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Inhibition, Executive Function, and Freezing of Gait

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Abstract

Background—Studies suggest that freezing of gait (FoG) in people with Parkinson's disease (PD) is associated with declines in executive function (EF). However, EF is multi-faceted, including three dissociable components: inhibiting prepotent responses, switching between task sets, and updating working memory.

Objective—This study investigated which aspect of EF is most strongly associated with FoG in PD.

Method—Three groups were studied: adults with PD (with and without FoG) and age-matched, healthy adults. All participants completed a battery of cognitive tasks previously shown to discriminate among the three EF components. Participants also completed a turning-in-place task that was scored for FoG by neurologists blind to subjects' self-reported FoG.

Results—Compared to both other groups, participants with FoG showed significant performance deficits in tasks associated with inhibitory control, even after accounting for differences in disease severity, but no significant deficits in task-switching or updating working memory. Surprisingly, the strongest effect was an intermittent tendency of participants with FoG to hesitate, and thus miss the response window, on *go* trials in the Go-Nogo task. The FoG group also made slower responses in the conflict condition of the Stroop task. Physician-rated FoG scores were correlated both with failures to respond on *go* trials and with failures to inhibit responses on *nogo* trials in the Go-Nogo task.

Conclusion—These results suggest that FoG is associated with a specific inability to appropriately engage and release inhibition, rather than with a general executive deficit.

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CONFLICT OF INTEREST
The authors have no conflicts of interest to report.

Keywords

Parkinson's disease; Freezing of Gait; Inhibition; Executive Function; Conflict Resolution

INTRODUCTION

Freezing of gait (FoG) is a serious problem for many people with Parkinson's disease (PD). It is a leading cause of falls, has a significant impact on quality of life, and is associated with mortality in PD. FoG is defined clinically as "a brief, episodic absence or marked reduction of forward progression of the feet despite the intention to walk" [1], and it is often described by patients as feeling as if their feet were "glued to the floor" when they try to walk. The prevalence of FoG increases with disease duration, with FoG occurring in 60% of patients after 10 years of PD and 80% after 20 years [2].

FoG episodes may be provoked by situations that are mentally or emotionally challenging [3] or by engaging in secondary tasks [4]. However, the relationship between FoG and mental function is not clear or straightforward. It is not sufficient to posit that FoG results from attentional deficits, because FoG often occurs when patients are paying full attention to their gait. Furthermore, FoG is not associated with orienting or alerting aspects of attention as measured by the Attention Networks Task [4] [5].

Numerous studies have suggested that FoG is associated with deficits in executive function (EF)[4] [6] [7] [8]. However, EF is a broad term encompassing a wide array of capacities. It is not yet clear which specific executive deficits are particularly associated with FoG or why. Prior work has looked for evidence of association between FoG and one or more aspects of EF [9] [10][11], but none has explored the relationship of FoG to EF in the context of a previously validated structure of EF subcomponents.

Miyake and colleagues [12] proposed a structure that divides EF into three components: Inhibition of Prepotent Responses (Inhibition), Mental Set Shifting (Shifting), and Information Monitoring and Updating (Updating). All three of these components can be affected by PD [13] [14] [15], but it is not known whether any of them is specifically related to FoG. We hypothesized that the EF most strongly associated with FoG would be inhibitory control, because we recently found that PD patients with FoG showed loss of white matter fibers between the midbrain locomotor area (PPN) and right-sided Cortical Area 8, shown to be important for response inhibition [16].

Furthermore, we have found that PD participants with FoG have abnormal postural preparation prior to a voluntary or involuntary postural step initiation [17]. Specifically, they often initially shift their weight onto the leg they will step with and then shift back to the other leg, sometimes repeating this alternating postural adjustment several times, which leads to a delayed step onset. This abnormal posture-gait coordination suggests that participants with FoG may fail to appropriately control and release inhibition of the postural weight shift or the step, so that the two are not functionally integrated into a cohesive motor program. Because coordination of forward stepping with lateral weight shifts continues to be important during ongoing walking (and may be even more salient when passing through

tight spaces or turning), this same causal mechanism could apply to freezing in all kinds of situations.

To determine which EF component is most strongly associated with FoG, we asked adults with Parkinson's disease (with and without FoG) and age-matched healthy adults to complete a battery of cognitive tasks that were each chosen to be primarily indicative of one of the three EF components (Inhibition, Shifting, and Updating).

MATERIALS AND METHODS

Participants

Our 44 participants included 28 adults who were diagnosed by movement disorder neurologists as having idiopathic PD and 16 healthy, age-matched adults (HC). See Table 1 for clinical details. Participants with PD were recruited from the Parkinson's Center of Oregon at Oregon Health & Science University (OHSU) and the Portland Veterans' Administration Medical Center. Healthy participants were recruited through OHSU's online participant recruitment service and at public lectures given by the investigators. All participants signed an informed consent form approved by OHSU's Institutional Review Board. Exclusion criteria were: dementia (Score < 18 on the Montreal Cognitive Assessment; MOCA [18]), other neurological diseases, vestibular disorders, musculoskeletal gait impairment, and inability to stand and walk for 20 minutes. We also excluded participants with tremor-dominant PD symptoms because we wanted to match the participants on aspects of PD apart from FoG. Parkinsonian medication generally reduces FoG. Testing was therefore performed in the morning, when participants were in a practical OFF state, without antiparkinsonian medications overnight. Participants with PD were assigned to the FoG group (FR) or the non-FoG group (NF) depending on their score on the New Freezing of Gait Questionnaire (NFOGQ) [19]. Subjects with a score of 0–2 were assigned to the NF group, and subjects with a score of 7 or higher were assigned to the FR group.

