# Non-motor Symptoms of Parkinson's Disease—Considerations for Subclinical and Atypical Seizures

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Parkinson's disease (PD) is traditionally conceptualized as a neurodegenerative movement disorder, but patients affected by this disease commonly experience a wide range of non-motor symptoms of PD (NMS-PD). These NMS-PD can occur at all disease stages yet are poorly understood and lack effective therapies. PD pathophysiology has been classically described following lesional models of the basal ganglia and dysfunctions at a neurotransmitter level. However, studies that describe PD utilizing wide network perspectives, demonstrate an aberrant connectome at different levels, defined as dysfunctions in neural cortical and subcortical connectivity. While connectome dysfunction is better recognized in Alzheimer's disease (AD), its clinical relevance in PD remains to be fully appreciated. Moreover, while AD has been significantly associated with an increased incidence of epileptic activity, only in recent times similar have findings been reported in patients with PD. This review aims to raise awareness on how cortical and sub-cortical disruptions in the PD connectome could generate aberrant neuronal activity, eventually resulting in an epileptogenic substrate for subclinical or atypical seizure manifestations. We will discuss how these manifestations may be easily under-recognized or mistaken for other NMS-PD. Finally, we will discuss the important practical implications for a prompt diagnosis and proper therapeutic management.

**Keywords**

Parkinson's disease, non-motor symptoms, subclinical epileptic seizures, non-motor epileptic seizures, connectome dysfunction

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Parkinson's disease (PD) is a multifaceted neurodegenerative disease that progressively affects individuals' mobility. In addition to the cumulative motor disability, a plethora of non-motor symptoms (NMS-PD) can be encountered at different stages of the disease. Some of these NMS-PD are indeed regarded as significant determinants of the patient's quality of life, functional independence, and overall prognosis.[1,2] As a degenerative movement disorder, PD has been traditionally linked to the progressive accumulation of aggregates of abnormal alpha-synuclein, as well as to oxidative stress and various environmental factors potentially operating in a context of increased genetic vulnerability.[3–5] Conceptual models of motor manifestation in PD have been traditionally based in the balance of the direct and indirect dopamine pathways at the basal ganglia, and its associated dysfunctions at a neurotransmitter level.[6] However, in the recent past, growing experimental evidence has supported the use of a wider neural network model to represent and explain various clinical phenomenologies of the disease and specially aid a better understanding of NMS-PD.[7,8]

The exact pathophysiology of NMS-PD remain elusive, preventing the development of effective interventions, thus stirring what some have referred to as "therapeutic nihilism".[9] In general, NMS-PD have been studied with the same approach used to investigate motor symptoms, i.e. primarily based on Lewy body brain pathology and changes in specific neurotransmitters.[10] Examining the nature of NMS-PD from the perspective of systematic neural connections, or the connectome, may provide insightful information, with potentially relevant practical implications.

While Alzheimer's disease (AD) and epilepsy share a well-known epidemiological association,[11,12] a similar link between PD and epilepsy has only recently been reported.[13] Translational discussions on the potential association between PD, connectome dysfunction, and NMS-PD are largely absent from the current literature and the dominant clinical constructs. The main purpose of this review is to discuss how disruptions occurring on a connectome level may generate aberrant patterns of neuronal activity eventually manifesting as subclinical or atypical seizures in patients with PD. These epileptic equivalents may be commonly mistaken for NMS-PD. We will describe how these manifestations, if untreated, could progressively impinge on patients' cognitive function, thus contributing to cognitive

decline, increased functional burden, and overall poorer prognosis. The clinical implications for proper diagnosis and therapeutic management will be finally discussed.

## Parkinson's as a disease of neuronal connectivity

The clinical manifestations of neurodegenerative disorders have been traditionally described from an impaired neuronal circuitry perspective.[14] Technological advancements have led to a surge of studies investigating the impact PD has on neural excitability and connectivity utilizing electroencephalogram (EEG), neuromodulation techniques, imaging modalities, and graph-analytical methods. Although the field of PD has been somewhat slower to incorporate these concepts compared to other disease models, clinicians now generally acknowledge the complex, multifaceted nature of the disease and the need to pursue multidimensional approaches to study it.

