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Featured Article

Neuroimaging and neuropsychological assessment of freezing of gait in Parkinson's disease

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Abstract

Introduction: Freezing of gait (FOG) is a disabling phenomenon characterized by a brief, episodic absence or reduction of forward progression of the feet despite the intention to walk. It is a common cause of falls and mortality in cases with Parkinson's disease (PD). This article reviews neuropsychological and neuroimaging studies to date and introduces a new study of multimodal imaging and cognition in PD-FOG.

Methods: A comprehensive literature search identified studies using neuropsychological evaluation and/or neuroimaging to evaluate PD-FOG.

Results: Several studies have evaluated PD-FOG, but few have combined neuropsychological and comprehensive neuroimaging and none longitudinally.

Discussion: A study using a combined approach longitudinally evaluating cognitive dysfunction and underlying neural networks in FOG is needed. We introduce the framework of a study which demonstrates the use of establishing an infrastructure for studying neurodegenerative disorders using the National Institutes of Health/National Institute of General Medical Science Center of Biomedical Research Excellence grant mechanism.

Keywords: Neuroimaging; Neuropsychology; Gait; Parkinson's disease

1. Introduction

Parkinson's disease (PD) is a chronic, progressive neurodegenerative disease characterized by both motor and nonmotor features. Similar to Alzheimer's disease (AD) and other neurodegenerative disorders, PD is caused by misfolding and subsequent accumulation of a brain protein. Accumulation of amyloid and tau proteins occurs in AD patients, whereas accrual of alpha-synuclein protein occurs in PD patients. In both the disorders, buildup of these proteins results in neuronal and synaptic dysfunction, as well as inflammation. The neuronal loss and synaptic dysfunction result in the phenotypic manifestation of symptoms in both the disorders. While cognitive and neuropsychiatric symptoms occur in both AD and PD patients, the cardinal features of PD are motor symptoms including bradykinesia, rest tremor, rigidity, and gait abnormalities including postural instability [1].

PD is the second most common neurodegenerative disorder after AD and is expected to double in prevalence in the next 20 years [2]. Approximately 60% of patients with PD fall each year [3], resulting in significant morbidity, mortality, and direct and indirect medical costs. It is therefore critical to identify modifiable factors that contribute to fall risks.

Freezing of gait (FOG) is one of the most common causes of falls and subsequent morbidity and mortality in PD patient [4]. FOG is a brief, episodic absence or reduction of forward progression of the feet despite the intention to walk [5].

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During these episodes, patients experience a feeling that their feet are "glued" to the floor and are unable to move [4]. During ambulation, four circumstances that most commonly induce FOG are starting to walk, attempting to turn, passing through narrow passages, or nearing the intended destination [6]. FOG is seen in other parkinsonian syndromes and normal pressure hydrocephalus and in patients with microvascular ischemic lesions but is most commonly associated with PD [7].

It is theorized that FOG is a motor manifestation of global dysfunction in the concurrent processing of information across neuronal networks [8]. This is supported by studies showing that FOG is correlated with limited dual-tasking ability [9] and inability to "set-shift" attention among motor, limbic, and cognitive networks [10]. In addition, freezing can occur during speech, handwriting, and other actions aside from gait, suggesting that the dysfunction occurs in generalized neural networks not solely related to ambulation [11].

PD-FOG usually occurs in the "OFF" state (the dopaminergic medication which improves PD symptoms has worn "off" and is not actively effective) but can also occur in the "ON" state (while the dopaminergic medication is effective and actively improving PD symptoms) [12]. Studies of the prevalence of FOG in PD patients indicate that approximately 50% experience FOG, with nearly 60% of these episodes occurring in the "OFF" state and 36%–38% of episodes occurring in the "ON" state [13].

A comprehensive approach to the evaluation of PD-FOG is needed to fully elucidate the underlying mechanisms and pathophysiology of this disabling phenomenon. Studies have evaluated the neuropsychological profile of patients with PD-FOG. Neuroimaging studies have also been performed using functional or structural connectivity to evaluate the networks involved. However, very few studies have combined functional and structural connectivity with neuropsychological evaluation. In addition, longitudinal studies are lacking, especially those that identify PD patients who later develop PD-FOG. This article reviews the current understanding of the neuropsychological profile and neuroimaging features of PD-FOG and discusses how longitudinal evaluation of PD-FOG with multimodal imaging, neuropsychological evaluation, and clinical evaluation can help advance our understanding in hopes of developing effective therapeutic interventions. The research is supported by a National Institutes of Health/National Institute of General Medical Science Center of Biomedical Research Excellence award establishing a Center for Neurodegeneration and Translational Neuroscience shared by the Cleveland Clinic Lou Ruvo Center for Brain Health and the University of Nevada, Las Vegas.