Demographic and Clinical Features of Participants

Fifteen participants in the FR group, 13 participants in the NF group and 16 participants in the HC group completed the protocol. The average ages of the participant groups did not differ (FR = 67.1, NF = 65.3, HC = 66.6 years; FR vs NF: p=.44; NF vs HC: p=.62). The number of years of education past high school was also not different across groups (FR = 5.7, NF = 4.8, HC = 4.9; FR vs NF: p=.26; NF vs HC: p=.92). The participants in the PD groups were primarily male (FR = 12m/2f, NF = 12m/3f) while the participants in the HC group included more females (6m/10f). Clinical differences between PD groups are shown in Table 1. There were no significant differences between the FR and NF groups in MOCA score or side of disease onset. However, participants in the FR group had longer disease duration and more severe PD, based on their motor symptoms on the Unified Parkinson's Disease Rating Scale (UPDRS III) and on their Hoehn & Yahr Stages [20]. Therefore, it was important to account for disease duration and disease severity in the statistical analysis of the results.

Procedure and Measures

After explaining the study and obtaining consent, experimenters administered the MOCA to screen for dementia, the motor section of the UPDRS to quantify disease severity, and the NFOGQ to assess severity of freezing. Participants were then videotaped while turning in place for 2 minutes (360 degrees to the right, then 360 degrees to the left, and so on until the time was up). Finally, participants performed a battery of cognitive tasks that included three tests measuring each of the three components of EF.

The turning videos were created to supplement the self-report measure of freezing with an objective measure that we hoped would be at least as sensitive as the NFOGQ. The video files were stored on a secure database, with file names that did not reveal the subjects' self-reported freezing status. Three different movement disorders neurologists watched the videos independently and rated each on a scale from 0 (absent) to 4 (severe with risk of fall). Example videos from one participant with each score may be found online. The three sets of physician-rated FoG scores from the videos were first examined for inter-rater reliability. The correlation between the scores assigned by Rater 1 and Rater 3 was .96, while the scores assigned by Rater 2 only correlated around .80 with the scores assigned by the other, more experienced raters. Therefore, the scores from Raters 1 and 3 were averaged without the data from Rater 2 to obtain a physician-rated FoG score for each participant.

The cognitive tasks are listed and categorized in Table 2, described briefly below, and described in detail in Appendix A. Each task took about 5 minutes. Computerized tasks were programmed in Microsoft PowerPoint, Matlab, and the Psychology Experiment Building Language (PEBL) [21]. Other tasks were administered with auditory or paper stimuli and oral responses. Because performance could be affected by fatigue, participants were tested in a consistent order (specified in Table 2); after every three tasks (one from each EF category) participants had a 5-minute break. Before EF testing, we administered a visuospatial attention test as a control task which should not be different between FR and NF groups [22]

Inhibition

The Conflict condition of the Stroop task [23] assesses participants' ability to inhibit their dominant tendency to read words in the context of instructions to instead name the colors in which the words are written. The Go-Nogo task [24] assesses participants' ability to respond quickly to *go* cues while withholding responses to *nogo* cues. The Flankers task [25] assesses participants' ability to respond quickly to visual cues while ignoring visual distractors.

Shifting

The Plus-Minus Task [26] compares the average time to complete addition problems and subtraction problems when they are presented in blocked conditions versus alternating conditions. The number of perseverative errors in the Berg Card Sorting Task (BCST) [27] reflects participants' ability to detect rule changes and act accordingly. The Trail-Making task [28] compares the amount of time it takes participants to connect numbers in sequential order with the time it takes to connect an alternating sequence of letters and numbers.

Updating

The Backward Digit Span [29] is the longest series of digits that a participant can repeat back in reverse order from how the numbers were presented. In the Letter Memory Task [30], participants have to keep track of the last 3 letters they saw, during a serial presentation of 5–10 letters. The Random Number Generation task [31] assesses participants' ability to spontaneously generate number sequences with a balanced frequency of digits.

Visuospatial attention

Mackworth's sustained attention test [22] requires participants to watch a moving cursor and report any deviations from its assigned path.

Statistical Analysis

Between-group comparisons—For each of the 10 cognitive tests, we conducted one-tailed independent-groups t-tests to test the hypotheses that (1) NF would perform worse than HC participants, and (2) FR would perform worse than NF participants. We did not correct for multiple comparisons because that would have increased the risk of false negatives (type II errors) [32]. Our aim was to determine which measures yielded significant results and which did not, so we could compare group performance among the three EF subcategories. Because our NF and FR groups differed in disease severity and duration, it was important to test whether the observed differences in cognition were merely due to these differences. We therefore followed significant results with an additional test comparing residuals from linear models incorporating disease duration and UPDRS score.

Within-group comparisons—We tested for a positive Spearman's correlation between deficits on each of the tests and physician-rated FoG from the turning videos. We followed each significant correlation with an additional test to determine whether the relationship remained significant after controlling for UPDRS score and disease duration, using partial correlation.

RESULTS

Physician Ratings

Out of the 15 subjects classified as FR based on their NFOGQ scores, only one had a score of 0 in the physician ratings of his turning video. Two others had scores of .5, indicating that one physician observed freezing and the other did not. There was also one subject with a score of .5 in the NF group. There was very good agreement between the two physician ratings, with a Pearson's correlation coefficient of .97.

