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REVIEW ARTICLE

Cognitive Decline in Parkinson's Disease: Theories and Implications for Rehabilitation

Katherine A Brown, PhD, CCC-SLP, CBIS[1], *Dale KL Summers, MS, CCC-SLP*[2] *and Kristie A Spencer, PhD, CCC-SLP*[2*]

[1]*Department of Communication Sciences and Disorders, Augustana College, USA*

[2]*Department of Speech and Hearing Sciences, University of Washington, USA*

***Corresponding author:** *Kristie A Spencer, PhD, CCC-SLP, Department of Speech and Hearing Sciences, 1417 NE 42nd Street, University of Washington, Seattle WA 98105, USA, Tel: 425-478-5962*

Abstract

Purpose: Cognitive changes in Parkinson's disease (PD) can occur at any stage of the disease and have been shown to significantly impact well-being and life participation. The nature and pattern of cognitive decline in PD remains unclear due to the heterogeneity of symptoms and lack of a clear explanatory model. This review aims to draw attention to several theoretical models of cognitive decline in PD to deepen our understanding of the complex milieu of symptoms and begin to offer clinical implications for rehabilitation fields.

Method: The domains of cognition typically affected by PD are reviewed along with key aspects of five prominent models of cognition in PD. Implications are discussed through the lens of cognitive heterogeneity and clinical practice.

Results: Multiple cognitive domains are vulnerable to PD neuropathology, however, variability exists in the presence and severity of functional changes. Theoretical models that highlight disease progression, vulnerable neural networks, and neurotransmitter involvement provide insight into the variability of cognitive changes.

Conclusion: Although one single model cannot account for the wide variability in presentation and rate of cognitive decline in PD, consideration of multiple models provides important insight for research and clinical practice, such as the delineation of cognitive phenotypes.

Keywords

Parkinson, Cognition, Cognitive decline, Dementia, Rehabilitation

Introduction

Idiopathic Parkinson's disease (PD) is a progressive neurological disorder characterized by the loss of dopaminergic neurons and spread of Lewy pathology throughout the brain. In the United States, it is estimated almost one million people have PD, with higher prevalence rates among men [1] and as age advances [2]. While the traditional conceptualization of motor system impairment is well established, current thinking suggests PD is a complex, multisystem disorder of motor and non-motor characteristics. The hallmark motor signs of PD include tremor, rigidity, akinesia, bradykinesia, and postural instability. Secondary motor characteristics are also common and include dystonia, dysphagia, and dysarthria. Beyond these changes to the motor system, individuals with PD are prone to a wide range of non-motor symptoms, such as autonomic disturbance, sleep issues, neuropsychiatric impairments, and cognitive deficits [3]. These issues negatively affect quality of life and are associated with increased mortality [4-6], thus it is imperative to fully understand and identify non-motor symptoms in individuals with PD.

Cognitive impairment is one of the most debilitating and pervasive non-motor symptoms of PD [7,8]. Within one year of diagnosis, up to 32% of individuals with PD experience cognitive changes, and as many as 80% will develop dementia during the disease course [9,10]. The Diagnostic and Statistical Manual of Mental

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Disorders, 5th Edition [11] provides a framework for defining the progression of cognitive impairment. *Mild neurocognitive disorder* from PD would apply to individuals who are (1) Showing evidence of a significant decline on measures of cognition (typically 1-2 standard deviations below the mean), (2) Expressing concern about the change to cognition (per the individual with PD or other knowledgeable informant), and (3) Maintaining independence in their instrumental activities of daily living, even though compensatory strategies may be needed to achieve this independence [12]. Mild neurocognitive disorder may be likened to mild cognitive impairment (MCI) [13] and is often used interchangeably. *Major neurocognitive disorder* follows the same general criteria with two primary differences. First, the documented cognitive decline is more pronounced (typically greater than 2 standard deviations below the mean). Second, the person is no longer independent in their activities of daily living. Major neurocognitive disorder is often used interchangeably with PD dementia. For both major and mild neurocognitive disorder, the evidence of cognitive decline can manifest in a broad range of areas, including attention, executive function, learning and memory, language, perceptual-motor, and social cognition. Both the nature and pattern of cognitive decline in PD is highly heterogeneous [14], leading to considerable challenges in the conceptualization and management of these symptoms. Understanding the possible sources of cognitive variability may support research and clinical efforts to better serve individuals with PD. To that end, this review is intended to describe cognitive heterogeneity in PD, first providing an overview of cognitive decline, followed by a review of the most prominent explanatory theories that may underlie cognition variability.