EEG is an easily accessible, non-invasive technique that provides evidence of neuronal dysfunction at the cortical level. Studies utilizing EEG have demonstrated differences in neural oscillations between the brains of patients with PD and healthy controls. Patients with PD have increased diffuse slow waves, increased frequency of rhythmic background activity, and decreased relative $\alpha$- and $\beta$-band powers,[15–17] confirming the alteration of cortical patterns of neural oscillations. Furthermore, EEG abnormalities correlated with cognitive function helping differentiate cognitively normal patients with PD from those suffering from PD dementia and Lewy body dementia (LBD).[18] A variety of EEG factors correlate with cognitive deterioration and could serve as biomarkers for PD dementia, such as increased slow waves and decreased fast waves along with low background rhythm frequencies.[16,19,20] While such findings may help to distinguish patients with PD from healthy controls, as well as to predict which patients may develop PD dementia, they merely touch the surface of the extent of connectome dysfunction involved in PD. These EEG findings reflect the importance of cortical dysfunction in PD physiopathology and its correlation with cognitive performance.

Neuromodulation techniques, such as transcranial magnetic stimulation (TMS) and deep brain stimulation (DBS) provide a complementary approach to study connectome dysfunction. TMS, like EEG, provides information at a cortical level but it may also be used to probe the integrity of distinct neuronal circuits by means of different neurophysiologic parameters. The study of motor cortex physiology of patients with PD indicates that the excitability of the motor cortex in PD is abnormal compared with healthy controls.[21] There is considerable variability in these measures related to inter-individual variations, different disease characteristics, and methodological considerations. While there have been some contradictory findings,[22] more recent studies have supported increased cortical excitability by increased intracortical facilitation, decreased intracortical inhibition, and shortened cortical silent period (CSP).[23–25] The functional significance of such a hyper-excitability state remains debated. While an aberrant cortical excitability may be directly involved in the pathophysiology of certain symptoms of the disease, it is also generally believed that it may represent an adaptive phenomenon progressively arising in response to a primary defective network dysfunction involving the basal ganglia output pathways.[25] Either a compensatory denervation state or additional spinal effects have been proposed to explain, in part, these excitability abnormalities despite the discrepancy with reduced thalamo-cortical signaling demonstrated by classical models of PD.[25,26] Motor symptoms of PD typically manifest asymmetrically and correlate with asymmetry in some neurophysiological measurements such as the duration of CSP in the more affected brain hemisphere. As the asymmetry of symptoms decreases over time, the CSP values increase towards the CSP recorded in the less-affected hemisphere, decreasing the interhemispheric CSP ratio,[27] which demonstrates the plasticity of the neural connections through the development of compensatory mechanisms that could lead to further downstream consequences. This hypothesis is further supported by studies utilizing DBS that show elevated high-frequency oscillations in the basal ganglia of patients with PD along with pathological synchronization as recorded by both microelectrode recordings and local field potentials.[28,29] As basal ganglia function progressively deteriorates, increased neuronal excitability and firing synchronicity is observed at striatal output level, by virtue of homeostatic plastic changes that are increasingly stressed. Moreover, long-term DBS can result in a topological reorganization establishing healthy functional networks in the brains of patients with PD.[30]

To further establish the clinical applicability of connectome network dysfunction, studies have demonstrated that circuit-specific modulatory therapies, such as repetitive TMS, can alleviate various symptoms of PD, from memory and motor symptoms to depression in PD.[31–34] Although from a therapeutic standpoint, there is much to streamline and corroborate with respect to repetitive TMS paradigms and methodologies, there is no denying the potential to providing individualized circuit-specific modulatory therapies.[35]