Cognitive Differences Between Participant Groups

Many of the EF tasks contain subtests that do not themselves reflect EF. On these subtests, performance of FR and NF groups did not differ significantly (Table 3). However, the HC group performed better in some tasks than either the FR or NF groups. Specifically, HC performed significantly better in the reading and color-naming Stroop subtests and made fewer errors in the congruent and neutral Flankers conditions compared to the NF group.

In EF scores, there were significant differences between NF and FR participants only in the tests of inhibition (Table 4). Of particular interest, two measures were significantly different between NF and FR groups but were not different between HC and NF participants: the Stroop Interference score and the Target Miss rate in the Go-Nogo task. Figure 1 shows the individual participant scores for the three measures in which FR and NF were significantly different, grouped by self-reported FoG.

The Stroop Interference score remained significant after controlling for disease duration (p=.02) but not after controlling for UPDRS (p=.16). The number of target misses in the Go-Nogo task remained significant after controlling for both disease duration (p=.0004) and UPDRS (p=.004).

In the Go-Nogo task, RTs were faster overall for false alarms (356 ms) than for hits (405 ms), $F(1,79) = 12.5$, p=.0006, but there was no group RT difference (p=.08) and no group x trial-type interaction (p=.79). Across all three groups of subjects, miss errors were disproportionately more likely after false alarms and less likely after successful Go trials, after correcting for overall prevalence of different trial types. In the FR group only, miss errors were half as likely as expected by chance to occur following a successful inhibition and ten times more likely than chance to occur following another miss. In fact, no subject in the HC or NF group ever missed more than once in a row, whereas six subjects in the FR group did.

Correlation between Physician Rating of FoG and Executive Inhibitory Control in Go-Nogo Task

To support the between-group results based on self-report, we examined the Spearman's correlations of physician-rated FoG with Go-Nogo target misses and false alarms. There were significant correlations between the physician-rated FoG scores and performance deficits in the Go-Nogo task; the correlation between FoG score and percentage of target misses was .61 (p=.0002), the correlation between FoG score and percentage of false alarms was .39 (p=.02), and the correlation between FoG score and total errors (target misses + false alarms) was .43 (p=.01). The scatter plots are shown in Figure 2. The partial correlations after accounting for UPDRS score remained significant, at .49 (p=.02) for target misses, .41 (p=.02) for false alarms, and .43 (p=.01) for total errors. Partial correlations after accounting for disease duration also remained strong at .52 (p=.003) for target misses, .40 (p=.02) for false alarms, and .45 (p=.01) for total errors.

Because even Spearman's correlations can be influenced by a large number of zero values, we also computed the correlations between Go-Nogo errors and physician-rated FoG excluding the subjects with FoG scores of zero. (See the dashed lines in Figure 2.) In this analysis, with N=14, only FoG score correlations with false alarms and total errors remained significant, with rho =0.479, p =0.048 and rho = .51, p=.04 respectively.

DISCUSSION

Summary and Interpretation of Results

The results of this study confirm and extend previous findings relating FoG to EF by demonstrating specific impairments in cognitive tasks requiring engaging and releasing inhibition. In non-EF cognitive tasks such as simple reading, color naming, simple reaction time, and visuospatial attention, there was a tendency for NF participants to perform worse than HC participants, but there was no performance difference between NF and FR participants. In EF cognitive tasks thought to reflect updating working memory and shifting among task sets, there were no significant differences between any of the groups. However, in two of the three tasks targeting inhibitory EF, there were clear differences between the PD groups with and without FoG: FR participants showed deficits in Stroop and Go-Nogo tasks, compared to NF participants. Furthermore, the Go-Nogo difference was supported by correlation with physician ratings of FoG and remained strong when UPDRS scores and disease duration were taken into account.

Response times in the Stroop Conflict condition were significantly different across all three groups. When Conflict scores were corrected for reading and word naming [33], the HC lost their advantage over NF entirely, while the gap between NF and FR remained large and significant. This finding emphasizes the importance of correcting Stroop scores to eliminate non-EF factors before drawing conclusions about EF based on Stroop. Previous results regarding the association between FoG and Stroop have been mixed. Some studies have found associations [6] and others have not; one study that did not find an association between Stroop and FoG used a button-pressing variation on the Stroop task. [8]. Although button-pressing variations of Stroop do require inhibition, the action that must be inhibited is not the highly-automatic response of converting written words to speech. Our result showing that the FR group had more difficulty than the NF group with a classic Stroop task lends support to the hypothesis that FoG is specifically associated with deficits in inhibitory control of automatic responses.

The results from the Go-Nogo task were also supportive of our inhibition hypothesis, in a surprising way. While there was a correlation between physician-rated FoG and false alarms (suggesting a straightforward failure of inhibition), the most striking result was a significant difference between groups in the target misses; participants in the FR group demonstrated intermittent failures to respond within the 1000-ms response window, as if they could not release their inhibition once it was recruited. The mean RT and SD for this task were 416 and 103, indicating that target misses (RT>1000ms) were more than five SD above the mean and could be considered as “freezing” responses [34].

A number of alternative explanations for this result can be ruled out, due to control conditions we included. First, note that the NF and FR groups did not differ in SRT. Therefore, the larger number of target misses were not due to slower overall responses in the FR group. Note also that there was no significant difference between groups in the amount of slowing in the Go-Nogo task relative to the SRT task, indicating that FR groups did not adopt a more conservative strategy. Furthermore, as shown in Table 3, there was no

difference between NF and FR groups in visuospatial attention, consistent with previous findings. [4,8]

These results suggest that the primary problem in FoG may be not a globally insufficient inhibition (as in a threshold set too low), but rather an insufficient ability to quickly discern whether, in a particular context, inhibition is needed or not, and to release no-longer-needed inhibition. This interpretation is consistent with prior studies indicating that failure to release proactive inhibition can delay responses [35,36]. Such an impairment could make it difficult to release a stepping program after completion of an anticipatory postural adjustment, consistent with our previous findings [17].

