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Point of view

'Cognitive freezing': A newly recognized episodic phenomenon in Parkinson's disease

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1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder recognized by its motor symptoms [1]. However, ample evidence suggests that patients with PD have associated cognitive decline that involves several domains [1]. The dominant pattern of cognitive deficits consists of impaired executive, memory and visuospatial function [2]. With advancing disease, several other cognitive domains show impairment such as reward based decision making and reversal learning [2]. As the understanding progresses of the underlying neurobiology of the cognitive symptoms associated with PD, several new cognitive phenomena may be described. We hereby report a previously unrecognized and undefined phenomenon which we term episodes of 'cognitive freezing' and propose potential mechanisms.

2. Case descriptions

Five patients with PD who presented with a unique cognitive phenomenon are described. The study was approved by the Western University Human Subjects Research Ethics Board (HSREB number 112975). Clinical details are summarized in Table 1. Based on the motor phenotype classification, all patients were of akinetic-rigid (AR) and postural instability gait difficulty (PIGD) phenotype except one, who was of the mixed phenotype [3]. Varying severity of cognitive decline and gait dysfunction was universally present suggestive of cholinergic deficits [4]. The details of the cognitive freezing episodes are summarized in Table 2. We selected an illustrative case to provide a comprehensive description about the episode, triggers and associated symptoms.

3. An illustrative case

Twelve years ago, a 68-year-old gentleman presented to the clinic with a 2-year history of deterioration in handwriting, hypophonia, stiffness in his right arm and decreased right arm swing without tremor. A diagnosis of idiopathic PD was confirmed and at this time he was doing well on 400 mg of levodopa. Subsequently, he developed freezing of gait and speech decline for the past 6 years and cognitive symptoms of poor attention for 2 years.

For the past 1 year, episodes of unresponsiveness occurring once per week and lasting 15–30 min were observed by the spouse. Trigger for these events was usually multitasking: for instance, while heading towards his recliner to sit down, he would momentarily get distracted by the television following which he would stop approaching the recliner and continue to stand in one place and stare at the television. He was unresponsive to any form of stimuli except on occasions his spouse could interrupt these episodes by insistently instructing him to move. He would finally emerge out of these episodes and behave as though nothing had happened. He does not lose muscle tone, sphincter control or consciousness during these episodes. He was observed by our team during one such episode which lasted around 10 min. He has had three full day ambulatory electroencephalographic (EEG) studies which have

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Table 1
Clinical characteristics of the patients.

Patient	Gender	Age at onset of PD (years)	Duration of PD (years)	LED* at onset/ follow up(mg)	History of FOG@	Frequency of falls while walking (in the last 5 years)	Cholinergic symptoms	Treatment with cholinesterase inhibitors	Treatment with anti-psychotics	Treatment with stimulant therapies$	Orthostatic hypotension	UPDRS ± motor score (108)	HOEHN YAHR stage	Motor phenotype at diagnosis$^{\beta}$	Cognitive symptoms	MoCA¥ score at last follow up (out of 30)	EEG ≠
1	Male	56	12	400/ 800	Yes	4-8/month	RBD€, constipation, urinary disturbance, gait impairment	No	No	No	No	44	3	AR/PIGD	Poor attention	27	Normal (in a total of 3 full day recording)
2	Male	62	18	300/ 1080	No	4/month	RBD€, hallucinations, delirium, constipation, urinary symptoms, abnormal sweating	Yes	No	No	No	22	2.5	AR/Mixed	Poor short-term memory	14	Normal
3	Male	77	10	300/ 900	Yes	< 1/month	Hallucinations, constipation, urinary symptoms, gait impairment	Yes	No	No	No	42.5	5	AR/PIGD	Poor short-term memory, confusion	10	Normal
4	Male	65	17	180/ 1332	Yes	4/month	Hallucinations, RBD€, constipation, urinary symptoms, gait impairment	Yes	Yes	Yes	No	60	5	AR/PIGD	Poor attention, confusion	8	Not done
5	Female	69	16	100/ 450	Yes	4/month	RBD€, constipation, urinary symptoms, gait impairment	Yes	No	Yes	No	30	3	AR/PIGD	Poor short-term memory, confusion	11	Not done

*Levodopa equivalent dose; €REM sleep behaviour disorder; ± Unified Parkinson's disease rating scale; ¥Montreal cognitive assessment; ≠ Electroencephalography;$^{\beta}$ Patients were classified based on the motor phenotype at initial presentation into tremor dominant/akinetic-rigid/mixed (TD/AR/mixed) as well as tremor dominant/postural instability gait difficulty/mixed (TD/PIGD/mixed) subtypes, @ Freezing of gait, $ methylphenidate.

