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Cognitive Contributions to Freezing of Gait in Parkinson Disease: Implications for Physical Rehabilitation

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Abstract

People with Parkinson’s disease (PD) who show freezing of gait also have dysfunction in cognitive domains that interact with mobility. Specifically, freezing of gait is associated with executive dysfunction involving response inhibition, divided/switching attention, and visuospatial function. In fact, the neural control impairments leading to freezing of gait have recently been attributed to higher-level, executive and attentional cortical processes involved in coordinating posture and gait rather than to lower-level, sensorimotor impairments. To date, rehabilitation for freezing of gait primarily focuses on compensatory mobility training to overcome freezing events, such as sensory cueing and voluntary step planning. Recently, a few interventions have focused on restitutive, rather than compensatory, therapy. Given the documented impairments in executive function specific to patients with PD who freeze and increasing evidence of overlap between cognitive and motor function, incorporating cognitive challenges with mobility training may have important benefits for patients with freezing of gait. Thus, we propose a novel theoretical framework for exercise interventions that jointly address both the specific cognitive and mobility challenges of people with PD who freeze.
Introduction

Freezing of Gait (FoG) is defined as a “brief, episodic absence or marked reduction of forward progression of the feet despite the intention to walk” 1. FoG affects approximately 26% of those with mild Parkinson’s disease (PD) and 80% with severe PD, and it is one of the most common reasons for falls and dependency 2,3. Thus, although it can occur throughout the course of PD, FoG is more common later in the later stages of the disease. Identifying whether an individual experiences FoG can be completed by: 1) observation during tasks that commonly elicit FoG (e.g. turning in place, short rapid steps 4,5), 2) self-report questionnaire6, or 3) frequency analysis of lower leg trembling with inertial sensors 7-9. Current therapies for PD, including deep brain stimulation and levodopa, are inadequate at treating FoG 10. Currently, the most common rehabilitative approach for helping patients overcome FoG episodes is to teach compensatory mechanisms, such as cueing (for review, see 11). While using external cues can be beneficial, success relies on participants having sufficiently preserved cognitive abilities to consolidate and retrieve these compensatory strategies. Further, the benefits of cues may be transient, as FoG episodes often return after withdrawal of cues 12. Therefore, approaches that also target the underlying dysfunction, i.e. restitutive rehabilitation, may be more effective than compensatory strategies alone for retention of improvements.

Cognitive function - specifically, executive function and attention - is critical for mobility, and rehabilitation interventions aimed at improving cognitive function as well as movement may be particularly beneficial for improving mobility. Indeed, recent work in healthy adults has shown interventions that incorporate cognitive and motor tasks to improve physical and cognitive fall risk factors 13. Integrating cognitive and motor rehabilitation may be especially important for individuals with PD who experience FoG (PD+FoG), as freezing itself may be due to impaired executive function and attention 14-16. However, although cognitive-motor training has begun to be used in healthy older adults and people with PD 17-19, no studies have incorporated FoG-specific cognitive remediation into mobility training. Given the specific and pronounced cognitive and mobility profiles of individuals with FoG, it may be useful to develop targeted rehabilitation strategies to improve functional mobility in this population.
In this paper, we will first summarize how mobility relies on executive, attentional, and visuospatial function. Then, we discuss common models of executive dysfunction and how they are impaired in people with FoG. Finally, we propose a theoretical framework to incorporate focused and specific cognitive challenges into exercise progressions.

**Mobility Requires Cognitive Function**

Early investigations suggested that locomotion was controlled primarily by central pattern generators in the spinal cord and brain stem. While these structures play a critical role in locomotion, converging evidence from behavioral and imaging studies shows that higher-level, cortical structures are also essential for functional gait (for reviews, see 20, 21). For example, intracortical recording in cats demonstrates the critical function of the frontal cortex during gait, particularly during precise stepping22, 23. In humans, brain imaging studies have shown that reduced volume of pre-frontal brain regions (areas which play a critical role in cognitive function) is related to reduced gait performance24. Similarly, transcranial magnetic stimulation over cortical regions, including the supplementary motor area, can alter stepping and step initiation25, 26. Further, a number of recent investigations using mobile brain imaging have shown considerable activity in prefrontal cortical regions related to executive function during gait27, 28.

