
<i>Age</i>	68.2	5.2	68.2	5.4	69.1	9.5	68.5	9.1
<i>Disease duration</i>	7.3	4.3	7.5	4.3	9.7	6.0	9.9	6.2
<i>MDS-UPDRS Part III</i>	44.9	11.8	43.1	10.2	50.0	14.3	50.3	15.1
<i>PIGD</i>	6.4	3.2	5.8	2.4	7.1	3.4	7.1	3.5
<i>Hoehn & Yahr</i>	2.4	0.7	2.2	0.5	2.6	0.9	2.5	0.8
<i>MoCA</i>	26.6	3.0	26.5	3.1	24.3	4.2	23.9	4.3

Table 2:

Mean and SD of the delta for each outcome measures. Effect sizes (SRM) and confidence interval (95% CI) are reported. Effect sizes larger than ± 0.4 are in bold.

Measurement	Delta Education		SRM	SRM 95% CI		Delta Exercise		SRM	SRM 95% CI	
	Mean	SD	Education	Low	High	Mean	SD	Exercise	Low	High
<i>Freezing</i>										
<i>NFOGQ</i>	0.41	3.51	-0.12	-0.43	0.20	-1.41	3.33	0.42	0.08	0.76
<i>FOG ratio</i>	-0.37	1.86	0.23	-0.09	0.54	-0.06	1.49	0.04	-0.29	0.36
<i>Perceived</i>										
<i>PDQ-39 Total</i>	0.24	4.88	-0.22	-0.55	0.12	-1.03	6.70	0.02	-0.32	0.35
<i>ABC scale</i>	2.11	16.83	-0.13	-0.45	0.20	-1.25	11.65	0.11	-0.21	0.44
<i>MDS-UPDRS Part II</i>	0.39	3.80	-0.12	-0.45	0.21	-0.92	3.77	0.24	-0.09	0.57
<i>Clinical</i>										
<i>MDS-UPDRS Part III</i>	-1.22	7.76	0.16	-0.15	0.46	-0.38	7.56	0.05	-0.27	0.37
<i>PIGD</i>	-0.49	2.18	0.22	-0.09	0.53	-0.84	2.37	0.35	0.02	0.68
<i>Mini-BESTest Total</i>	-0.17	3.21	0.05	-0.25	0.36	1.51	3.37	-0.45	-0.78	-0.11
<i>Gait objective</i>										
<i>DT Gait speed (%)</i>	-1.74	7.59	0.23	-0.15	0.55	7.07	9.63	-0.73	-1.12	-0.34
<i>DT Stride length (%)</i>	0.34	11.08	-0.03	-0.09	0.29	4.24	8.70	-0.49	-0.85	-0.12
<i>DT Cognitive accuracy (%)</i>	6.24	24.36	0.20	-0.25	0.52	-0.60	15.56	-0.03	-0.35	0.30
<i>Cognitive</i>										
<i>SCOPA-COG</i>	1.00	3.55	-0.28	-0.60	0.04	1.30	2.86	-0.45	-0.79	-0.11
<i>Stroop Interference</i>	-0.06	0.59	0.09	-0.22	0.41	-0.15	0.7	0.22	-0.12	0.55
<i>TMT B/A</i>	0.016	0.78	-0.02	-0.34	0.30	-0.15	0.64	0.23	-0.11	0.57
<i>Flankers</i>	-0.08	0.82	0.10	-0.22	0.41	0.04	0.75	-0.05	-0.39	0.28
<i>rsfMRI</i>										
<i>R SMA-PPN</i>	-0.037	-0.16	0.24	-0.37	0.83	-0.149	-0.15	0.97	0.29	1.62
<i>L SMA-PPN</i>	0.028	-0.2	0.14	-0.73	0.46	0.003	-0.16	0.02	-0.56	0.53