Summary of vulnerable cognitive domains in PD

Attention: Attention processes are foundational to cognition and interwoven with other cognitive domains, such as memory formulation and orientation. Deficits in this area can substantially affect independence during activities of daily living [15,16] and are considered by some to be the strongest predictor of caregiver quality of life relative to other cognitive domains [17]. Individuals with PD are reported to have an impaired supervisory attentional system, and consequently show abnormal reliance on cortical executive control for automatic tasks, in addition to the typical non-routine tasks [18,19]. Thus, persons with PD may tax their executive and attentional processes for all types of tasks, even automatic or routine tasks such as walking and talking [20]. Internal control of attention may also be impaired Dujardin, et al., including tasks requiring sustained and alternating attention [21,22]. Disruption to attention neural network connectivity, and the associated behavioral manifestations, may be prominent even in mild cognitive impairment from PD [23].

Executive functions: Many consider executive dysfunction to be the hallmark cognitive impairment for individuals with PD, including those who are mild and newly diagnosed [24-26]. Individuals with PD are reported to have deficits in a wide range of executive abilities, such as set shifting, inhibition, planning, set acquisition, and working memory [27,28]. Executive dysfunction can similarly disrupt independence in activities of daily living and negatively impact quality of life Vlagsma, et al. Dopaminergic medication may also cause or exacerbate executive dysfunction; use of these medications has led to difficulty with impulse control and set-shifting ability in approximately 13% of individuals with PD [29,30].

Learning and memory: PD may lead to deficits across the stages of declarative memory (encoding, consolidation, storage, and retrieval/recognition), particularly for episodic memory [31]. These deficits are thought to stem not only from fronto-striatal associated dysfunction but also from medial temporal lobe disruption [32]. Impairments in prospective memory have also been reported in PD, particularly in advanced stages of the disease [33]. Moreover, working memory and reinforcement learning are prone to decline in PD and susceptible to levels of dopamine. Dopaminergic medication may differentially affect these processes, transiently improving working memory capacity and altering the effectiveness of positive/negative reinforcement learning [34-36]. With respect to non-declarative/implicit memory, deficits in procedural learning have historically been thought to emerge with progression of PD [37], particularly the impaired maintenance of procedures and routines [38]. However, more recent literature [39] indicates that individuals with PD are impaired at some, but not all, types of implicit learning. As with declarative memory, the common approach of assigning implicit memory functions to the basal ganglia and explicit memory functions to the medial temporal lobes has been oversimplified; these systems are thought to jointly contribute to behavior, advancing a more integrated view of basal ganglia function and its involvement in memory and learning [39].

Language: Language is another area susceptible to decline in PD, with an estimated prevalence of 50-60% [40], though motor and cognitive contributions often complicate the clinical picture. Language comprehension difficulties have been reported [41], particularly the processing and comprehension of complex grammar and syntax [42]. With respect to language production, there is some evidence of reduced cohesive adequacy [43] and informativeness [44] of discourse. Additionally, verbal fluency impairments are reported, but the findings are generally mixed [45]. This variability may be pharmacologically mediated, as the

use of dopaminergic medication may improve verbal fluency deficits [46]. Alternating verbal fluency (e.g., alternating between letters and vegetables) tends to be more impacted, likely because it involves set shifting in addition to language activation [47]. Emerging evidence also suggests a disproportionate impairment in the use of action verbs versus nouns; the proposed explanation is that the same brain regions necessary for learning and executing actions are also necessary for storing the semantic meaning of the word for the action [42,48]. Verb production is thus thought to be more susceptible to decline than noun production and may be indicated by greater pausing before verbs than nouns when speaking [45].