Table 2
Descriptions of the cognitive freeze episodes.

Patient	Duration of episodes at last follow up visit (years)	Frequency (per month)	Duration of each episode	Triggers	Transition from the episode to awareness	Walk or talk during episode	Insight regarding episodes	Relation to LD timing?	Effect of modification of levodopa dose
1	1	> 10	15–30 min	Multi tasking	Spontaneously and sometimes facilitated by external stimuli (repeated verbal commands)	Sometimes	Yes	no	Not attempted
2	2	4	12–24 h	Not known	Spontaneous	No	No	no	Not attempted
3	1.5	2	10 min	Multi tasking	Spontaneous	No	No	before receiving levodopa	Dose increased without any influence on the episodes
4	2	3	6–12 h	Not known	Spontaneous	No	No	no	Not attempted
5	5	1	2–6 h	Multi tasking	Spontaneous and sometimes facilitated by painful stimuli or cold exposure	No	No	no	Not attempted

been normal. However, no episodes occurred during these recordings.

4. Discussion

We present these 5 cases to bring to attention a unique phenomenon that we have observed in patients with advanced PD. Although we have described the episodes for only one patient, the rest of them had similar presentations but with varying durations, frequencies and intensities and the episodes were predominantly triggered by multitasking. We hereby propose a few theories to explain the underlying mechanisms of these episodes as well as the reasons for the disparity noticed amongst patients.

5. Dysfunction of parallel and integrative circuits underlying the cognitive freeze episodes

Based on the cortical connections, the striatum is subdivided into different territories: sensori-motor, cognitive and limbic striatum [5]. Although, the 'parallel cortico-striatal circuits' are well segregated, they also have overlaps, interconnections and convergence across these striatal subdivisions [5–7]. The transfer of information from one parallel functional circuit to the next is carried out by a feed-forward loop which constitutes the 'integrative circuit' [6]. Therefore, the striatum serves a dual organizational purpose; parallel as well as integrative processing of information via the cortico-striatal and intra-striatal circuits [8]. Hence, in order to proceed from having an intention to perform a task to actual movement, information must be transferred from the limbic to cognitive to motor striatum [6,9]. Therefore, the ability to carry out a goal-oriented task depends on the parallel loops and to modify the task based on any internal or external cues depends on the integrative network [10].

The clinical history of our patients suggests that they have impaired processing of both parallel and integrative circuits. Patients had motor as well as cognitive impairments implicating dysfunction in at least two parallel circuits, namely, motor and cognitive. The ability to uncouple the execution of motor task from mental deliberation (dual tasking) requires that the parallel basal ganglia circuits remain segregated [11]. During an exclusively cognitive task, ventro-anterior putamen is activated and during an exclusively motor task the dorso-posterior putamen. However, due to predominant dopamine depletion in the dorso-posterior putamen in PD, the execution of motor task now depends on relatively preserved anterior putamen, the so called 'bottle necking' of information [9,11–14]. This causes an information overload passing through the same pathway leading to an inability to do these two processes simultaneously [13,15]. Therefore, the competing processes of watching television (cognitive portion) and walking towards the recliner (motor portion) try to access the same pathway resulting in an inability to continue to do the task simultaneously thereby precipitating the cognitive freeze. A second mechanism can also be inferred based on these observations. Our first patient would experience these episodes triggered by a distraction such as television while carrying out a motor act (approaching the recliner) and his inability to adapt to this distraction (ignoring it) suggests that the integrative network may also be dysfunctional.

The parallel cortico-striatal pathways not only have overlaps across the striatal subdivisions but also share common output nuclei, namely GPi/SNr (Globus pallidus internal segment/Substantia nigra *pars* reticulata), providing another anatomical location for integration of different circuits that are involved in different functional modalities [16]. Under normal circumstances of locomotion, the motor circuit inhibits the output nuclei GPi/SNr, which in turn leads to disinhibition of the pedunculopontine nuclei (PPN) thereby promoting movement. In patients with PD, in addition to dysfunction of the motor circuit, there is also involvement of cognitive and limbic circuits. Since all three circuits converge on common output nuclei which in turn has profound effect on modulating the activity of PPN, it can be deduced that disturbances

