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Featured Article

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

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Abstract 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 subsequent morbidity and mortality in Parkinson's disease. There are few therapeutic modalities for FOG; therefore, research to determine the underlying neural mechanisms is paramount. Studies have evaluated the neuropsychological profile of those with FOG in Parkinson's disease or used neuroimaging to identify underlying deficits in structural and functional connectivity. A combined approach longitudinally evaluating the associated cognitive dysfunction and underlying neural networks in FOG is needed. This article reviews neuropsychological and neuroimaging studies to date and introduces a new study of multimodal imaging and cognition in Parkinson's disease FOG. The study 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]. 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

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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.