The role of cognition in functional mobility is illustrated by real-world scenarios. Take, for example, the mental operations required to successfully cross a busy intersection. One must attend to a number of different, often conflicting, stimuli, including walk/stop signs, traffic lights, other pedestrians, and velocities of approaching vehicles. Success requires not only an ability to divide attention, but also the ability to effectively focus attention on particular stimuli while ignoring others. For example, one may have to inhibit a response, such as obeying the walk signal, if other important information is present (e.g. an oncoming car). Attention needs to be divided or switched between, on the one hand, the coordination of balance and gait to step down the curb, and, on the other hand, the dangers of traffic. Visuospatial function is also needed to judge the height of the curb and to estimate time to potential contact of oncoming vehicles. Cognitive dysfunction may lead to an
inability to appropriately respond to such complex situations, resulting in decrements in gait coordination and functional mobility.

Navigating such a scenario is especially challenging to PD+FoG. As will be discussed in the following sections, we believe this is due, in part, to the fact that PD+FoG often have impaired cognitive function compared to PD-FoG 11. These cognitive deficits are inter-related with the motor deficits, and can lead to reduced functional mobility and increased freezing events during complex scenarios such as the one described above.

Models of Executive Function and Attention

In the following sections, we will outline changes in cognition in PD+FoG and describe a framework for the incorporation of relevant cognitive challenges into exercise. For clarity, it may be helpful to briefly review some prominent models of executive function and attention.

Although there are many models of executive function and attention (for review, see: 29); for the purposes of this manuscript, we will summarize Miyake’s model of executive function 30, Posner & Petersen’s model of attention 31, and McDowd’s model of attention 32. Miyake and colleagues define executive function as “general purpose control mechanisms that modulate the operations of various subprocesses and thereby regulate the dynamics of human cognition“. Miyake’s model describes three primary domains of executive function: shifting (shifting back and forth between multiple tasks, operations, or mental sets); inhibition (deliberately inhibiting dominant, automatic, or prepotent responses when appropriate); and updating (updating and monitoring working memory representations). With respect to attention, we draw upon two prominent models described by McDowd 2007 32 and Posner & Petersen 1990 31. McDowd suggests that attention can be parsed into four partially overlapping components: divided, switching, sustained, and selective 32. These components, described in detail below, overlap with some components of Miyake’s model of executive function (see Figure 1). They also overlap with Posner & Petersen’s model of attention 31 that suggests attention is related to three “attentional networks” (executive control, orienting, and alerting). These networks can be assessed by the Attention
Network Test (ANT; 33). The executive control network, defined as resolving conflict among responses, is assessed by the Erikson flankers test embedded in the ANT. Alerting, defined as achieving and maintaining an alert state, and orienting, defined as selection of information from sensory input, are assessed by changes in reaction times in the presence or absence of cues placed above and below the flankers stimuli 33.

Although there is no consensus regarding the independence or overlap of the cognitive domains described above, it is clear that these models are not fully distinct from one another. In fact, the same cognitive test is often used to assess domains described by different models. For example, the flankers task can be used to assess domains of all 3 models: the executive control component of attention, defined by Posner & Petersen33, selective attention, defined by McDowd32, and inhibition, defined by Miyake and colleagues30. Similarly, cognitive tasks that measure the ability to shift focus (e.g. the trail-making test, which involves drawing a path between alternating letters and numbers) have been used to measure the shifting component of executive function, as defined by Miyake and colleagues, as well as attentional switching, as defined by McDowd 2007. Such overlap demonstrates the commonality of some domains described by these models. In Figure 1, we lay out the domains of each model, with similar domains from each model grouped together to illustrate the similar and distinct components of these common models.

Also discussed in our framework, though not included in Figure 1, is visuospatial function. Visuospatial function consists of several components including, but not limited to, visuoperceptual abilities (i.e. identification of a stimulus, its orientation, and its location) and visuoconstructional abilities (i.e. organization and manipulation of spatial information to make a design) 34-36. Visuospatial function is often considered somewhat distinct from executive function and attention. However, as described below, some tests designed to assess visuospatial functions do tap into domains of both executive function and attention.

Altered cognition affects mobility in patients with PD who freeze

Individuals with PD often exhibit altered cognition with respect to healthy adults37, 38. However, PD+FoG often exhibit even more pronounced cognitive dysfunction than those who do not experience FoG. In particular,
FoG is associated with deficits in attention, especially divided attention and attentional switching \(39-44\); executive function, especially shifting and inhibition\(15, 45-48\); and visuospatial function \(34, 49-52\). In the following section, we provide a brief review describing evidence of cognitive deficits in PD+FoG and discuss how these deficits may lead to FoG events. Then, we suggest ways in which executive and attention function deficits may be related to motor dysfunction. Table 1 outlines and describes some neuropsychological tests commonly used to probe these cognitive domains.