2. Neuropsychologic profile of PD-FOG patients

PD-FOG correlates with cognitive dysfunction in specific domains. Executive dysfunction involving response inhibition, problem solving, divided attention, or switching attention have been implicated [14].

Studies evaluating the neuropsychological deficits in patients with PD-FOG indicate that competing frontostriatal pathways reduce the ability to "set-shift" from one response set to another and may trigger episodes of freezing [10]. One study found deficits in set-shifting, as indicated by poor performance on Trail Making Test B, correlated with PD-FOG. However, there was only a mild correlation between PD-FOG and Trail Making Test A, which focuses more on visuospatial scanning and motor speed [10]. Another study evaluating motor and cognitive determinants identified attention and memory deficits in PD-FOG patients but also found no associated visuospatial deficits [15]. Anxiety is common in patients with PD-FOG and may contribute to the deficits in attentional set-shifting [16].

A study evaluating response inhibition and suppression in PD-FOG patients with the attention network task and Stroop task demonstrated that those with FOG show a deficiency in general conflict-resolution ability compared with those without the deficiency and healthy controls [17]. Another study evaluating executive function in PD-FOG patients found deficiencies in response inhibition correlated with severity of PD-FOG but did not identify significant deficits in set-shifting or updating working memory [18]. Deficiencies in response inhibition in PD-FOG patients are believed to be associated with structural deficits in the right hemisphere's locomotor network involving prefrontal cortical areas [5].

A study of early PD patients with FOG in the "ON" state found frontal dysfunction, as evidenced by decreased total Frontal Assessment Battery scores and phonemic verbal fluency, potentially implicating the dorsolateral prefrontal cortex, anterior cingulate, and left inferior frontal gyrus [19].

Clinical investigations of FOG support the neuropsychological observations of frontal executive dysfunction involving set-shifting of motor programs, deficiencies in attention, and poor response inhibition. FOG may result from an inability to generate normal amplitude in step length, and asking PD-FOG patients to reduce their step length can induce episodes of FOG [20]. Modulating locomotion by changing gait speed, pattern, or direction in obstacle avoidance may also trigger episodes of FOG [21].

2.1. Limitations of neuropsychological studies of PD-FOG

Studies exploring neuropsychological deficits associated with PD-FOG often focus on certain cognitive domains rather than performing a comprehensive evaluation. Therefore, the results are limited to the tests chosen in each study and do not provide a full cognitive profile. In addition, not all PD patients with executive dysfunction develop FOG, which

indicates there are other deficits involved which need to be elucidated. Longitudinal and prospective studies of cognition in PD-FOG patients may better identify the specific deficits involved and should be correlated with imaging findings to determine their relationship to underlying structural defects.

3. Neuroimaging of PD-FOG patients

Neuroimaging studies of PD-FOG have identified abnormalities in connectivity in motor and nonmotor pathways [8,22,23]. Several neuroimaging protocols have been used to evaluate PD-FOG. Most commonly, neuroimaging is performed with the participant in the resting state. However, other protocols involve performing task-based neuroimaging during motor imagery or virtual reality after prolonged walking, while lying supine and simulating walking, and after an intervention (i.e., deep brain stimulation) [24]. This section focuses on magnetic resonance imaging-based functional and structural connectivity analyses of PD-FOG.

3.1. Functional connectivity

3.1.1. Resting-state functional magnetic resonance imaging

Functional magnetic resonance imaging (fMRI) evaluates functional associations among brain regions by measuring temporal correlations between spatially remote neurophysiological events [25]. Blood oxygen level–dependent signal fluctuations represent areas of brain activity. Anatomically separated but functionally connected regions display a high level of correlated blood oxygen level–dependent signal activity. These reproducible neural networks are called resting-state networks.

fMRI of PD patients (not specific to FOG) shows that levodopa significantly changes the motor and cognitive networks of the corticostriatal pathways, with improvement of motor symptoms due to increased functional connectivity of motor circuits [26]. This partial improvement in circuit function may account for the partial responsiveness of PD-FOG to dopaminergic therapy, although corticostriatal connectivity in PD-FOG in the "OFF" versus "ON" state has not been comprehensively evaluated.