Other convincing evidence to illustrate network dysfunction in PD has so far been provided by brain imaging studies. Investigators have utilized structural, functional, and diffusion magnetic resonance imaging (MRI) to generate computational models to depict a reflection of the complexities that make up the human connectome. Many studies have used region-of-interest and voxel-based morphometry-based approaches to study cortical atrophy in patients with PD, particularly those with PD dementia.[36–39] A meta-analysis on such studies showed that patients with PD dementia had more gray matter atrophy in the medial temporal lobe bilaterally and basal ganglia compared to healthy controls with greater atrophy in the medial temporal lobe correlating with worse dementia.[40] Computational models, especially graph theory analysis, have elaborated on the effects that PD has on the connectome on a structural and functional level.[41] Even in the early stages of PD, patients appear to experience disruptions in global, large-scale coordination of brain networks and topological organizations that correlate with cognitive function, while motor symptoms tend to correlate with disruptions in local connections.[8,42]

Several fortuitous observations provide evidence towards PD manifestations occurring secondary to connectome dysfunction and a hyper-excitable state. For example, zonisamide, an antiepileptic drug, provided to a patient with PD with epileptic seizures led to not only resolution of the seizures but also improvements in PD motor symptoms.[43] A clinical trial subsequently corroborated the finding that zonisamide improved PD symptoms, even in non-epileptic patients.[44] Others have reported the use of zonisamide to improve motor symptoms in patients with PD dementia[45] and patients with PD and psychiatric symptoms.[46] This introduces a point that will be further addressed in the following sections, i.e., the possibility of under-recognized and under-diagnosed subclinical or atypical seizures secondary to connectome dysfunction.

## Relationship between disrupted neuronal connectivity and epileptic seizures

Epilepsy is considered a disease of network dysfunction.[47,48] At a microscopic level, both simple and complex partial seizures involve disruptions in the excitatory interactions between cerebral cortex pyramidal cells.[49] From a neurophysiology view, the EEG-graphic representation of an epileptic event is characterized by the paroxysmal onset of hyper-synchronized sharp waves disrupting the neuronal background activity. This activity is often multifocal, reflecting a broader network dysfunction.[50,51] Moreover, TMS studies demonstrate similar neurophysiologic features between epilepsy and PD characterized by a state of increased cortical excitability as indicated by reduced intra-cortical inhibition and increased intra-cortical facilitation observed in both patient populations.[25,52–55] As mentioned before, in PD, cortical neurons innervating the basal ganglia become hyperexcitable, possibly as a compensatory mechanism following the incremental rise in the output threshold of striatal dopaminergic neurons. As such, it would not be surprising if this putatively maladaptive phenomenon may eventually lead to the generation of epileptiform activity. While epidemiologically, epilepsy-increased comorbidity in patients with PD remains questioned,[13,56] our group published the largest case series of patients with PD with concomitant epilepsy[57] raising the possibility that epileptic activity in these patients may indeed be under-diagnosed and under-recognized.

### Epilepsy in neurodegenerative and neuro-psychiatric disorders

In the general population, epilepsy occurs approximately in 1% of people >60 years old.[58–61] Neurodegenerative disorders have been recognized as potential risk for developing epilepsy in adults. In a recent study, Feddersen and colleagues reported that 2.6% of patients with PD develop epilepsy.[62] In addition, a previous report by Bodenmann et al., described a prevalence of 2.4%.[63] These values are slightly higher than those expected in the general population, but much less than the prevalence of epilepsy in AD, which is about 10%.[56] Autism spectrum disorder has been recently linked to increased risk of developing epilepsy.[64,65] Additionally, patients with other degenerative movement disorders, such as Huntington's disease,[66] LBD and Creutzfeldt-Jakob disease,[67] have shown to be at increased risk of experiencing seizures.[11,12,68–70] Conversely, people with epilepsy are three times more likely to have PD and eight times more likely to have AD.[71] An important aspect that remains to be elucidated is whether the aforementioned changes in network connectivity and cortical excitability may constitute the underlying substrate that eventually triggers seizures or, alternatively, if these changes represent the indirect consequence of a primary epileptiform activity. Given the association between PD and other neurodegenerative diseases with epilepsy, examining the precise nature of such may hold relevant clinical implications. Moreover, evidence of epileptic activity is typically confirmed from cortical EEG recording studies, but the potential for deep cortical and subcortical epileptic generators, particularly in the limbic regions, should be considered.[52,72] These generators may be simply undetectable by surface electrodes because of their anatomic location and therefore escape from routine electrophysiological assessments.