**Attention**

*Divided attention* is the ability to complete two different attention-demanding tasks at the same time. In physical therapy, this is commonly tested by having patients complete a secondary cognitive task (i.e. dual task; DT) during stance or gait and measuring decrements in performance of each task during DT performance compared to when it is performed alone. This DT analysis allows clinicians to quantify the cost to mobility of adding a secondary task and also to determine if a person prioritizes mobility over the cognitive task. Analysis of prioritization of tasks is particularly important for people with PD. Previous work shows that people with PD may prioritize the secondary, cognitive task over mobility, a so-called “posture second” strategy \(53\), although recent work suggests this strategy may not be a consistent feature of DT performance in PD \(54\). If utilized, a posture-second strategy could result in disproportionate posture and gait dysfunction in DT situations. Interestingly, individuals who experience freezing may exhibit even more pronounced “posture second” prioritization\(39, 42, 44\).

Gait characteristics during DT walking are more affected in PD+FoG than PD-FoG \(39, 42, 44\), and the changes in gait while dual-tasking may have a causal role in FoG. Indeed, gait variables affected by DT walking (e.g. smaller step length, increased variability, etc.) have been linked to FoG\(55, 56\), and recent work suggests that there may be a threshold of gait dysfunction beyond which freezing occurs\(56-58\). Thus, the reduced gait function during DT walking may bring PD+FoG closer to this hypothetical threshold, increasing the chances of a freezing event\(55, 58\). In addition, prioritization of cognitive tasks over gait tasks in conjunction with already
reduced cognitive resources may further increase the risk of freezing. Importantly, previous reports have shown that people with PD show benefits in DT walking with practice\textsuperscript{41, 42}. However, DT training has not been carried out explicitly on PD+FoG, and thus the degree to which freezing is reduced from these exercises is not known.

\textit{Attention switching} refers to alternation of the focus of attention between two different tasks or sources of information\textsuperscript{32}. As noted above, “attention switching” is similar to the “shifting” domain described in Miyake’s model of executive function. These domains are commonly assessed by trail-making test\textsuperscript{59}, plus-minus task\textsuperscript{60}, and shifting task\textsuperscript{61}. The ability to switch or shift attention has been shown to be associated with clinical severity of freezing and is worse in PD+FoG\textsuperscript{40, 41, 43, 62}; although a recent report showed no differences in switching ability in PD+FoG and PD-FoG\textsuperscript{45}. Smulders and colleagues showed that shifting between lower extremity motor tasks (stepping forward and backward) resulted in larger delays in people who freeze than PD-FoG, suggesting that switching deficits may contribute to the occurrence of FoG\textsuperscript{63}. Mobility in complex environments requires constantly switching attention among posture, locomotion, and surrounding sensory input. In PD+FoG, the inability to quickly and effectively switch attention during walking, turning, or initiating gait, particularly when completing secondary tasks such as conversing with a friend, may contribute to freezing episodes and falls. Training that incorporates switching attentional focus improves retention of DT training benefits in healthy elderly\textsuperscript{64} and may lead to improvements in DT gait in people with PD\textsuperscript{65, 66} (for review see\textsuperscript{67}). To our knowledge, no reports have investigated the effects of training attention switching on postural or locomotor control in PD+FoG. However, given the promising prior results and the attention switching dysfunction observed with FoG, incorporating this type of training into exercise for PD+FoG may improve their mobility during complex gait and posture tasks.

\textit{Sustained attention} refers to the ability to maintain attention to a task over prolonged periods. This domain of attention has not been thoroughly investigated with respect to FoG. However, one recent study found that performance on Mackworth’s sustained attention task\textsuperscript{68} was similar between PD subjects with and without FoG\textsuperscript{45}.
Selective attention is the ability to intentionally focus attention on one source of information while excluding irrelevant information. As noted above, this domain shares some similarity to the inhibition domain of executive function (described by Miyake et al. 2000) and executive control (described by Posner & Petersen 1990). These domains are commonly assessed with the flankers task, in which the subject must discern the direction an arrow is pointing while ignoring the directions of the flanking arrows. Two recent investigations compared selective attention in PD subjects with and without FoG using the ANT, which has a flankers task embedded in it. Results showed that subjects with FoG performed worse on the flankers portion of the ANT, suggesting that selective attention may be worse in PD+FoG than in PD subjects without FoG. Other components of attention defined by Posner & Petersen, namely the orienting and alerting networks of attention, were not affected by freezing status. Clearly, the flankers task may call on a number of cognitive functions other than selective attention, including inhibition of unwanted responses. Furthermore, a study that examined performance on the flankers task outside of the context of the ANT did not find a difference in performance between PD subjects with and without FoG. Additional work is necessary to determine whether sustained and selective attention are altered in PD+FoG; however these results suggest altered attention in PD+FoG.