Resting-state fMRI studies in PD-FOG patients have implicated dysfunctional connectivity between cortical and subcortical regions. One study demonstrated reduced functional connectivity in the executive (frontoparietal) and visual (occipitotemporal) networks, and the extent of reduced connectivity correlated with the severity of FOG [27]. Another study showed increased connectivity between the supplemental motor area and mesencephalic locomotor region (MLR), theorized to compensate for decreased connectivity between the supplemental motor area and basal ganglia [28]. A recent study found reduced connectivity of the primary motor cortex and supplementary motor area bilaterally in the sensorimotor network, frontoparietal regions in the default mode network, and occipital cortex in the visual associative network [23].

3.1.2. Task-based fMRI

This technique uses the same acquisition protocol as resting-state fMRI but requires the subject to perform a task, usually in connection with a projection screen instructing the subject of what to do with task buttons to measure the subject's behavioral response.

3.1.3. Actual task

To investigate network-related changes that occur during episodes of FOG, Shine et al. used a virtual reality gait task during a 10-minute fMRI session. The subjects were positioned in the scanner to view a screen on which the virtual reality task was displayed while their feet rested on a pair of foot pedals. During FOG episodes, participants were unable to coordinate foot movements to depress the pedals, which correlated with decreased blood oxygen level–dependent response in sensorimotor areas and subcortical regions (basal ganglia, thalamus, and MLR). The extent of functional changes on fMRI correlated with the severity of FOG [29].

Subsequently, in further studies, the virtual reality paradigm was modified by adding a cognitive interference task (Stroop color task) that allows probing the influence of prefrontal executive function on the occurrence of FOG. Patients with FOG froze more often with increased cognitive load, supporting the notion that FOG is due to functional decoupling between cognitive control networks and motor networks [29].

Using a similar virtual reality paradigm, Gilat et al. investigated FOG when turning versus walking. FOG patients froze more while turning, with increased activation of the visual cortex and inferior frontal regions, implicating the recruitment of a motor-stopping network [30].

3.1.4. Imagined task

Gait planning while imagining walking (without using pedals to advance) through a virtual reality paradigm has been used as an fMRI task in FOG [4]. FOG patients tended to have increased response in the MLR and reduced activity in mesial frontal and posterior parietal regions.

Other fMRI studies using virtual reality tasks simulating FOG have identified increased basal ganglia inhibitory output with subsequent reduction in thalamic and brainstem information processing [31] and abnormal functional connectivity of the pedunculopontine network, mainly affecting the corticopontine-cerebellar pathways as well as visual temporal areas involved in visual processing [32].

3.2. Structural connectivity

Magnetic resonance imaging evaluation of structural connectivity is based on structural associations among and

between different neuronal elements. Morphometric correlation (i.e., voxel-based morphometry) assesses cortical thickness, gray matter volume, and surface area between the brain regions. This allows comparison of the local brain matter (gray matter and white matter) density between groups of subjects based on high-resolution MR images with T1 contrast. True anatomical connectivity analyzes white matter fiber connections between gray matter regions using diffusion tensor imaging (DTI), an MR imaging technique that determines the diffusion properties of water molecules in white matter tracts.

In using VBM, one study found that FOG severity was related to bilateral caudate volumes in the entire cohort, whereas there was significantly reduced gray matter in the left inferior parietal lobe and right angular gyrus in a matched group of those with PD-FOG compared with PD patients without FOG [33]. Another study using VBM found that PD-FOG subjects had specific cortical volume reduction of the posterior parietal cortex, theorized to be an associative area involved in spatial control of motor behavior [34].

One DTI study found reduced structural connectivity between the pedunculopontine nucleus (PPN) and the cerebellum, thalamus, and multiple regions of the frontal cortex [5]. Another DTI study specifically evaluating the PPN found an absence of cerebellar connectivity and increased visibility of the decussation of corticopontine fibers in the anterior pons in PD-FOG patients [35].

3.3. Combined functional and structural connectivity

A study combining VBM and fMRI analysis, using a virtual reality paradigm with motor imagery of gait, found that PD-FOG participants had gray matter atrophy in the MLR, with decreased activity in the mesial frontal and posterior parietal lobes and increased activity in the MLR on fMRI. The increase in activity on fMRI correlated with the severity of FOG episodes [4].