in any of these circuits will have an impact on motor output. In fact, this conclusion has been drawn in the 'interference model' used to explain freezing of gait (FOG) by Lewis and Barker [16]. FOG is an episodic motor phenomenon [17] more commonly associated with the PIGD phenotype and was noted in 4 out of 5 of our subjects. In PD there is striatal dopamine depletion which leads to limited striatal reserves. Therefore, when there is activation of a single pathway, for instance walking (motor circuit), the reserve of dopamine is just about sufficient to maintain suppression of GPi/SNr activity thereby disinhibiting PPN which allows locomotion. However, under situations where competing parallel circuits are activated (motor, cognitive or limbic) simultaneously, there develops a transient 'shortage' of dopamine. This shortfall in dopamine prevents the maintenance of inhibitory control over the output nuclei GPi/SNr which in turn leads to inhibition of PPN resulting in FOG. A similar 'jamming' of the parallel circuits at the output nuclei due to dopaminergic loss would also explain cognitive freezing which occurs when multiple parallel pathways are activated simultaneously. It is interesting to note that although FOG and cognitive freezing appear to be similar in their clinical expression, there are several differences between the two phenomena. FOG is an episodic motor phenomenon that lasts seconds and awareness is maintained. On the other hand, there is lack of awareness for the cognitive freezing episodes which occur for prolonged durations (minutes to hours). Therefore, it can be inferred that mechanisms beyond those explaining FOG are involved in the expression of cognitive freezing.

To summarize, the loss of segregation of the parallel circuits needed for execution of individual components of a task leads to 'locking up' of the overlapping parallel circuits and inability to modify the ongoing task based on external cues is due to 'locking across' the intra-striatal circuits. Impaired output due to dopaminergic denervation exacerbates 'jamming' of the parallel circuits providing a basis for cognitive freeze.

6. Severity of striatal neurodegeneration contributing to cognitive freeze

The five patients described here had varying severity, duration and frequency of these episodes. One theory to explain this difference amongst patients could be the severity of underlying striatal neurodegeneration as well as the degree of dopaminergic and cholinergic depletion. The advancing stages of neurodegeneration may produce increasing 'bottle necking' and intrastriatal over-lapping across the circuits. This could potentially explain the prolonged duration of episodes in three out of the five subjects who had longer durations of the disease (18, 17 and 16 years respectively) thus more severe neurodegeneration.

Apart from the duration of the disease, another important factor which determines the severity of this neurodegeneration is the age at onset. Younger age at symptom onset (less than 55 years) has been known to delay the onset of cognitive decline, presumably with lesser amount of neurodegeneration [18]. This could explain why the episodes of cognitive freeze were less severe in our first case (described above) who had onset of PD at the age of 56 years.

The degree of neuropathology would not only determine the severity of the episodes, but also the ability of an externally applied stimulation or medication to restore the circuits to a normal functioning state. In our first case the cognitive freeze could be broken after several explicit external cues, similar to auditory or visual cueing overcoming freezing of gait [19]. This further emphasizes that earlier age of onset of symptoms is responsible for lesser amount of striatal degeneration which could lead to 'unlocking' of the intra-striatal circuits on persistent external cueing, thereby allowing the system to pass the information from cognitive to motor circuit.

7. Influence of phenotype of PD on the cognitive freeze episodes

PD is traditionally classified based on motor symptoms into a tremor dominant (TD) and non-tremor dominant (NTD) phenotype [3]. Furthermore, the NTD phenotype is subclassified into akinetic-rigid (AR) or postural instability gait difficulty subtype (PIGD) depending upon the methodology of classification [3]. All our patients had an AR phenotype at presentation with the PIGD phenotype also appearing early in all subjects except one who had a mixed phenotype.

Several studies have shown that the NTD in particular PIGD compared to TD phenotype is most often associated with cognitive decline [3,20–22]. The underlying neural mechanisms for these differences could be both abnormal structural and functional connectivity across the cortico-striatal circuits in the NTD group [22]. Gray matter atrophy has been demonstrated both in the cortical and subcortical structures in the PIGD subtype [20,22–24]. A study by Rosenberg-Katz et al. showed that subjects with PIGD phenotype had more severe atrophy in the medial frontal and inferior frontal gyrus, regions that are involved in the cortico-striatal circuits sub serving cognition [22]. Similar patterns of subcortical gray matter volume loss in the amygdala and caudate which are involved in cognitive circuit have also been reported in the PIGD subtype [22–25].