## Subclinical or atypical epileptic seizures could masquerade as non-motor symptoms of Parkinson's disease—clinical implications

While the non-motor questionnaire and non-motor symptoms scale (NMSS)[73,74] allow improved detection and tracking of NMD-PD, the symptoms often remain under-recognized and under-appreciated by clinicians and caretakers. Recently, six different clinical phenotypes of PD were recognized on the basis of prevalent NMS-PD.[75] These non-motor signatures included cognitive impairment, apathy, depression/anxiety, REM behavioral disorder (RBD), lower limb pain, and weight loss/olfactory dysfunction. This distinction may help in promoting the incorporation of NMS-PD into routine assessments, emphasizing the importance of these features for an adequate appreciation of the patient's clinical picture. On the other hand, a rigid categorization may challenge the flexible and consistent monitoring of these dynamic and overall nonspecific symptoms along the disease course.

In AD, awareness regarding the potential occurrence of different kinds of epileptic events has been increasing. The phenomenology of these events ranges well beyond the spectrum of classic motor paroxysms and includes the possibility of both subclinical and non-motor seizures. As a case in point, despite the known prevalence of epilepsy in AD being near 10%, it was recently found that more than 40% of patients with AD had subclinical epileptiform activity. Notably, this ongoing paroxysmal activity would have not been captured if not expressly investigated by the authors.[12] Even though the pathophysiological relevance of this subclinical epileptiform activity cannot yet be confirmed, its high prevalence in AD highlights the possibility of underdiagnosed seizures in this population. More recently, PD has also been recognized for its increased prevalence of epilepsy[62,63] and 1.7 increased odds of epileptic seizures.[13] These findings support the possibility of under-recognized epileptiform activity in this population as well. Epileptic activity has been linked to accelerated neuronal death, poorer executive functioning, and global cognitive decline.[76] In patients with epilepsy, excitotoxic damage to neurons is generally mediated by excessive calcium inflow during seizures. The high level of calcium triggers the activation of nitric oxide synthase, thereby disrupting oxidative metabolism and creating free radicals. These free radicals ultimately damage the neuronal membrane. Pro-caspases are activated as well, leading to necrosis, apoptosis or autophagy mechanisms of neuronal death. The prompt recognition and adequate treatment of these phenomena may therefore hold great prognostic relevance.

In the following section, we will focus on clinical features frequently displayed by patients with PD that may signal an ongoing subclinical or non-motor epileptic event masquerading as NMS-PD.

### Excessive daytime sleepiness

In a longitudinal study, 43% of patients with PD reported excessive daytime sleepiness (EDS) at baseline and by the end of a 5-year follow-up period, 46% of the remaining patients had developed EDS with poorer nighttime sleep, cognitive dysfunction, and hallucinations.[77] Patients with PD frequently experience EDS that is reported to be associated with disrupted neuronal networks in PD.[78] Patients with idiopathic RBD who experience EDS are more likely to develop a neurodegenerative disease, especially PD, compared to patients with idiopathic RBD without EDS.[79] EDS could indeed reflect poorer sleep quality, but recurrent episodes of drowsiness and confusion throughout the day should carefully be investigated to differentiate those related to post-ictal events or unrecognized non-motor seizures manifesting clinically with impairment of consciousness and alertness.