3.4. Studies combining neuropsychological and neuroimaging evaluation in PD-FOG

Several studies using VBM and neuropsychological evaluation have been performed. One found reduced gray matter volume in the left inferior frontal gyrus, precentral gyrus, and inferior parietal gyrus. FOG severity correlated with the extent of frontal executive deficits, as well as bilateral frontal and parietal cortical gray matter volume [36]. A similar study found reduced gray matter volume in the left cuneus, precuneus, lingual gyrus, and posterior cingulate cortex. FOG clinical severity significantly correlated with gray matter loss in posterior cortical regions, and patients with FOG scored lower on tests of frontal lobe function on neuropsychological evaluation [37]. Another study of VBM and neuropsychologic evaluation found PD-FOG subjects had lower cognitive performance in frontal executive and visual-related functions, and the latter correlated with significantly reduced thalamic volumes [38]. A study assessing the neuroanatomical correlation of executive dysfunction and gray matter atrophy in PD-FOG patients found atrophy of the right dorsolateral prefrontal cortex correlated with severity of both executive dysfunction and FOG [39]. Jha et al. found that PD-FOG subjects performed worse than PD patients without FOG on verbal memory, executive functions (including response inhibition, set-shifting, phonemic verbal fluency, and semantic verbal fluency), visuospatial, and attentional domains. These PD-FOG subjects had reduced gray matter volume in the left temporal and right parietal lobe regions (correlating with the neuropsychological findings), as well as reduced gray matter volume in the cerebellum [40].

A study of PD-FOG evaluating dual-task interference, executive function, and structural connectivity of the PPN in PD-FOG patients found attentional deficits correlated with reduced connectivity of the right PPN and reduced go/no-go target accuracy (a measure of response inhibition). The authors proposed that the attentional deficit in PD-FOG patients may be related to structural degeneration of the PPN, with diminished cholinergic input into the basal ganglia and an adverse impact of the deficit of acetylcholine on cognition [41].

3.5. Limitations of neuroimaging studies of PD-FOG

A general limitation of neuroimaging studies is reproducibility, which is supported by the disparate findings of the studies described previously. Abnormalities identified on resting-state fMRI can be construed only as correlated to PD-FOG, rather than causative, as the findings may be unrelated or may reflect compensatory mechanisms. Task-based fMRI is performed while lying supine, which eliminates several important aspects of gait control, most importantly balance. Structural connectivity abnormalities identified may be unrelated to PD-FOG and therefore can be deemed only as associated rather than directly related to this phenomenon. DTI of the PPN is intrinsically difficult to perform because the seed location of the PPN needs to be specified for each subject and may vary among subjects due to the small diameter of the PPN [24]. It is also important to ensure that PD-FOG and PD groups are matched in regard to disease severity when evaluating structural connectivity and to ensure that abnormalities identified are not simply due to a more advanced stage of PD.

4. A longitudinal study of multimodal imaging and cognition in Parkinson's disease FOG

The National Institute of General Medical Science has provided funding to support our study, which seeks to elucidate the underlying pathophysiology of PD-FOG using a combination of multimodal imaging, neuropsychological

Table 1
Neuropsychological tests to be used for analysis in proposed Project 2

Outcome measures	Test	Justification
Overall cognitive outcome measures	Dementia Rating Scale II (DRS) total score	Accurately screens for level of cognitive impairment [42]
	Montreal Cognitive Assessment (MoCA) total score	Global assessment of cognitive function
Key cognitive outcome measures (executive function)	Phonemic verbal fluency	Assessment of mental flexibility and evaluation of frontal lobe function
	Go/no-go task	Measure of response inhibition
	Frontal Assessment Battery	Assesses frontal lobe function by evaluating conceptualization and abstract reasoning, lexical verbal fluency and mental flexibility, motor programming and executive control of action, self-regulation and resistance to interference, inhibitory control, and environmental autonomy
	Trail Making Test A and B	Measures ability to "set-shift"
	Stroop task	Measures mental flexibility (response inhibition/conflict resolution and set-shifting) [26]

testing, and clinical evaluation. This multifaceted approach will help identify the relationship between abnormalities identified by neuropsychological testing and underlying brain network dysfunction specific to FOG. Combining analysis of both functional and structural connectivity provides more insight than using either modality alone. By longitudinally following up PD patients with FOG and evaluating patients with and without dopaminergic medication, we will expand on previous studies and more concretely define which networks are involved in the pathophysiology of the disorder.