Flankers, the third task we selected to test inhibitory control did not discriminate among any of the groups in our study. Some researchers have previously found increased interference effects in the Flankers task in PD subjects compared to HC [37,38]. However, other studies have found no difference in NF compared to HC subjects [4,8]. Although there are no previous papers comparing simple Flankers performance between PD participants with and without FoG, two studies have found differences between these groups when a Flankers task was embedded in the Attention Networks Task (ANT)[5] [4] [8].

We can think of two possible reasons why Vandenbossche et al. found differences between FR and NF participants in the Flankers effect, while we did not. First, it is possible that the PD participants in the two groups were different in an important way. FoG tends to increase with disease severity, which makes it challenging to match NF and FR groups on severity. Because the UPDRS gives a lot of weight to tremor, one way to achieve a close match on UPDRS scores is to include mainly participants with tremor-dominant PD in the NF group, while including more PIGD-type participants in the FR group. However, PIGD has itself been linked to motor impulsivity [39]; therefore, it is possible that the FR vs. NF differences seen in the ANT were due to differences between PD participants with PIGD and non-PIGD subtypes, rather than being specifically associated with FoG.

Another possible explanation for the difference in findings between the results reported here and those of Vandenbossche et al [4] is that the ANT differs from a simple Flankers test in ways that could be particularly important for participants with PD. The ANT task embeds Flankers stimuli in a task that may or may not include an alerting stimulus, which may or may not contain spatial information. Thus, the context is much more complex than in a simple Flankers task. In the ANT, the conditions are intermixed, so participants need to keep track of multiple task elements at all times. The complexity of a task context may have wide-reaching effects, as we saw in our Go-Nogo task, where the inclusion of Nogo trials influenced the Go trials in that same block. In support of this argument, we observe that overall RTs for Flankers were around 500 ms in the current study, and around 700 ms in the aforementioned ANT task [4].

To try to understand why the FR group would perform differently than the NF group on Stroop and Go-Nogo but not on Flankers, we looked more closely at the different types of inhibition the tests measure. According to Barkley's classification system [40], the Go-Nogo task tests inhibition of prepotent responses, whereas the Flankers task tests interference

control, and the Stroop task combines both kinds of inhibition. Thus, FoG seems to be more strongly related to inhibition of prepotent responses than to interference control, consistent with our proposed causal mechanism.

Inhibition, Conflict Resolution, and Stepping

Successful conflict resolution relies on context-dependent selective inhibition and release of responses; our results are therefore consistent with previous conclusions that impaired conflict resolution contributes to FoG [4] [41]. In a context where multiple actions are possible, it is necessary to inhibit the unintended action(s) in order to carry out the intended act [42]. For instance, in walking, lifting of the stepping leg must be delayed until the weight has been shifted off of the stance leg, but no longer [43]. The kind of inhibition required for assembling a motor program may have more in common with the fast, low-level inhibition tested by laboratory measures of inhibitory control (such as Stroop and Go-Nogo) than with tests of longer-lasting, “behavioral inhibition” or impulsivity as defined by clinical psychologists [44].

Recent evidence from our laboratory supports the importance of inhibition for rapid voluntary and compensatory step initiation in healthy adults [45]. Stepping is delayed when participants shift their body weight in the incorrect direction before shifting it in the correct direction. These weight shift errors are more common in choice reaction time trials than simple reaction time trials, suggesting that failure to inhibit a prepotent response (in a context where multiple responses are possible) leads to errors in postural control and delayed step initiation. In addition, incidence of weight shift errors is correlated with performance deficit on the Stroop interference task, consistent with a relationship between deficits in postural preparation and deficits in executive inhibition. In the presence of other PD-related deficits (such as the loss of automaticity for simple motor patterns), failure to release inhibition of stepping after a weight shift may lead to repeated weight shifts without stepping, resulting in the so called “trembling of the legs” associated with FoG [1, 17].

Possible Extension to Other Motor Blocks

An intriguing hypothesis has recently been put forward claiming that FoG may actually be the most obvious manifestation of a broader underlying motor problem [46]. Emerging evidence indicates that PD patients who experience FoG are also likely to experience a motor block when attempting to execute alternating upper limb movements [46] [47]. The specific task of generating alternating upper limb movements is known to rely on inhibitory control, as well-timed interhemispheric inhibition is necessary in order to achieve regular alternating movement. [48] [49]. Thus, failures of inhibition could be important for upper limb motor block as well as for FoG. However, the inhibition usually discussed in the context of interhemispheric interaction is at the level of the motor and premotor cortices rather than the prefrontal regions normally associated with executive control, so this connection remains speculative.

Neural Links Between Inhibitory Deficits and FoG

At least three brain areas have been associated with both FoG and inhibition: the subthalamic nucleus (STN) of the basal ganglia; the supplemental motor area (SMA) of the frontal cortex, and the pedunculopontine nucleus (PPN) of the brainstem.

Evidence linking the basal ganglia to both FoG and inhibition comes from studies of deep brain stimulation. Some symptoms of severe PD are relieved by stimulation of the STN. However, the connection is far from simple, as STN stimulation at the commonly used frequency of 130 Hz may actually exacerbate FoG, while stimulation at 60 Hz may improve it [50] [51]. Similarly, STN stimulation may either weaken or enhance inhibitory control [52] [53] [13][54]. Therefore, the STN may play a key role in conflict resolution and inhibitory control, and it may also be crucial for FoG.