### Cognition

Cognitive decline is the most recognized NMS-PD; 25–30% of patients with PD without dementia have mild cognitive impairment (MCI)[80] and the

progression rate from PD-MCI to PD dementia is reported to be around 60% over 4 years.[81] The extent to which patients experience cognitive decline can range from subjective cognitive decline, to MCI, to PD dementia, all without clear divisions. PD dementia has characteristic features that separate it from AD, including cognitive fluctuations, hallucinations, depression, and sleep disturbances. Patients with PD have been shown to be at increased risk of developing dementia if they experience any of these factors during the course of their disease, particularly visual hallucinations.[82]

Clinically fluctuating cognition could present with drowsiness, episodes of illogical thinking and confusion in patients with PD dementia. This set of episodic non-motor complaints could be non-motor epileptic seizures or post-ictal states. In a patient with PD dementia, EEG will unlikely be among the first tests ordered, and even if it is, epileptiform activity may not be detected with a routine EEG. The possibility of recurrent events that remain undetected for several years have the potential of interacting with the progression of cognitive symptoms in these patients.[83] Furthermore, undetected, persistent epileptic activity could promote neuronal death and accelerate patients' cognitive decline, eventually leading to, or worsening the progression of, PD dementia. The molecular mechanisms involved in this phenomenon may include a seizure-induced excitotoxicity, which could potentially amplify neuronal sensitivity to alpha-synuclein-mediated degeneration, thus resulting in a complex cascade of cellular damage and network dysfunction.

## Hallucinations

Patients with PD often have visual and auditory hallucinations with prevalence rates of 22–38% and 22–48%, respectively.[84] While attributable to NMS-PD, there is anecdotal evidence that they may also be manifestations of non-motor seizure activity.[57] Various reports of patients with PD with hallucinations and other NMS-PD demonstrating epileptiform activity on EEG and treated with anti-epileptic drugs (AEDs), have shown improvement not just in their hallucinations but in their other NMS-PD as well,[57,85] suggesting a potential epileptic substrate in these cases.

## Diagnosing Lewy body dementia—a familiar list of complaints

From a clinical perspective, one of the cardinal features of LBD is the fluctuating temporal pattern of its cognitive, behavioral, and motor symptoms. Typically, patients affected by LBD display dramatic diurnal variability in their attention, alertness, interactivity, arousal, and motor performances. In this setting, differentiating the temporally variable phenomenology of the disease from potentially overlapping epileptic events can be particularly challenging. Further, the potential contribution of an underlying epileptogenic substrate to the "paroxysmal" pattern of LBD symptomatology remains to be investigated. Overall, there is much overlap in the non-motor manifestations of PD, PD dementia, and LBD, and the fields of PD and LBD have each created screening tools independent of each other that are strikingly similar. Based on typical diagnostic criteria of LBD[86] a composite score was created to help quickly screen for LBD in clinical settings.[87] Items include the cardinal Parkinsonism motor symptoms, EDS and drowsiness, episodes of illogical thinking or incoherent thoughts, frequent staring spells, visual hallucinations, and RBD. While playing an important tool in both clinical and research settings, the symptoms chosen for this screening tool bear a striking resemblance to the NMS-PD that we propose could be epileptic seizures going unnoticed. This is a scintillating comparison, especially considering that abnormalities observed in EEGs of patients with PD dementia with fluctuating cognition resemble the abnormalities in EEGs of patients with LBD.[18] It is tempting to speculate that some of the symptoms commonly used to diagnose LBD could actually be manifestations of epileptic seizures in their very nature. These manifestations may be easily unrecognized by a patient with dementia and potential altered self-awareness, and/or undiagnosed by physicians given the fact that many of these episodic events are attributed to common symptoms of LBD and have not been formally challenged as epileptic in nature thus far.

## Potential therapeutic implications for non-motor symptoms of Parkinson's disease and future investigations

Current available therapies for treating NMS-PD include pharmaceutical therapies, exercise, and brain stimulation to improve various NMS-PD.[88,89] Cognitive deficits contribute largely to the morbidity of NMS-PD and have remained without efficient therapy. AEDs have been proposed to prevent the cellular death and cognitive worsening associated with the presence of epileptic seizures in AD.[90] In light of the aforementioned similarities between PD and AD constructs, we believe that the long-term impact and therapeutic implications of AEDs on the natural course of PD should indeed be adequately investigated through properly designed clinical trials in the future.