Visuospatial abilities: Individuals with PD are susceptible to deficits in visuospatial and visuoperceptual functioning [49] even early in the disease process [50]. Additionally, visual complaints (e.g., diplopia) and visual hallucinations may occur [51]. Deficits in visuospatial functioning can result in the diminished ability to perceive spatial relationships of objects, increasing the risk of falls and accidents [15,52]. While visual recognition tends to be preserved in individuals with PD, tasks that require visuospatial analysis and orientation are often affected, with greater loss of motor function associated with greater visuospatial impairment [53-55].

In sum, there is robust evidence that individuals with PD can experience deficits across cognitive-linguistic domains. Table 1 summarizes these impairments, along with examples of how functioning in each of these domains is often measured, including the discrete tests typically used in the aforementioned studies. As discussed, these cognitive issues are not universal or uniform, but rather lead to diverse impairment profiles. Numerous factors have been associated with this heterogeneity, such as the degree and location of neural degeneration. Disease characteristics and concomitant diagnoses may also influence the presentation of cognitive deficits. For instance, individuals with non-tremor dominant subtypes of PD, such as a predominance of postural instability and gait disturbance, tend to have more severe cognitive deficits than those with a tremor-dominant subtype [56]. Additionally, neuropsychiatric issues (e.g., anxiety, apathy, depression), sleep disturbance, and

Table 1: Domains of cognition and common methods of measurement.

Domain of Deficit		Example Methods of Measurement
General Cognition	Test Battery	Mattis Dementia Rating Scale-2 (Matteau, et al. 2012)
		Mini-Mental State Examination (Hoops, et al. 2009)
		Mini-Mental Parkinson (Mahieux et al. 1995)
		Montreal Cognitive Assessment (Hoops, et al. 2009)
		Neuropsychological Assessment Battery (Stern & White, 2003)
		Parkinson Disease-Cognitive Rating Scale (Pagonabarraga, et al. 2008)
Attention	Test Battery	Test of Everyday Attention (Robertson, et al. 1994)
• Sustained	Discrete Tests	Cancellation Tests (Zeltzer & Menon, 2008 a,b)
• Alternating/divided		Paced Auditory Serial Addition Test (Gronwall, 1977)
• Selective		Test of Variables of Attention (Greenberg, et al. 2017)
		Trail-Making Test (Bucks, 2013)
	Questionnaire	Moss Attention Rating Scale (MARS; Hart, et al. 2019)
Executive Functions	Test Battery	Behavioral Assessment of the Dysexecutive Syndrome (Wilson, et al. 1996)
• Planning		Functional Assessment of Verbal Reasoning and Executive Strategies (MacDonald, 2005)
• Judgment	Discrete Tests	Wisconsin Card Sorting Test (Grant & Berg, 1981)
• Inhibition		Stroop Color-Word Test (Golden & Freshwater, 2002)
• Set shifting		Tower of London, 2nd Edition (Culbertson & Zillmer, 2005)
• Reasoning		Digit Symbol Substitution Test (Bettcher, et al. 2011)
• Self-regulation		Design Fluency Test (Ruff, 2011)
		Verbal Fluency (Patterson, 2011)
		Alternating Verbal Fluency Test (Paula, et al. 2015)
		Porteus Maze Test (Porteus, 1965)
	Questionnaire	Behavior Rating Inventory of Executive Functions (Gioia, et al. 2013)

Learning & Memory • Working memory • Free recall • Visual memory • Recognition memory	Test Battery	Wechsler Memory Scale-4th Edition (Wechsler, 2009) Rivermead Behavioral Memory Test-3rd Edition (Wilson et al. 2008) Test of Memory and Learning-2nd Edition (Reynolds &Voress, 2008) Hopkins Verbal Learning Test-Revised (Belkonen, 2011) California Verbal Learning Test-3rd Edition (Delis et al. 2017)
	Discrete Tests	N-back Task (Coulacoglou & Saklofske, 2017) Digit span (Wambach et al. 2011) Benton Visual Retention Test-5th Edition (Sivan, 1991) Selective Reminding Test (SRT; Randall & Kerns, 2018)
	Questionnaire	Everyday Memory Questionnaire (Sunderland et al. 1984)
Language • Semantic fluency • Phonemic fluency • Confrontation naming • Sentence comprehension • Pragmatics	Test Battery	Assessment of Pragmatic Abilities and Cognitive Substrates (Arcara & Bambini, 2016)
	Discrete Tests	Boston Naming Test-2nd Edition (Roth, 2011) Test of Adolescent/Adult Word Finding-2nd Edition (German, 2016) Verbal Fluency (Patterson, 2011)
Visuospatial Abilities • Visual integration • Visual perception • Spatial navigation • Visuomotor functioning	Discrete Tests	Judgement of Line Orientation (Irani, 2011) Intersecting pentagons (Jefferson et al. 2002) Visual Patterns Test (Sergio et al. 1997) Simple Copy Task (Dridan et al. 2013) Clock Drawing Test (Eknoyan et al. 2012)

Table 2: Summary of theories of cognition and the clinical implications.