Evidence that the SMA is important for inhibition comes from direct brain stimulation studies [55] as well as functional imaging [56]. The SMA receives most of its input from the basal ganglia and is thus affected by PD [57]. A recent fMRI study comparing motor imagery to visual imagery found reduced activation in SMA for FR vs. NF participants [58]. Thus, SMA is also implicated in both inhibition and FoG.

A third brain area recently recognized as possibly important for FoG is the PPN. This midbrain region is thought to be important for initiating gait and inhibition of muscle tone [59] and startle responses [60]. Stimulation of the PPN may help reduce FoG [61]. Interestingly, the PPN is the source of a large number of cholinergic cells [60], and acetylcholine deficits have been linked to cognitive decline in PD [62]. In fact, our recent study using diffusion tensor imaging found reduced right-sided white matter connectivity between PPN and right medial frontal cortex, a region previously been shown to be activated in healthy subjects during both initiation and inhibition of voluntary movement [63] [64] [65]. Therefore, the PPN provides another plausible physiological link between inhibition and FoG.

Limitations

Subject matching is always a difficult issue when comparing PD subtypes. We chose not to match on UDPRS because it can lead to a separation between tremor-dominant and PIGD dominant types of PD. Instead, we controlled statistically for severity. We also did not completely match for gender in the groups. For our main comparisons (NF vs FR) the genders were well-matched, but for the comparisons of lesser interest (HC vs NF) there were more women in the HC group than the NF group. This could have affected some of the less-important outcomes; for instance, HC had much faster reading times than NF, which could be due to the greater verbal ability in older women than older men [66].

Another limitation inherent to this kind of study is the interconnectedness of the aspects of EF. Although we used tasks that have been previously validated as reflecting *primarily* one or another aspect of EF, we cannot claim that any of them measures one aspect of EF *exclusively*.

Yet another possible limitation of this study is our use of the classic Stroop test, in which time to correct an answer adds to response time and increases variability. Although the difference in error rates in the conflict condition (6.8% for NF vs 11.6% for FR) was not statistically significant (p=.17), time needed for error correction may still have affected the results.

Conclusion and Future Directions

This study related cognitive deficits to self-reported FoG and to physician-rated FoG severity. Other studies have demonstrated that EF is more strongly associated with FoG than other cognitive functions; this was the first study to specifically investigate the relation of FoG to the three components of EF. The results indicated that FoG in PD was strongly associated with deficits in EF tasks relying on inhibition of prepotent responses and (plausibly) with release of inhibition, but that FoG was unrelated to EF tasks relying on working memory updating or task switching. We hope that our results will help to focus the search for a causal role of cognitive factors in FoG, but there is still a long way to go, because inhibitory control is itself a complex construct. Future studies could look more specifically at the roles of proactive inhibition (a central set prepared in advance) versus reactive inhibition (the stopping or delaying of an action in response to a signal). [67] In addition, recently developed methods may make it possible to directly investigate whether freezing is caused by failure to release inhibition [35,36]. Finally, future studies could investigate whether secondary tasks designed to challenge inhibitory control are more likely to trigger a FoG episode than other kinds of cognitive tasks. This information could be used to develop and improve rehabilitation programs for FoG based on cognitive training and dual-task methods.

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APPENDIX A

Cognitive testing included two measures each of the Inhibition, Shifting, and Updating components of Executive Function, as well as a measure of visuospatial attention.

1. Inhibition (Stroop, Go-Nogo, Flankers)

The Stroop task included three conditions [23]. Before beginning the test, participants were asked to name sample blocks of the colors used (red, blue, green, black, and purple), to assure that their color vision was adequate. Then, in the Color Naming condition, participants were presented with a page of 50 colored blocks and asked to name the colors aloud as fast as they could. In the Word Reading condition, participants were given a list of 50 color names printed in black ink (Times New Roman, 20 point font) and asked to read them as quickly as possible. In the Conflict condition, participants were given a list of 50 color names printed in different colors; they were instructed to inhibit the urge to read the words, and instead to name the ink colors in which the words were printed. The color names used in the second and third conditions corresponded to the ink colors used in the first and third conditions. In all cases, an experimenter monitored performance and instructed participants to correct errors before proceeding. Therefore, errors led to increases in reaction time rather than to a separate error score.

The simplest dependent measures in the Stroop task were the average time per word in each condition, with the Conflict condition representing inhibitory control. In addition, to look at

differences in inhibition uncorrupted by differences in speech motor ability or color recognition, we used an Interference Score based on the work of Golden and Freshwater [33], defined as the difference between the time to complete the Conflict condition and the sum of the times to complete the Color Naming and Word Reading conditions.

The Go-Nogo task is a computerized test of response time and response inhibition [24] [14] [69] [70]. Our version was programmed using the Psychology Experiment Building Language (PEBL) [71] [72] It began with a simple reaction time (SRT) task. The screen displayed one letter at a time for 250 ms (the *go* cue), with interstimulus intervals ranging from 1000 to 2000 ms, and the participant was instructed to press the space bar as fast as possible when a letter appeared. Participants completed 108 SRT trials in six 18-trial blocks. Following the SRT task, participants were informed that the next task would be the same but with one important difference: they were to withhold their response if the letter on the screen was 'X' (the *nogo* cue). They then completed 108 Go-Nogo trials in 6 blocks.