Many mechanisms of cognitive decline and other NMS-PD have been proposed in PD. These include progressive alpha-synuclein disease, affected neurotransmitter systems, synaptic changes, inflammation, mitochondrial dysfunction, genetic risk factors,[91] white matter lesions,[92] and network dysfunction.[93,94] While studies in AD have begun to support the role of connectome dysfunction in accelerating cognitive decline through recurrent epileptic events, this possibility remains to be investigated in patients with PD. As such, properly designed studies should be conducted to better characterize these phenomena in this specific population.

Compelling evidence could be gathered by the joined implementation of population-level EEG studies, and the extensive clinical and neurophysiologic characterization of those patients displaying "episodic" or "paroxysmal" non-motor features during the disease's course given the potential for AED therapeutic intervention. Prospective, well designed studies in patients with PD with recurrent 'episodic' symptoms are needed to determine the real incidence of epilepsy, its characteristics, impact, and treatment response. There are no studies on the efficacy and tolerability of AEDs in patients with PD. Furthermore, considerations and precautions should be taken for the introduction of AEDs in elderly patients. In this population, AED toxicity, adverse effects, and tolerance can be complicated by numerous pharmacodynamic and pharmacokinetic factors: drug interactions, renal clearance, adipose mass, hepatic metabolism, etc. In addition, elderly population sensitivity to psychotropic medications should also be considered. AEDs are recommended to be introduced very gradually, with systematic monitoring of side effects and interactions (i.e., biological and clinical assessments), and periodic blood levels of AEDs are recommended.

Different neuromodulation techniques can be used to improve mood and cognitive symptoms in PD.[88] For example, DBS of the subthalamic nucleus can improve certain NMS-PD, with particular respect to sleep/fatigue and perceptual problems/hallucinations.[95] While these improvements may

certainly be explained in light of a functional rearrangement of dopaminergic circuitries, it is also possible to speculate that, at least in part, DBS may act by normalizing a potential epileptic substrate involved in the generation and maintenance of these symptoms.

## Conclusions

As investigators continue to unravel the human connectome, we expect a growth in studies integrating neurophysiology, neuroscience, and clinical neurology. The human brain can be regarded as a complex biologic system in which an exponential number of interacting elements are constantly maintained in a state of dynamic balance by virtue of different homeostatic mechanisms ensuring the overall functioning of its constituting networks. When certain elements begin to fail, pathological changes ensue and can manifest in the vast neurological disorders known to medicine. Notwithstanding the obvious risks of mechanical reductionism inherent to such an approach, we believe that conceptualizing neurodegenerative disorders as network diseases may indeed contribute to better understand some of their most complex and elusive symptoms. Decreased cortical inhibition and increased cortical excitability have been reported both in PD and in epilepsy-affected patients; this hyper-excitable state may contribute to the onset of epileptiform activity. The complexity of clinical phenomenology and the lack of a well-defined and accepted cause of cognitive fluctuations and other episodic NMS-PD, highlight the necessity to re-think the current paradigm by considering novel mechanisms and alternative diagnostic constructs. Subclinical epileptiform activity and potentially under-recognized non-motor seizures have been associated with fluctuations in cognition, rapidly progressive cognitive decline, or early-onset of disease in AD and may play a similar role in PD. While epileptic activity has been consistently observed in the setting of primary dementing illnesses, particularly in their advanced stages, the precise occurrence and nature of this potential association in PD remains elusive.

NMS-PD already present a significant clinical challenge, but if complaints previously attributed to NMS-PD are indeed subclinical or non-motor epileptic seizures in disguise, appropriate treatment could improve quality of life and slow or even prevent cognitive decline to some extent. As such, for patients experiencing recurrent 'episodes' of drowsiness and/or confusion, new recurrent 'episodes' of illogical thinking, staring spells, visual or auditory hallucinations, an epilepsy workout should be strongly considered. In addition, as epileptiform activity is not always easily detected via EEG or video-EEG, an empiric AED trial might be considered *ex juvantibus* when the suspicion level supports the diagnosis. ❑


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