Theory	Summary	Clinical Implications
The Braak Model Braak, et al. (2003)	• PD progresses in a caudal-rostral fashion via 6 stages. • Stages 1-2: Pathology initiates in peripheral regions. Patients are initially asymptomatic. Autonomic dysfunction present by stage 2. • Stages 3-4: Pathology progresses to the subcortex. Symptoms include disturbed sleep, tremor, rigidity, and slowness of movement. MCI may arise due to disrupted neural connectivity. • Stages 5-6: Pathology progresses to the cortex. Symptoms include cognitive impairment, possibly dementia.	• Non-motor symptoms (e.g., sleep, decreased olfaction) regulated by peripheral regions appear early in the disease, often before the traditional motor symptoms. • Younger patients who have a longer clinical course tend to have pathology that fits with Braak's model of progression, compared to those with older onset and shorter disease duration. • Clinicians should continually assess non-motor symptoms as they often present in a dynamic manner.
The GO/NoGo Model Frank (2006) Frank, et al. (2004)	• The direct and indirect basal ganglia pathways interact to facilitate desired actions and inhibit undesired actions. • Alterations in dopamine levels either enhance or impede functioning of the direct and indirect pathways. • The effectiveness of positive versus negative feedback varies depending on dopaminergic medication status.	• Errorless learning approaches may be particularly useful with individuals with PD given impaired trial-and-error learning capabilities. • Medication status may influence the effectiveness of reinforcement during therapy, with negative reinforcement more effective off medication and positive reinforcement more effective on medication. • Some individuals with PD are particularly susceptible to pathological gambling and addiction with dopamine supplementation.

The Dopamine-Overdose Hypothesis Cools, et al. (2001) Swainson, et al. (2000)	• Dopaminergic medication will "refill" the dorsal striatum and enhance the associated cognitive functions (e.g., set-shifting), but can "overdose" the ventral striatum and degrade associated cognitive functions (e.g., reward performance, impulsivity).	• Improvement in the motor functions of PD can come at the expense of cognitive functions. • Variability in treatment outcomes for cognitive goals may be driven by medication status. • Motor sequence learning, important for instrumental activities of daily living such as technology use and driving, can become impaired by medication in early PD.
The Neural Networks Framework Gratwicke, et al. (2015)	• Cognitive functions are influenced by overlapping neural networks. Degradation of these networks can lead to MCI or dementia. • Executive dysfunction in PD results from dopamine depletion in the striatum and subsequent interruption of fronto-striatal networks. • Impairments in attention, memory, and visuospatial perception may be attributed to degenerating cholinergic and noradrenergic pathways.	• Patients prescribed noradrenergic or cholinergic medications may have more advanced cognitive decline. The presence of these medications should cue clinicians to conduct thorough cognitive evaluations.
The Dual-Syndrome Hypothesis Kehagia, et al. (2013)	• There are two primary cognitive phenotypes in PD. • Dysexecutive syndrome: Primary deficits in working memory and executive functions, is mediated by fronto-striatal pathways, and is affected by dopaminergic medication. • Dementia syndrome: Early-presenting deficits of visuospatial function and semantic fluency that are mediated by posterior-cortical regions, and not affected by dopaminergic medication. Impairments may be amenable to cholinergic medications.	• Early deficits in visuospatial skills and semantic fluency are associated with progression to dementia. • Individuals may present with variable performance on cognitive tasks related to the dysexecutive syndrome once beginning medication.

fatigue have all been shown to affect cognition [57-59]. Current models have yet to clearly reconcile the heterogeneity that results from this complex milieu of neuropathological and neurochemical underpinnings of PD. However, these models may inform the presence and progression of cognitive impairment and therefore serve as a plausible framework for clinical practice.