Because we were interested in inhibition not merely as the ability to withhold a response but also as an integral element of response timing (e.g., the ability to withhold a stepping response until the appropriate APA has been prepared), we measured target misses as well as false alarms in the Go-Nogo task. We defined *target misses* as failures to respond within 1000 ms to go cues and *false alarms* as responses to the nogo cue within that same time window [73]. To assess whether and how much participants slowed down their overall responses in consideration of the possible presence of nogo cues (adopting a more conservative strategy), we subtracted mean reaction times in the SRT task from mean reaction times in successful go trials.

The Flankers task is a common paradigm in cognitive psychology for the study of low-level attentional control and inhibition [25]. Our task was implemented in MATLAB using the Psychophysics Toolbox extension [74], following the procedure used by Wylie and colleagues [75]. On each trial, an array of 5 side-by-side stimuli was displayed on a computer screen. The central of the five stimuli, the target, was a 4.0-cm wide × 3.5-cm tall arrow pointing either left or right (with probability .5 of each direction). The two stimuli to the left and right of the target (flankers) were identical to one another and were randomly selected on each trial from three experimental conditions: 1) Congruent: Each flanker was identical to the target; 2) Incongruent: Each flanker was an arrow facing the opposite direction as the target; and 3) Neutral: Each flanker was a diamond. The participant's task was to press a button with his or her left forefinger if the target pointed to the left, and to press a different button with his or her right forefinger if the target pointed to the right. Participants completed 4 test blocks of 48 trials each, with target arrow direction and condition fully counterbalanced. A shorter practice block (30 trials) with analogous composition preceded the test blocks; if it seemed the subject did not understand the task, experimenters would interrupt this practice to clarify and start over.

The dependent measures for the Flankers task were reaction times and errors. If reaction times were slow or error rates were high in the incongruent condition (especially compared with the neutral or congruent conditions), this would indicate a deficit in attentional inhibition.

2. Shifting (Plus-Minus Task, Berg Card Sorting Task, Trail-Making Task)

The Plus-Minus Task has three conditions: blocked addition, blocked subtraction, and alternating addition and subtraction [26]. In the first condition, participants completed 20 addition problems. In the second condition, they completed 20 subtraction problems. In the third condition, they completed 20 arithmetic problems that alternated between addition and subtraction. Stimuli were presented on a sheet of paper, and responses were given orally. In all cases, participants saw a two-digit number followed by either “+3” or “−3”. The dependent measure was the difference between the average time to complete the addition and subtraction problems in the blocked conditions versus in the alternating condition.

The Berg Card Sorting Task (BCST) is a computerized version of the Wisconsin Card Sorting Task, in which participants have to sort cards according to a rule (color, shaper, or number) and detect when the rule has changed [27]. This task was very challenging for our pilot participants, so we used a simplification in which only one rule at a time could ever be correct for any given trial [76]. The task was implemented in PEBL [71]. Participants completed a total of 48 trials. The critical measure we used to assess Shifting ability was the number of perseverative errors – that is, errors in which a participant continued to respond in accordance with an old rule after the rule had changed.

The Trail-Making Test consists of two parts [28] [77]. In the first part, TMT-A, the participant is provided with a piece of paper containing the encircled numbers from 1 to 25 in scrambled locations and is asked to connect the circles in numerical order (beginning with 1) as quickly as possible with a pen. The second part, TMT-B, is similar, but it contains letters and numbers, and the examinee must alternates between them (1-A-2-B, and so forth). An experimenter monitors performance and instructs participants to correct any errors before proceeding, so that errors increase completion time. The time to complete TMT-A is a measure of visual search and movement speed, while the difference in time to complete TMT-B and TMT-A is considered a measure of Shifting.

3. Updating (Backward Digit Span, Letter Memory Task, Random Number Generation)

To test backward digit span, the experimenter says a sequence of digits (0–9) aloud at a pace of one digit per second, and then the participant is asked to repeat the digits back, but in reverse order [29] [78]. The length of the sequence begins at 2 and increases by 1 each time the participant completes a sequence correctly. When the participant makes an error, a different sequence of the same length is presented. If that sequence is also completed incorrectly, the test is over. A participant’s backward digit span is defined as the length of the last sequence completed correctly.

In the standard Letter Memory Task, one letter at a time appears on a computer screen in front of participants, at a standard pace of one letter every 2000 ms [30, 79]. After each letter appears, the participant attempts to say aloud the last four letters that have appeared, in the order they were shown. Thus, after the fourth letter, the task requires dropping the oldest letter from the beginning of the sequence and adding the newest letter to the end of the

sequence. A trial consists of 5 to 10 letters. Pilot testing revealed that even some healthy older adults had trouble with the standard version of this task; therefore, we modified the task so that participants were instructed to recall the last 3 digits instead of 4, with a presentation rate of 1 letter per 2.5s (implemented in Microsoft Power Point) [30]. After three practice trials, all participants completed the same 8 test sequences. To score this task, we counted and summed the errors made at the end of each trial (the last set of 3 letters recited). Thus, the maximum possible number of errors was 24.

In the Random Number Generation task, participants heard a series of computer-generated beeps at 1500 ms intervals [31]. They were instructed to say aloud a number between 0 and 9 every time they heard a beep, and to try to produce a random string of numbers. The experimenter asked participants to avoid saying the same number twice in a row, to avoid ascending or descending strings of numbers, and to use all numbers with the same frequency. Typically, the Random Number Generation task includes several subscores, each reflecting a different kind of error. Because we used this task as a measure of working memory updating, we looked only at how evenly distributed the responses were. Because this aspect of the task requires subjects to update and keep track of what numbers they have already used, it is thought to reflect working memory [12,80]. To compute this score, we calculated the standard deviation of the number of occurrences of each digit. Thus, a perfect distribution with all digits represented equally would have a score of zero, and higher numbers indicate worse (less balanced) distributions.