Executive function

Of the three domains of executive function described by Miyake (shifting, inhibition, and updating), shifting and inhibition are most consistently altered in PD+FoG.

Shifting (shifting back and forth between multiple tasks, operations, or mental sets) shares considerable overlap with the attention domain described in the previous section: “attention switching”, and is described in detail there.
Inhibition (commonly assessed via the go-nogo task, various stimulus-response compatibility tasks, stop signal task, flanker task, and Stroop task) is the aspect of cognition most consistently found to be altered in PD+FoG. For example, Cohen and colleagues showed that performance on a go-nogo task was worse in PD+FoG than in people with PD who do not freeze. Further, both false alarms and misses in the go-nogo task were associated with severity of physician-rated FoG, illustrating difficulty both with inhibiting responses and with allowing responses to proceed after inhibition. Performance on the Stroop task has also been related to FoG, as PD+FoG perform worse than people who do not freeze. Further, PD+FoG demonstrate faster decline in Stroop performance over time than those who do not freeze. Fling and colleagues also showed that among PD+FoG, performance deficits on the Stroop task were correlated with asymmetry of white matter tracts between deep brain (pedunculopontine nucleus) and cortical (supplementary motor area) locomotor regions. A recent report by Matar and colleagues provides an additional link between performance in Stroop-like tasks and freezing events. Using virtual reality, researchers assessed step latency, a measure directly related to FoG, in PD+FoG and PD-FoG after conflicting stimuli in a Stroop-like task. Results showed that conflicting, Stroop-like stimuli increased step latency more in subjects with FoG than in subjects without FoG. Applied to real-world environments, a reduced ability to interpret conflicting sensory input, inhibit inappropriate responses, and allow appropriate responses during gait could delay stepping, leading to freezing and falls.

Previous work from our laboratory suggests that freezing may be directly related to alterations in inhibition and release of motor programs. Jacobs & colleagues (2009) found that the coupling of a weight shift (or anticipatory postural response; APA) with a step was altered in individuals with PD who experience freezing. Further, the 4-6 Hz trembling of the knees often observed during a freezing event prior to step initiation may represent multiple unwanted APAs. This potential inability to couple the APA to the stepping motor program may be related to cognitive dysfunction, as noted above. For example, dysfunctional response inhibition could be related to an inability to effectively inhibit unwanted movements (extra APAs) or to release wanted (stepping) movements. Recent neuroimaging results provide further evidence suggesting a link between freezing and inhibition. Fling and colleagues showed that freezers exhibit altered functional connectivity in the...
hyperdirect pathway between the subthalamic nucleus and supplementary motor area \(^75\), regions known to play important roles in inhibition \(^76\). Together, these results suggest that the same neural circuits may be involved in both motor and cognitive inhibition, and that they may be altered in PD+FoG. These results are also partially consistent with the suggestion by Vandenbossche and colleagues that alterations in inhibition and release of movements may reflect, in part, impaired movement automaticity in PD+FoG\(^48,77\). This idea is consistent with previous observations that suggest automatic movement is altered in FoG (See \(^10\) for review). Importantly, recent research shows that in healthy adults inhibitory control can be improved with training\(^78,79\). These improvements have not yet been replicated in people with PD, however, given the dysfunction observed in this domain, research investigating improvement in inhibition with training in PD is warranted.