Models of cognitive impairment in PD

Numerous neuropathological, neurocomputational, neurochemical, and pharmacological models have been proposed that elucidate the nature of cognitive deficits in PD. In this next section, descriptions of several theories, models, and hypotheses are summarized, as well as highlighted in Table 2.

The Braak model: The Braak model is a staging model that suggests that PD pathology begins at two sites and progresses in a sequential and predictable pattern [60]. PD is considered a synucleinopathic disease, marked by the ongoing accumulation of Lewy body proteins. Braak and colleagues [60,61] propose that Lewy body pathology attacks a specific type of vulnerable neuron, resulting in brain lesions that evolve in a predictable and relatively consistent manner across individuals. Susceptible neurons feature an axon that is disproportionately long and slender relative to the size of the cell body. In addition, all vulnerable cells contain the protein α-synuclein [62]. This protein is thought to act as a modulator of synaptic transmission in nondiseased neurons [63], giving α-synuclein a central role in neurotransmitter release. An abnormal aggregation of α-synuclein leads to a buildup that comprises the bulk of the Lewy body protein, leading to eventual neuron dysfunction and death in most cases. The notion that a neuron must possess specific qualities to be susceptible to an aggregation of α-synuclein and Lewy body formation allows the Braak method to predict the location and subsequent patterns of disease growth. This model also provides an explanation for why some neurons become lesioned despite neighboring neurons remaining intact.

The Braak model further bridges an understanding of Lewy pathology susceptibility with disease pattern prediction by proposing a staging model. This model accounts for the span of PD pathology from the earliest known prodromal phase through end stage. It suggests that despite being largely considered a result of dopaminergic breakdown, PD does not begin in the

basal ganglia [64]. Instead, the Braak model purports that the earliest accumulations of α-synuclein that form Lewy bodies develop simultaneously in two areas of the body: The dorsal nucleus of the vagus nerve within the lower medulla and the anterior olfactory structures [60,65,66]. This initial growth marks Braak *stage one*. From here, Lewy body pathology is thought to appear in the dorsal motor nucleus of the vagus nerve. Along with decreased olfaction, autonomic symptoms such as constipation, urinary and sexual dysfunction, and blood flow changes are important pre-motor symptoms that are attributed to this early Lewy pathology [67].

Stage two specifically implicates the locus coeruleus, a prominent noradrenergic nucleus with a role in integration of sensory information and maintenance of homeostasis [68]. Throughout stage two, Lewy bodies remain isolated to the medulla and dorsal pons, while lesions within the vagal nerve increase. At this point, the disease is said to be progressing in an "asymptomatic" state; however, this is more accurately described as a premotor state, where subtle changes are often presumed to be typical age-related changes, and PD is not suspected due to the absence of the traditional motor symptoms. Breakdowns of the noradrenergic system in stage two have been deemed responsible for changes in the sleep/wake cycle and arousal [68,69].

Braak *stage three* is marked by involvement of the amygdala as well as cholinergic axons in the basal forebrain. The substantia nigra is also invaded during stage three, where a dense population of poorly myelinated dopaminergic neurons reside. Braak and colleagues propose that once Lewy pathology reaches the substantia nigra, affected neurons decline more rapidly than in previous stages. Individual differences and environmental factors influence the timing and neurodegeneration, with clinically recognized symptoms emerging for some at this stage [60,70]. Emerging symptoms include the hallmark signs of PD such as bradykinesia, tremor, and rigidity. Currently, it is estimated that approximately one-third of dopaminergic neurons in the substantia nigra are depleted when clinical motor symptoms emerge [60,63,64] a lower figure than the 50%-80% depletion that was traditionally cited to mark the symptomatic phase [71,72].

The neocortex remains uninvaded throughout *stage four*, with preexisting lesions becoming more severe [60] and Lewy pathology emerging in the mesocortex [73]. Individuals who have not yet presented with clinically recognizable symptoms in stage three will become symptomatic at this point [73]. PD pathology in the mesocortex is said to result in changes to emotion, including anxiety, depression, and avolition. Motivation and reinforcement learning/reward processing are important cognitive processes influenced by the mesolimbic system, which are thought to become impaired during Braak stage four [74]. Additionally, eroding of the mesocortical pathway initiates during this stage, paving the way for executive dysfunction and potential dementia [60].