In addition to the gray matter atrophy, the functional connectivity in the cortical and sub cortical regions is also impaired in the NTD phenotype [20,26]. This impairment could be partly attributed to the severe nigral pathology in the PIGD subtype that leads to dopamine depletion in the striatal subdivisions [26]. This dopamine depletion leads to loss of segregation and increased interactions and overlaps between parallel cortico-striatal circuits leading to the 'bottle neck' phenomenon described previously [9,27]. To understand the neural activity patterns in the two subtypes of PD namely TD and PIGD, a study utilizing resting state functional MRI in combination with regional homogeneity method was performed [20]. The brain regions showing abnormal pattern of neural activity in the PIGD phenotype included cortical and sub-cortical structures that are involved in the parallel circuits of sensorimotor, cognitive and limbic functions [20,28]. Since all our patients were of the PIGD subtype at presentation except one, who was of the mixed subtype, it could be hypothesized that the severe dysfunction of the cortico-striatal circuits as well as gray matter volume loss in this sub set of patients could be contributing to the cognitive freeze episodes.

8. Role of neurotransmitters in cognitive freezing episodes

A universal phenomenon in our patients during these episodes was the poor response or lack of correlation with levodopa intake. This suggests that a different neurotransmitter might have a critical role in the pathophysiology of 'cognitive freezing'. Several studies have shown a multisystem degeneration affecting different neurotransmitter systems in PD especially cholinergic dysfunction which plays an important role in cognitive decline [4,29–32]. The presence and severity of this cholinergic dysfunction could explain the prolonged durations and inability to interrupt the cognitive freezing episodes in some of our patients. These patients had a longer disease duration and the episodes of cognitive freezing resembled 'cognitive fluctuations', a core criterion for diagnosis of Dementia with Lewy bodies (DLB) [33,34]. PD dementia (PDD) and DLB share many clinical and neuropathological features in their advanced stages [34]. The episodes of cognitive freezing could be a part of the spectrum of these cognitive fluctuations.

The pathophysiology of cognitive symptoms in PD is related to an altered striatal cholinergic tone, dopamine–acetylcholine striatal imbalance and/or a degeneration of the cholinergic nuclei [4,30]. The maximum cholinergic dysfunction in PD is seen in thalamus and nucleus accumbens [35,36]. Thalamus has a central role in attention, arousal, vigilance and several cognitive functions including language, memory and visuospatial function. The thalamic nuclei that are important for these functions include the intralaminar, midline and mediodorsal nuclei. The central lateral nuclei of intralaminar thalamus have extensive projections to the anterior cingulate and prefrontal

cortices and degeneration of these nuclei are associated with onset of dementia in PD [37,38]. Several other studies have also shown that thalamic atrophy and volume loss is associated with development as well as progression of dementia in PD [36,39,40]. A similar impairment of the thalamocortical connectivity and damage to thalamic regions that project to prefrontal and parieto-occipital cortices of the thalamus has also been observed in patients with DLB who have significant episodes of fluctuating cognition [41]. Therefore, thalamic cholinergic dysfunction which is central to the development of cognitive fluctuations in DLB may also be implicated in the development of these prolonged episodes of cognitive freeze, clinically resembling cognitive fluctuations. Hence, in an already compromised cortico-striatal circuit, a progressive worsening of balance between dopaminergic-cholinergic innervation could destabilize the system and tip the system to a locked state for prolonged durations.

9. Limitations

There are some limitations to our observations. Two subjects did not have EEG studies. The EEG recordings in the other 3 patients were made in the interim period between episodes and were reported as normal. Nevertheless, the first case had 3 full-day EEG studies at different time points which were normal. Another limitation is that these patients were not subjected to full autonomic function testing and the cognitive freezes could be unidentified episodes of postural hypotension. However, the length of these episodes as well as absence of loss of postural tone during the episodes argues against this. It could also be reasoned that these episodes are fluctuations in cognition, a well-known phenomenon in patients with PD dementia (PDD). However, fluctuating cognition is described as a decrease in the alertness level which occur spontaneously, but our subjects predominantly had these episodes while trying to multi-task. Despite these limitations, we believe that we have recognized a unique phenomenon not previously described in patients with PD. It warrants further functional and EEG mapping studies in order to better understand this phenomenon providing a new perspective on cognitive dysfunctions in PD, where the classic parallel model with single neurochemical dysfunction is probably too simplistic.

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Author's roles

Mandar Jog: Conception, execution, review and critique.

Maria Florencia Alamos, Soumya Sharma, Niraj Kumar: Writing of the first draft, Manuscript preparation, review and critique.

Declarations of interest

Dr. Mandar Jog reports no disclosure related to this study. Outside of this study, he receives speaker and consultant honoraria from Merz Pharmaceuticals, Allergan, AbbVie. He also receives research grants from CIHR, AMOSO, Allergan, Merz Pharmaceuticals and Lawson Health Research Institute and is part of the AGE-WELL Network of Centers of Excellence (NCE) of Canada program. From time to time, he serves on advisory boards of Allergan, Boston Scientific, AbbVie and Merz Pharmaceuticals.

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