**Visuospatial Function**

Visuospatial function can be assessed with a number of tests including the judgment of line orientation (JLO\(^80\), the Rey-Osterrieth complex figure task\(^81\), the matrix reasoning task \(^82\), the block design task\(^82\), or clock drawing test \(^83\) (Table 2). Previous reports suggest that individuals with PD exhibit visuospatial deficits, and that these deficits relate to difficulties in everyday life\(^84\). Two recent investigations have directly compared visuospatial function specifically in PD+FoG. Nantel and colleagues showed that PD+FoG scored worse than PD-FoG on matrix reasoning and block design tests, and scores on these tests were correlated to FoG severity\(^52\). Lord and colleagues also showed dysfunction of visuospatial function in PD+FoG, as this population took longer to match angles presented on a screen (a task similar to the JLO) than PD-FoG\(^34\). In partial support of these findings, a recent resting state functional connectivity assessment demonstrated that visual networks may be altered in PD+FoG with respect to PD-FoG\(^85\). It should be noted, however, that as with many “executive function” tests, complex visuospatial tasks such as the matrix reasoning and block design tasks incorporate a number of cognitive functions, including visuoconstructional abilities and non-verbal problem solving\(^36\), which could confound conclusions specific to visuospatial function. Adding to the above findings, two recent investigations showed that walking through doorways is particularly problematic for PD+FoG\(^49,50\), suggesting
that altered visuospatial function may contribute to freezing in this scenario. Similarly, Matar and colleagues showed that while moving through a virtual reality environment with wide, narrow, and sliding doorways, PD+FoG exhibited larger delays in stepping during narrow and sliding door conditions. Interestingly, follow up studies showed that PD+FoG are able to effectively predict door size\textsuperscript{50, 86}. However, they do not correctly predict how their gait will be influenced by the narrowness \textsuperscript{86}. Thus, it is possible that freezing while approaching or moving through doorways could be related to the integration of visuospatial information. Alternatively, moving through doorways adds an additional distracting task that could contribute to freezing, as noted above. Clearly, additional research is necessary to better understand the specific visuospatial dysfunction associated with FoG, and whether this dysfunction plays a causal role in FoG.

\textit{Overall, the data summarized above suggest that the most prominent cognitive dysfunctions exhibited by PD+FoG are divided attention, attention switching/shifting, inhibitory control, and visuospatial function.} With emerging evidence of the relationship between cognition and mobility, improving cognition could reduce freezing and improving mobility in PD+FoG. Indeed, recent evidence suggests that improving cognition with training may improve mobility in healthy older adults\textsuperscript{87} and individuals with PD\textsuperscript{88}. Additional studies have shown that training incorporating both cognitive and motor components may also be effective at improving cognition in healthy\textsuperscript{89} (for review; see\textsuperscript{13}), and parkinsonian\textsuperscript{19} individuals. However, considerably less research has focused on the effects of cognitive and/or motor programs on PD+FoG\textsuperscript{90}, and therefore it is unknown whether this population will benefit from such an intervention. Given the fact that PD+FoG typically exhibit more pronounced cognitive dysfunction than PD-FoG, this cognitive dysfunction could impede mobility and cognitive benefits to training PD-FoG. However, a recent Cochrane review\textsuperscript{91} suggests that even individuals with non-parkinsonian dementia may improve cognitive function through exercise. Thus, it is unlikely that the cognitive dysfunction alone in PD+FoG would abolish the ability to improve cognitive ability through cognitive and/or mobility training.

\textbf{Combining Cognitive and Exercise Training for People with PD who Freeze}
In clinical practice, cognitive training is typically carried out separately from mobility training. This model can clearly be effective for PD \(^{88, 92}\) (for reviews see \(^{11, 90, 93, 94}\)). The improvements in function include reductions in FoG severity, as a number of recent investigations have demonstrated improvements in FoG after mobility or cueing interventions \(^{11, 95}\). However, given the evidence of overlap between cognition and mobility, training cognitive and mobility together (rather than separately) may enhance gains of each area, increasing global function in people with FoG. Although PD+FoG exhibit clear overlap between cognitive and motor deficits (e.g. increased FoG episodes with stress), research to date has not focused on the integration of freezing-specific motor and cognitive therapies for this population. Given previous literature demonstrating how interventions that incorporate cognition and motor tasks can improve function in healthy adults and PD-FoG \(^{13, 17-19, 65, 87, 89, 96}\); (for review, see: \(^{97}\)), research investigating the effects of targeted cognitive and motor interventions on FoG severity is warranted. Thus, in the following section, we provide examples of exercises that integrate cognitive and motor components. As the previous sections have provided rationale for the integration of cognition and motor training, the following examples are meant to provide a starting point for evaluation of such targeted cognition-mobility training in PD+FoG and have not yet been tested.

Integrating FoG-specific cognitive training with mobility training

Table 2 lists some of the cognitive domains we suggest as targets for rehabilitation for FoG, as well as examples of tasks that integrate these domains into exercise.