From this point, Lewy proteins progress to the neocortex, marking *stage five* of the disease. Severity of degeneration increases at sites previously invaded in earlier stages, and the autonomic, limbic, and somatomotor systems exhibit substantial functional impairments [60]. Balance disruptions emerge and the disease is said to correlate with Hoehn and Yahr stages III and IV [60,75]. As Lewy pathology settles in the neocortex, sensory association areas are affected. Visual disturbances manifest as difficulty reading, diplopia, and visuospatial misjudgments [75,76]. *Stage six* is the final stage of the Braak model, wherein PD pathology has spread to its fullest topographic extent. Specifically, the primary fields of the neocortex that include the first order sensory association fields and premotor areas are affected [73,77]. Preexisting damage is compounded, and individuals are likely to become immobile [62].

The Braak model is widely cited as the gold-standard for understanding symptom progression. However, the assumption that PD progresses in a predictable and consistent pattern, with only individual factors altering the course, is not universally accepted. Namely, the Braak model proposes that Lewy pathology in the lower brainstem is necessary for the later development of PD, and that this is sufficient to represent early, prodromal PD [61,78-80]. This assumption has left the Braak model open to significant criticism. Specifically, Braak's inclusion criteria of Lewy invasion of the dorsal motor nucleus in all cases systematically exclude cases with Lewy pathology in higher brain regions if the dorsal motor nucleus is not involved [78]. This has led to several studies demonstrating the opposite pattern- a clinical diagnosis of PD with no involvement of the dorsal motor nucleus [80,81] or individuals with a limbic-predominant presentation [82]. Additionally, it has been suggested that the Braak model may be selectively explanatory, depending on the clinical phenotype of PD [83,84]. That is, those with a younger age of onset and a long clinical course most closely align with the progression of the Braak model. In sum, the Braak model provides a useful foundation to map cognitive symptoms but may be primarily applicable to a select subset of the PD population.

The GO/NoGo model: As evidenced earlier by the Braak model, multiple neural networks are involved in cognitive and motor processing. Expanding from a progressive location-based model to a focus on functional loops is helpful to explore cognitive breakdowns in PD and to understand the delicate balance between activation and inhibition. One such model is Frank and colleagues' GO/NoGo model. This neurocomputational model is grounded in reinforcement learning and can help explain cognitive impairment in PD [34,85]. In the

GO/NoGo model, the basal ganglia are described as having structurally alike circuits that connect distinct regions of the cortex, with two opposing pathways that facilitate and suppress behaviors [86,87]. The "GO" pathway is a direct pathway wherein excitation creates a gating function allowing for the thalamus to receive further signals from other projections [88], facilitating action plans from the frontal lobe. Conversely, the "NoGo" pathway is an indirect pathway that inhibits the thalamus and suppresses action execution. Dopamine signals mediate these loops; they occur as the result of reward or punishment, driving learning and modulating behavior response and inhibition [34,88].

In this model, the basal ganglia do not encode specific motor responses but instead modulate execution of responses by signaling GO versus NoGo. Therefore, GO and NoGo pathways compete and result in the execution of desired behavior with simultaneous inhibition of unwanted behavior. Reinforcement learning results when repetition of a specific context causes dopamine to flood and stimulate the direct/GO pathway. Conversely, a lack of dopamine surging reinforces the indirect/NoGo pathway, contributing to an increased likelihood of suppression of desired behavior during future encounters. As dopamine decreases, the indirect/NoGo pathway is no longer suppressed, and unwanted behaviors manifest.

While this model is often considered a motor model, Frank and colleagues have extended this model to explain cognitive dysfunction in PD. The authors suggest that increased activation (resulting from lack of suppression) in the NoGo pathway can account for impaired working memory and improved avoidance learning in PD [34,87,88]. Historically, cognitive deficits were thought to arise from functional decline in the frontal lobe; however, this model highlights the important role that the basal ganglia play in cognitive processes [87]. Learning from trial-and-error feedback is particularly impaired in PD, due to a synaptic plasticity loss in the direct/GO neurons that respond to a dopamine surge during positive reinforcement. With a reduction in the response from dopamine, there is a reduction in an individual's ability to learn from a positive outcome. Conversely, this model suggests that learning from negative reinforcement is spared, and possibly enhanced, in PD [85,87,88].