4. Visuospatial attention

In Mackworth's sustained attention task, the screen showed a large ring made up of 60 small circles [22]. The small circles lit up one at a time, in clockwise order around the large ring, at a pace of 1 circle each s. When one circle lit up, the previously lit one returned to its original empty state. Occasionally (with P = .4) one of the circles was skipped. The participant's task was to press the space bar when that happened. The time window for a response was about 580 ms. The dependent measure was the number of errors. This task was implemented in PEBL [71].

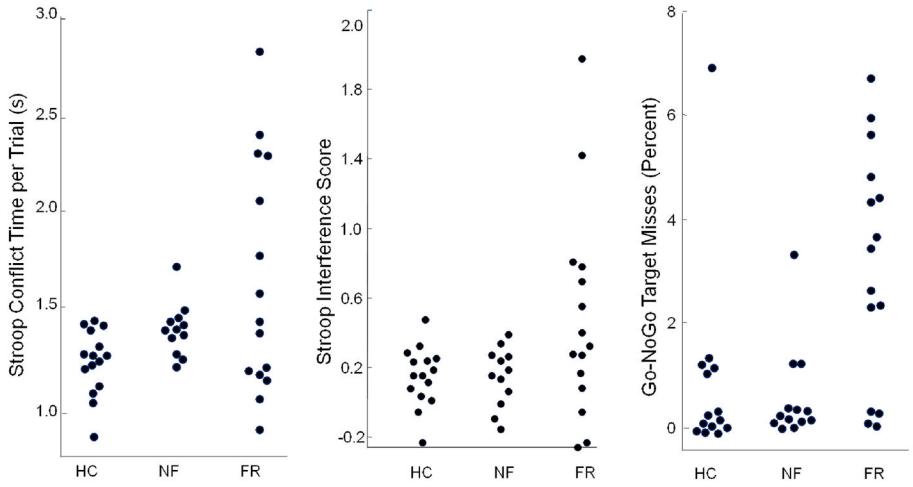

Figure 1.

Individual participant scores for the EF measures in which FR and NF were significantly different. Left plot: Average time to name a color in the Stroop conflict condition requiring inhibition of reading. Center plot: Average time to name a color in the Stroop conflict condition, corrected for both color naming time and reading time. Right plot: Percent of target misses in the Go-Nogo task (failure to respond to a Go stimulus within 1000 ms). Note: all of the points clustered around zero have an actual value of zero. One NF subject's Stroop score was not recorded due to experimenter error.

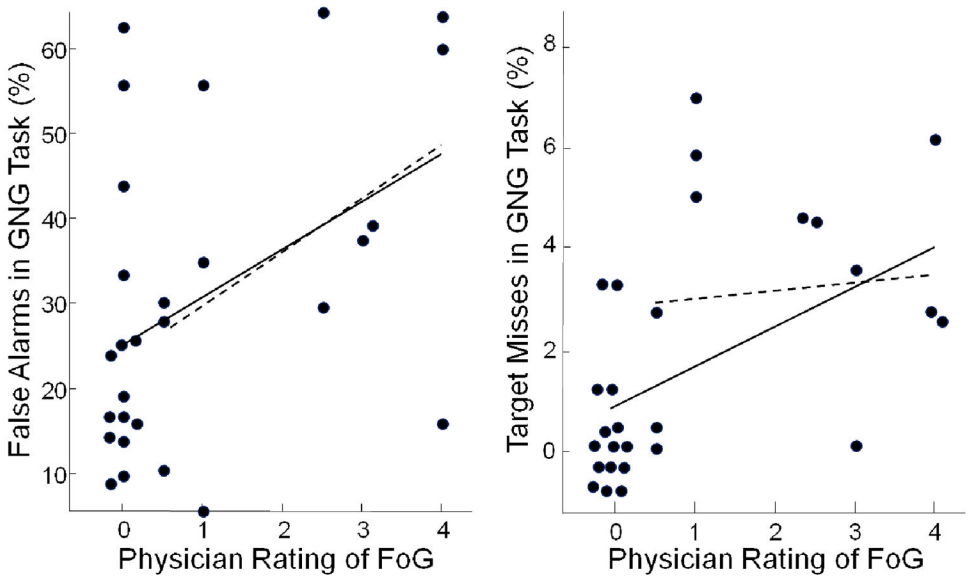

Figure 2.

Correlations between FoG ratings assigned by two physician observers and performance deficits in the Go-Nogo task, with best fitting linear regression lines. Left plot: percentage of false alarms (failure to withhold response to a Nogo stimulus). Right plot: percentage of target misses (failure to respond to a Go stimulus within 1000 ms). Note that all of the points clustered around zero have an actual value of zero. The solid regression lines were computed using all PD subjects, and the dashed lines were computed excluding subjects with a FoG rating of zero.

Table 1

Mean (and standard deviation) values of clinical features of PD participants in OFF state.

	NF	FR	p-value
Disease duration (yrs)	6.5 (4.1)	10.6 (5.5)	.02 *
Side of Onset (R/L/N)	6/6/1	4/8/3	.25
Hoehn & Yahr Stage	2.1 (0.3)	2.7 (0.6)	.007 *
UPDRS III	29.9 (7.1)	36.5 (9.2)	.02 *
MOCA	27.5 (2.1)	26.0 (3.0)	.08
LEDD (mg)	714 (242)	1465 (1245)	.04 †
Physician Rating of FoG	0.2 (0.1)	1.8 (1.5)	.0003 *

HC=healthy control subjects; NF=PD subjects without freezing of gait; FR=PD subjects with freezing of gait; UPDRS III = Unified Parkinson's Disease Rating Scale Part III (motor symptoms); MOCA = Montreal Cognitive Assessment; LEDD = Levodopa Equivalent Daily Dose [68];

* statistically significant ($p<.05$);

† one outlier in the FR group (with LEDD of 13,750 mg) was removed from the LEDD comparison.