**Attention (divided attention & attention switching)** Attentional control can be integrated into exercise by instructing patients to carry out a secondary cognitive task (e.g. arithmetic, phonetic/categorical naming, conversations, etc.) while exercising. Many physical therapists already incorporate DT elements into gait training to assess attention or to increase difficulty of gait tasks, and recent reports have demonstrated that DT practice may improve DT ability \(^{65, 87, 96}\). However, despite the fact that the ability to divide attention is particularly altered in PD+FoG, the effect of DT practice on this population is not well characterized.
The ability to switch attention is also likely altered in PD+FoG, and recent work has demonstrated the feasibility of integrating attentional switching tasks into walking (Figure 2a). For example, Perrochon & Kemoun (2013) used a trail-making walking task to differentiate healthy older adults from those with mild cognitive impairment. In this task, participants walked along a mat with numbers and letters. Similarly to the traditional paper and pencil trail-making test, participants stepped on alternating and ascending letters & numbers (e.g. 1-A-2-B…)\textsuperscript{98}. Shifting can also be integrated into non-gait exercises. Well-established tests to challenge shifting ability, such as the shifting task \textsuperscript{61}, can be integrated into upper or lower limb movements.

Boxing and agility courses also provide opportunities to incorporate dual tasking into exercise. During boxing, the trainer can cue punches verbally (saying left or right arm) and visually (moving the target to the left or right). With multiple cueing modalities, the patient is forced to switch attention between visual and auditory cues, prioritizing one over the other as instructed. Thus, through the application of multiple cues during mobility tasks, patients can practice divided attention and switching attention between cues (Figure 2a). As will be discussed later, this paradigm also allows practice responding to conflicting cues and practice inhibiting prepotent responses (Figure 2b). Agility courses can also integrate DT practice. Such courses integrate obstacles associated with FoG (i.e. doorways, turning, tight spaces, backward walking, stepping over obstacles, change in surface etc.)\textsuperscript{99,100}, and/or secondary cognitive tasks, forcing practice with divided attention. Further, the patient can be instructed to switch focus between primary (locomotion), and secondary (cognitive or motor secondary) tasks to practice switching task/attention priorities. In this way, patients receive practice with divided attention, switching attention, and integration of internal and external cues.

**Inhibition**: Inhibition tasks can also be integrated into motor training (see Table 2 for examples). Exercises such as boxing and lunges are particularly well suited to incorporate these challenges while maintaining a level of aerobic challenge. Aspects of go-nogo, stimulus-response (SR) compatibility, stop signal, flankers, and Stroop tasks can all be incorporated into these mobility exercises. For example, during a partnered boxing station, participants can be instructed to punch or step as quickly as possible in response to certain stimuli
(given by instructor) while ignoring other stimuli (analogous to a go-nogo task). Participants can also be instructed to punch with the opposite arm as what is cued (i.e. “Right”= punch with left arm), thereby forcing participants to inhibit pre-potent responses and resolve stimulus-response compatibility. As noted above, partnered boxing can integrate multiple cueing modalities (e.g. visual, verbal). In addition to allowing the patient to practice switching attention between cues, these cues provide practice of inhibition tasks. For example, the trainer can provide conflicting information by verbally cueing the participant to punch with the left hand while visually cueing a punch with the right hand by moving the right target (Figure 2b). This provides conflicting stimuli that the patient must decipher, as in a Simon, flankers, or Stroop task, requiring inhibition of inappropriate responses. Similarly, stop signal tasks can also easily be incorporated: after the instructor cues a movement, they may occasionally give a stop signal, forcing inhibition of movement.

Finally, tasks related to response inhibition can also be integrated into walking such as a Stroop walking task. In this task, participants walk on a mat with different words (e.g. RED, BLUE, YELLOW) printed in different colors. Subjects hear color word cues and, depending on the condition, they step either on a printed version of the word they heard or on a word that is printed in the same color ink as the word they heard. Subjects can also practice doing the Stroop task mounted on a large board while they practice lunging in various directions.

**Visuospatial function:** A common functional outcome of visuospatial dysfunction in PD+FoG is a change in gait when approaching doorways or walking surface transitions. Thus, incorporating such obstacles (e.g. doorways of varying widths or obstacles) into training courses can provide individuals practice with these challenges. Previous investigations provide support for such an approach. Plotnik et al. showed that obstacle-based training that incorporated narrow passages led to improvements in FoG. Though this intervention incorporates a number of approaches, including cueing before and after FoG-provoking obstacles, it provides some evidence that practicing gait through obstacles including doorways may be beneficial in reducing FoG. A recent study also showed that gait in patients with PD can be improved by treadmill training walking over
virtual obstacle with visual feedback of foot trajectories. Providing additional visual information about body motion in relation to environmental obstacles may allow compensatory mechanisms to control locomotion or may be restitutive.