This dopamine-driven discrepancy in reinforcement learning has been confirmed in research by Frank and colleagues [34], whereby individuals on dopaminergic medication more readily made decisions based on positive learning, while decisions by those in an off-state were influenced by a desire to avoid a negative response. Subsequent work has also demonstrated this bias [89-91]. The authors of the GO/NoGo model use this bias to explain the susceptibility towards pathological gambling and addiction that is documented in some individuals with PD using dopaminergic supplementation [87]. They further posit that an interaction exists between inherent individual differences that predispose healthy individuals to reduced learning from negative outcomes and dopaminergic medication, creating the variability in addictive behavior seen in PD.

Viewing cognitive impairment through the lens of the Go/NoGo model provides a useful paradigm to help understand the role dopamine plays in discrete cognitive processes, such as reinforcement learning, but does not provide an integrated view of cognitive impairment across domains. This model is especially important to consider in tandem with other models, particularly those that address the effects of dopamine supplementation.

The Dopamine Overdose Hypothesis: The Dopamine Overdose Hypothesis [92,93] posits that cognitive processes in PD are impacted as the result of a dopamine "overdose" from pharmacotherapy. Cognitive decline occurs when dopaminergic medications disrupt sensitive fronto-striatal channels with excess dopamine, impairing cognitive tasks that rely on these channels. While dopaminergic supplementation successfully aids neural areas with dopamine loss, those areas that are not yet depleted of dopamine are vulnerable to overstimulation (overdose) [92,93].

The Dopamine Overdose Hypothesis identifies four fronto-striatal loops that are differentially impacted by dopamine loss, and conversely, supplementation. For example, cognitive and motor tasks which rely less on the relatively preserved ventral striatum become susceptible to dopamine overdose when an individual is taking dopamine medication. Tasks that are most vulnerable to overstimulation by dopamine include reward processing, impulsivity control, reversal learning, and motor sequence learning. Conversely, tasks that rely more heavily on the dorsal striatum, such as set-shifting, integration, and decision-making, are improved with medication, since the dorsal striatum is thought to be heavily depleted of dopamine.

Paradigms to investigate these claims have largely substantiated the Dopamine Overdose Hypothesis [94]. For example, positive medication effects have been documented for set shifting [92,95-97] while deleterious effects have been shown for reversal learning [92,98,99] and motor sequence learning [100-102]. The dopamine overdose hypothesis thus provides a conceptual framework for understanding differential effects to cognition from dopaminergic medication. While there are commonalities regarding typically preserved and disrupted cognitive functions, there is considerable variability related to an individual's striatal topography, genotype, and pharmacotherapy regimen [93].

The Neural Networks Framework: This framework, introduced by Gratwicke and colleagues [49],

acknowledges the cognitive heterogeneity underlying PD and suggests that non-uniformity in anatomical distribution of disease pathology is a likely cause. The authors further suggest that topographical distribution does not always correspond with expected symptoms and that genetic and comorbid factors are confounding [49]. Thus, the Neural Networks Framework seeks to aggregate neurophysiological, pharmacological, and neuroimaging approaches into a more generalizable model. This model suggests that cognitive heterogeneity stems from the widely dispersed and deeply interconnected networks that are differentially influenced by neurotransmitter deficits [49]. Four domains are discussed in the context of the Neural Networks model, including executive function, attention, memory, and visuospatial domains.

Executive dysfunction is linked to decreased activity in the critical fronto-striatal loops that connect the basal ganglia with the frontal lobe [103]. This has been empirically validated through decreased task performance when the striatum is impacted, compared to the frontal lobe alone [49,104-106]. Thus, the fronto-striatal breakdown responsible for early executive dysfunction in PD is likely the result of striatal deficit rather than frontal lobe impairment. To expand on this and capture a more complex picture of the interconnectedness of neural circuits, the Neural Networks Framework implicates the mesocortical dopamine network in addition to the fronto-striatal loops [49]. The mesocortical network originates in the midbrain ventral tegmental area and projects to the prefrontal, insular, and cingulate cortices. This network releases dopamine that mediates prefrontal receptors involved in cognitive flexibility [107]. Specifically, the authors suggest that the mesocortical dopaminergic network facilitates recruitment of other cognitive networks, a core component of cognitive flexibility. Non-dopaminergic networks are also cited by the Neural Networks Framework as modulators of executive dysfunction. The authors turn to pharmacological research, including Cools' dopamine overdose hypothesis [90], to support this claim.