All participants are evaluated with the same comprehensive neuropsychological testing battery, with a focus on aspects of executive dysfunction previously found to be affected in PD-FOG patients (Table 1). Anxiety and other nonmotor, noncognitive data pertinent to PD-FOG are being collected. Data points for each test are collected and analyzed between the groups to determine the strength of correlation between imaging and cognitive findings. Creation of a neuropsychological profile of PD-FOG will help identify PD patients at risk of developing FOG, improving early identification of subjects for clinical trials, and potentially allowing for intervention before PD patients develop FOG.

Neuroimaging using functional and structural connectivity is performed. Functional connectivity results are generated by both seed-voxel and independent component analysis. These results are then analyzed to determine between-group functional network differences using mixed-effect models in combination with bootstrapping validation. This approach enables us to examine differences in resting-state connectivity between PD and PD-FOG patients, with and without dopaminergic medication. Connectivity maps generated by the seed-voxel analyses are compared.

Structural connectivity is performed using both probabilistic tractography and tract-based spatial statistics, a method that allows a voxel-wise comparison of fiber tracts. The method is applied to fractional anisotropy maps obtained by fitting a tensor model to the raw diffusion data and aligning the maps into a common space. Then, a mean fractional anisotropy skeleton map is created for each group of subjects, and each subject's aligned fractional anisotropy map is projected onto this skeleton to enable voxel-specific cross-subject statistics (Fig. 1).

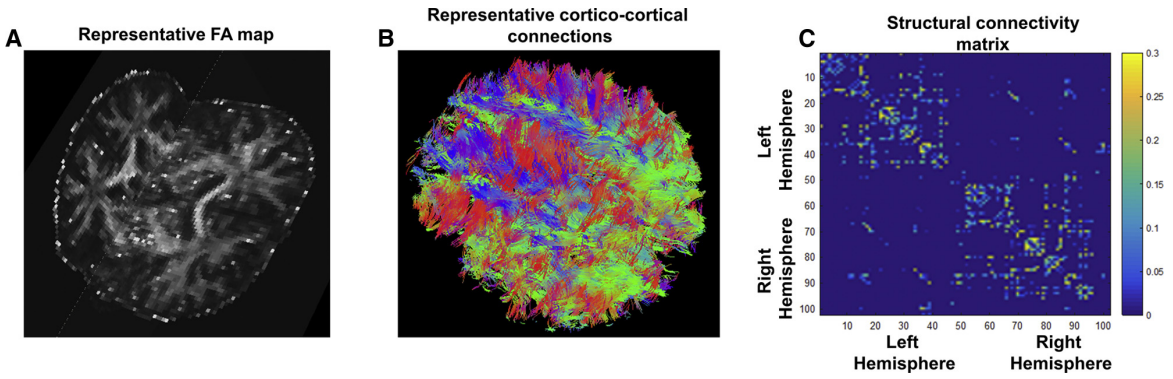

Fig. 1. Structural connectivity analysis. Abbreviation: FA, fractional anisotropy.

The striatal seeds derived from the probabilistic tractography are used in the seed-voxel analysis of functional connectivity. The results of the whole-brain Tract-Based Spatial Statistics analysis identify areas of disrupted white matter integrity. Tractography to and from the TBSS-identified white matter abnormalities are then performed to determine the structural connectivity of these pathologic regions. These results are compared with the functional connectivity data through regression analysis, permitting a combined functional and structural connectivity analysis to be performed in the same patients. This is an important step in development of a combined functional and structural magnetic resonance imaging-based biomarker for PD-FOG.

fMRI will be performed while participants view a modified virtual reality paradigm showing a first person view of the participant walking through a course designed to induce freezing (including starting to walk, multiple turns, walking through a doorway, and attempting to sit upon reaching the final destination). This will enable comparison of resting-state and task-based functional connectivity in PD-FOG patients and to expand upon findings from previous studies.