**Challenges in FoG Rehabilitation**

The cognitive dysfunction in people with PD in general, and PD+FoG specifically, can create challenges to rehabilitation. Some previous interventions aimed to improve FoG use compensatory strategies, such as providing external cues to trigger and guide movement and encouraging altered allocation of attention (i.e. task prioritization). While this type of compensatory training often improves FoG, the cognitive dysfunction often observed in PD+FoG may limit the ability of PD+FoG to deploy such strategies in daily life. Indeed, recent results suggest that when cues are removed, PD+FoG revert back to dysfunctional movement more than PD-FoG. Alternatively, attempts to improve the underlying dysfunction, i.e. restitutive rehabilitation, may be able to reduce the cognitive limitations of this population. For example, training individuals to take larger more consistent steps through, for example, treadmill walking, may partially circumvent attentional cues such as lines (visual) or tones (auditory). However, this approach relies, in part, on implicit motor learning, which has been shown to be deficient in PD+FoG. Due to the drawbacks of both treatment approaches, we feel that incorporating both restitutive and compensatory approaches will provide the greatest chance of cognitive-motor improvements. Therefore, we have incorporated each of these approaches into the current framework.

Cognitive dysfunction can create specific challenges for application of therapeutic approaches. For example, DT walking is challenging for people with PD, and too much cognitive challenge may lead to breakdown of gait and FoG. Thus, therapy must be tailored to the individual to find the level of dual-tasking that challenges the system but does not fully overload it. Indeed, further research on ways to quickly indicate or contraindicate different cognitive approaches is necessary. DT training may also increase risk of falls during training. However, despite these concerns, the use of DT training seems to be beneficial in people with PD and, given appropriate assessment and safety assessments, can be used effectively.
A third challenge to rehabilitation is the possible effect of levodopa on cognition. A number of recent studies suggest that levodopa, the most common pharmacological therapy for PD, may have negative effects on specific cognitive tasks. These effects are thought to be most pronounced in the early stages of PD, and may result from “overdosing” the ventral striatum with dopamine\textsuperscript{107-109}. This hypothesized “overdosing” of the ventral striatum may impede certain types of probabilistic reversal learning and, particularly important for rehabilitation, motor learning. In fact, a number of investigations suggest that upper extremity motor learning may be subtly inhibited by levodopa\textsuperscript{110,111}. Although recent studies have not confirmed these findings in postural motor learning\textsuperscript{112,113}, additional research will be necessary to identify the effect of levodopa on neurorehabilitation.

Although a number of barriers exist for efficient treatment of FoG, it is also important to keep in mind that despite the cognitive deficits and incomplete recovery noted above, individuals with PD+FOG can improve FoG symptoms through training\textsuperscript{11,95}. Thus, while improvements can be made to rehabilitation for PD+FoG, there is strong evidence that such efforts can have important positive effects on mobility and quality of life in this population.

**Summary and Conclusions**

Given the immense burden of FoG and cognitive deficits on quality of life, rehabilitation strategies should be designed based on current evidence to provide maximum benefit to both domains to patients with PD. Previous investigations have provided evidence that cognitive and mobility training are each separately beneficial in PD. We propose that FoG-specific cognitive training integrated with mobility training may enhance the benefits of both in PD+FoG. However, this approach has not yet been investigated as an intervention targeting FoG. Thus, we have developed a framework for integrating cognitive-motor training for people who experience FoG, and provided specific examples of exercises that integrate cognitive and motor challenges. Future research should assess the effectiveness of such a program on cognitive and mobility function in people with PD who freeze.
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Dr Horak and OHSU have significant financial interests in APDM, a company that might have a commercial interest in the results of this research and technology. This potential conflict of interest has been reviewed and managed by OHSU and the Integrity Oversight Council. No other authors declare any conflict of interest.

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Table 1: Common exams to assess domains of executive function, attention, and visuospatial function.