Table 2

The tasks chosen to represent each of the three subcategories of executive function.

Executive Function	Cognitive Task	Test Order	How Administered (Stimulus/Response)
Inhibition	Stroop Conflict, [23]	1	Visual/Oral (Paper)
	Go-Nogo [24]	6	Visual/Keyboard (PEBL)
	Flankers Incongruent RT and Errors [25]	8	Visual/Keyboard (Matlab)
Shifting	Plus-Minus Task [26]	4	Visual Oral (Paper)
	Berg Card Sorting Task [27] (BCST)	9	Visual/Touchpad (PEBL)
	Trail-Making Task, B-A [28]	2	Visual/Manual (Paper)
Updating	Digit Span Backward [29]	3	Auditory/Oral
	Letter Memory Task [30]	5	Visual/Oral (PowerPoint)
	Random Number Generation, distribution[31]	7	Auditory (Metronome)/Oral

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Table 3

Mean (and standard deviation) scores on cognitive tasks that do not primarily reflect executive function.

Cognitive Task	HC	NF	FR	p-value (NF vs HC)	p-value (FR vs NF)
Stroop: Reading (ms per word)	452 (62.3)	534 (86.4)	542 (151)	.007 *	.43
Stroop: Color Naming (ms per word)	658 (88.5)	726 (83.7)	788 (203)	.03 *	.14
Go-Nogo: Simple RT (ms)	304 (27.9)	314 (58.8)	312 (44.2)	.28	.54
Go-Nogo: Slowing (ms)	97 (33)	86(30)	102(31)	.60	.91
Flankers: Congruent RT (ms)	479 (70.2)	467 (80.0)	527 (126)	.65	.08
Flankers: Neutral RT (ms)	496 (62.1)	486 (86.8)	551 (132)	.63	.08
Flankers: Congruent Error Rate (%)	0.4 (0.7)	1.5 (1.9)	3.3 (5.0)	.04 *	.10
Flankers: Neutral Error Rate (%)	1.2 (1.9)	3.8 (3.0)	5.0 (8.7)	.008 *	.67
Trail Making Task: Part A (s)	31.1 (9.1)	31.8 (8.77)	42.0 (25.5)	.42	.08
Plus-Minus Task: Addition (s)	28.5 (10.9)	35.0 (10.8)	34.0 (13.4)	.08	.60
Plus-Minus Task: Subtraction (s)	43.5 (20.7)	51.1 (15.8)	45.8 (20.0)	.24	.68
Visuospatial Attention (miss rate)	.24 (.17)	.38 (.26)	.32 (.27)	.06	.74

HC=healthy control subjects; NF=PD subjects without freezing of gait; FR=PD subjects with freezing of gait; RT = Reaction Time; Slowing = difference between Simple RT and RT in successful Go trials.

* statistically significant ($p<.05$).

Table 4

Mean (and standard deviation) scores on EF tests, p-values associated with one-tailed independent-groups t-tests, and Spearman's correlation coefficients relating metrics to clinical FoG scores.

		HC	NF	FR	p-value: HC - NF	p-value: NF vs FR	rho: FoG
	Inhibition						
Stroop	Conflict (ms per word)	1263 (161)	1406 (139)	1811 (813)	.01 *	.04 *	.21
	Interference Score (ms)	152 (170)	148 (170)	481 (603)	.52	.03 *	.11
Go-Nogo	False Alarm Rate (%)	26.7 (13.9)	28.0 (17.0)	32.9 (20.0)	.41	.24	.39 *
	Target Miss Rate (%)	0.7 (1.7)	0.4 (1.0)	3.1 (2.3)	.72	<.001 **	.61 **
Flankers	Incongruent RT (ms)	522 (69.1)	510 (85.2)	558 (138)	.65	.15	.18
	Incongruent Errors (%)	3.0 (4.1)	7.5 (7.2)	5.9 (6.8)	.03 *	.72	.01
	Shifting						
BCST: Perseverative Errors		10.6 (5.5)	9.8 (2.83)	11.6 (5.5)	.70	.16	.19
Plus-Minus Task (s)		10.2 (8.5)	11.5 (8.8)	10.9 (11.9)	.35	.56	.05
Trail-Making Task:	B (s)	60.0 (23.6)	72.9 (28.1)	103.3 (63.5)	.10	.06	.26
	B-A (s)	28.9 (19.8)	41.1 (24.9)	61.3 (49.7)	.70	.09	.13
	Updating						
Backward Digit Span		5.1 (1.23)	5.3 (1.1)	4.5 (1.8)	.71	.07	.14
Letter Memory: Errors		5.0 (4.6)	5.1 (4.6)	6.1 (5.7)	.48	.33	.08
Random Generation (Distribution)		1.7 (.39)	1.4 (.34)	1.6 (.47)	.95	.16	.07

HC=healthy control subjects; NF=PD subjects without freezing of gait; FR=PD subjects with freezing of gait; Interference Score = Stroop conflict naming time - color naming time - word reading time. rho: FoG = correlation with physician-rated FoG during turning;

* statistically significant (p<.05);

** p<.01.