All PD-FOG, PD patients without FOG, and healthy participants enrolled in the study underwent clinical assessment using the Mini BESTest, Timed Up and Go, and FOG assessments. These tests are validated measures of assessing PD patients at risk for falls, incorporate evaluation of FOG, and assess cognitive deficits in domains associated with FOG [42–44]. PD-FOG and PD patients without FOG perform these assessments (as well as neuroimaging) in the "OFF" state and then 60 to 90 minutes after taking their morning dose of dopaminergic medication, in the "ON" state. Results from the clinical evaluation are combined and compared with findings from the neuropsychologic and neuroimaging data obtained, to acquire a comprehensive profile of PD-FOG patients.

5. Early experimental data

Analysis of preliminary data from our study emphasizes the importance of combining neuroimaging and neuropsychological evaluation of PD-FOG in one study.

First and perhaps most importantly, standard measures used to identify PD-FOG appear to be inaccurate. Of the initial 15 PD patients enrolled in our study, 11 patients self-reported FOG, four patients had FOG during clinical evaluation, and eight patients had FOG according to physical therapy assessment. Almost all studies to date have classified PD-FOG based on self-report and/or clinical evaluation. Self-report of PD-FOG appears to be an overly sensitive measure, whereas clinical evaluation is brief and therefore specific but not sensitive. The validated FOG assessment score used in physical therapy may be the most accurate measure, as participants are observed walking through a course designed to induce FOG, including walking while dual-tasking, through a narrow doorway, and clockwise and counter-clockwise 360° turns. Previous studies of PD-FOG may have erroneous results based on data collection from an improperly stratified cohort. It is possible the foundation of knowledge we have gained from previous studies of PD-FOG may be largely inaccurate.

Preliminary analysis of the effects of levodopa on functional connectivity in PD-FOG patients correlates with the neuropsychological findings. We found greater connectivity of the supramarginal gyrus in both the PD groups in the OFF state than in healthy participants. The supramarginal gyrus is a component of the frontoparietal network that is activated for phonological processing during both language and verbal working memory tasks. Supramarginal gyrus hyperconnectvity essentially normalized in PD without FOG with levodopa but remained abnormal in PD-FOG patients. Neuropsychological testing in the ON state found no differences in executive function between the PD without FOG group and healthy participants. However, the PD-FOG group exhibited executive dysfunction, and frontoparietal functional connectivity was positively correlated with dysfunctional phonological processing. The consistency between neuropsychological and neuroimaging results helps confirm that executive dysfunction is pertinent to the development of PD-FOG and identifies its neuroanatomical structural correlate within the frontoparietal network. This demonstrates how a combined approach using both neuroimaging and neuropsychological analysis can augment interpretation of scientific results in the broad spectrum of neurodegenerative disorders.

6. Summary and conclusion

Numerous studies evaluating PD-FOG have been performed with some overlap in findings, but no unified etiologic or pathophysiologic framework has been identified. A comprehensive approach combining multimodal imaging, neuropsychological evaluation, and clinical findings in a longitudinal study is needed and underway. Evaluations performed in both the OFF and ON state allow us to better understand the role of levodopa therapy in PD-FOG. Elucidating the mechanisms underlying PD-FOG is critical to understanding how pharmacologic and neuroprotective interventions could impact its development. Furthermore, a means of anticipating which PD patients will develop PD-FOG is needed. Ultimately, a better understanding of PD-FOG may promote development of therapeutic modalities to treat this disorder. The neuroscience infrastructure provided by the National Institute of General Medical Science in supporting the Center for Neurodegeneration and Translational Neuroscience supports this important advance in understanding PD and PD-FOG. Improving

our evaluation of phenomena such as PD-FOG provides a guide by which we can investigate phenotypic manifestations of other neurodegenerative disorders, such as AD.

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RESEARCH IN CONTEXT

1. Systematic review: A comprehensive literature search identified studies using neuropsychological evaluation and/or neuroimaging to evaluate freezing of gait in Parkinson's disease.
2. Interpretation: Numerous studies evaluating PD-FOG have been performed with some overlap in findings, but no unified etiologic or pathophysiologic framework has been identified.
3. Future directions: A combined approach of neuropsychological evaluation and innovative neuroimaging to longitudinally evaluate FOG is needed to determine the relationship between the associated cognitive dysfunction and underlying neural networks involved. This review highlights the findings of previous studies and places the current Center for Neurodegeneration and Translational Neuroscience study, "a longitudinal study of multimodal imaging and cognition in Parkinson's disease freezing of gait," in this context.

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