<table>
<thead>
<tr>
<th>Domain</th>
<th>Test</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Executive</td>
<td>Inhibition</td>
<td><strong>Go-nogo</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Stimulus response compatibility</strong>&lt;sup&gt;70&lt;/sup&gt;</td>
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<td></td>
<td><strong>Stroop Task</strong>&lt;sup&gt;72&lt;/sup&gt;</td>
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<td></td>
<td><strong>Flanker Task</strong>&lt;sup&gt;69&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Stop Signal Task</strong>&lt;sup&gt;71&lt;/sup&gt;</td>
</tr>
<tr>
<td>Attention</td>
<td>Divided</td>
<td><strong>Dual task walking</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Trail making test</strong>&lt;sup&gt;59&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
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<td><strong>Shifting Task</strong>&lt;sup&gt;61&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Plus-Minus Task</strong>&lt;sup&gt;60&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Mackworth’s sustained attention task</strong>&lt;sup&gt;68&lt;/sup&gt;</td>
</tr>
<tr>
<td>Selective</td>
<td><strong>Flanker Task</strong></td>
<td>See above</td>
</tr>
<tr>
<td><strong>Visuospatial function</strong></td>
<td><strong>Matrix Reasoning</strong>&lt;sup&gt;82&lt;/sup&gt;</td>
<td>The participant is presented with incomplete matrices, each of which is a series of abstract patterns and designs. The participant must choose the pattern that best completes the matrix.</td>
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<td>--------------------------</td>
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<td><strong>Block Design</strong>&lt;sup&gt;82&lt;/sup&gt;</td>
<td>The participant organizes blocks with varying shapes and colors into specific designs.</td>
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<td></td>
<td><strong>Judgement of Line Orientation (JLO)</strong>&lt;sup&gt;80&lt;/sup&gt;</td>
<td>Participants visually match angled line pairs to 11 numbered radii forming a semi-circle.</td>
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<td><strong>Rey-Osterrieth Complex Figure Test</strong>&lt;sup&gt;81&lt;/sup&gt;</td>
<td>Participants reproduce a complex figure. This test also includes immediate and delayed recall, where the participant reproduces the figure from memory immediately and after 20-30 minutes.</td>
</tr>
<tr>
<td></td>
<td><strong>Clock Drawing</strong>&lt;sup&gt;83&lt;/sup&gt;</td>
<td>Participants are asked to draw in the numbers of a clock within a 4 inch circle, then set the clock to ten past eleven.</td>
</tr>
</tbody>
</table>
Table 2: Examples of cognitive domains associated with freezing and exercises that challenge these deficits.

<table>
<thead>
<tr>
<th>Cognitive Domains</th>
<th>Cognitive Tests</th>
<th>Integration into Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Attention</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Divided</td>
<td>Dual tasks</td>
<td>Dual task walking / agility course</td>
</tr>
<tr>
<td><strong>Shifting</strong></td>
<td>Shifting test</td>
<td>Shifting focus between tasks</td>
</tr>
<tr>
<td></td>
<td>Trail-making test</td>
<td>Trail-making test walking 98</td>
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<tr>
<td><strong>Selective</strong></td>
<td>Flanker task</td>
<td>Visual / auditory cue conflict</td>
</tr>
<tr>
<td><strong>Executive function</strong></td>
<td></td>
<td></td>
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<tr>
<td>Inhibition</td>
<td>Go-nogo task</td>
<td>Go-nogo punching</td>
</tr>
<tr>
<td></td>
<td>Stimulus response compatibility</td>
<td>“Left” punch at “Right” cue</td>
</tr>
<tr>
<td></td>
<td>Stop signal task</td>
<td>Stop signal punching</td>
</tr>
<tr>
<td></td>
<td>Flanker task</td>
<td>Visual / auditory cue conflict</td>
</tr>
<tr>
<td></td>
<td>Stroop task</td>
<td>Stroop walking task 101</td>
</tr>
</tbody>
</table>
**Figure 1:** Overlap across models of executive function\textsuperscript{30} and attention\textsuperscript{31,32}. Domains within each model are grouped to show similarity between models (e.g. Inhibition, executive control, and selective attention). The domains in the shaded red box (broadly: inhibition and divided/switching attention) are most commonly dysfunctional in people with PD who freeze. Dysfunction of these domains can lead to changes in functional mobility and falls in this population (see text).

**Figure 2:** A) Example of task prioritization during agility training: The patient completes a secondary cognitive task during agility training, and is instructed to switch prioritization between the mobility/stepping component (left) and the cognitive component (right). B) Example of visual-auditory cue conflict during boxing. Simultaneously, the instructor visually cues for a left punch and verbally cues for a right punch. For this trial, the patient is instructed to respond to the visual cue only and ignore the auditory cue.
Cognitive domains most affected in people with PD who freeze

Posner & Petersen 1990 (Attention)
- Executive Control
- Alerting
- Orienting

Miyake et al., 2000 (Executive Function)
- Updating
- Shifting
- Inhibition

McDowd 2007 (Attention)
- Switching
- Divided
- Sustained
- Selective