Attention is another domain considered by the Neural Networks Framework. Networks within the frontal lobe, cingulate cortex, and posterior parietal lobes converge to involve motor, spatial, and sensory components, respectively [108]. Gratwicke and colleagues [49] build upon this notion with the Neural Networks Framework, delineating executive control, orienting, and alerting as the three requisite subsystems contributing to attention, all mediated by a cholinergic network. The executive control component is considered the volitional attentional factor, dependent upon the fronto-parietal circuit to initiate a top-down signal. Orienting is thought to be a bottom-up task, as salient stimuli are attended to while irrelevant stimuli are ignored. Alerting, the final attentional component in this model, also referred to as vigilance, refers to an increased arousal required to maintain orientation [49]. A breakdown in cholinergic loops results in attentional deficits, such as those often seen in PD dementia [109].

Memory impairment in PD is described by the Neural Networks Framework as an interruption in structures responsible for storage and retrieval of information, which are regulated by the cholinergic network, seemingly independent of dopaminergic frontal lobe processes. Thus, memory is considered an interdependent process that relies on attentional orientation for encoding and executive function for retrieval. This notion has been supported by Costa and colleagues [110], who demonstrated that impaired memory in PD results from inability to access stored information independently, and that in the face of impaired executive function, stored information becomes accessible once a semantic cue is provided.

Visuoperceptual impairment, the fourth and final domain detailed in the Neural Networks Model, accounts for deficits in peripheral vision, object and motion perception, visuospatial construction, mental rotation, facial recognition, and visual hallucinations. As with other domains, multiple circuits are implicated in visual deficits in PD, to include bottom-up and top-down processes regulated by dopaminergic, cholinergic, and noradrenergic neurotransmitters [49].

The Neural Networks Framework does not specifically describe, or account for, cognitive heterogeneity in the form of distinct profiles. Instead, the box-and-arrow model highlights the overlap of neurotransmitters and neural connections that innervate cortical structures and influence cognitive processes. Thus, this model is useful to predict cognitive deficits that might arise when different (or multiple) network breakdowns occur. In addition, breakdowns at a specific site, as the result of a depleted neurotransmitter, or resulting from an impaired circuit, can be differentially portrayed in terms of effect on cognition. In this manner, the neural networks model can be used to view different cognitive profiles from a bottom-up approach by first identifying a cognitive impairment and then examining the ascribed networks that modulate it.

One drawback of the Neural Networks Framework is that it does not explain severity of cognitive impairment, levels (i.e., weighting) of neurotransmitter involvement, or the point at which symptoms will arise. However, the clinical utility of this model increases if considered in tandem with a staging model. Specifically, the Neural Networks Framework's implication of cholinergic breakdown as a primary predictor of dementia aligns with the Dual Syndrome Hypothesis, described below.

The Dual Syndrome Hypothesis: The Dual Syndrome Hypothesis, coined by Kehagia and colleagues [111], considers cognitive heterogeneity in PD through the lens of task performance differences that are accounted

for by distinct neurotransmitter involvement. The authors combine data from neuropsychological task performance, neuroimaging, genetic differences, and pharmacological manipulation to explain cognitive heterogeneity. The Dual Syndrome Hypothesis recognizes the varied neurodegeneration which occurs throughout the disease process, affecting individuals in different neural distributions and at different rates, as the foundation for cognitive heterogeneity. This diversity is thought to result from the aggregation of α-synuclein proteins coupled with additional neuropathological features such as vascular disease or other plaque buildup [111,112]. As a departure from Braak's model [60], Kehagia and colleagues posit that neurodegeneration happens in a varied and asymmetrical pattern [111,112], where the basal ganglia are degraded in an uneven, dorsal to ventral gradient. Subsequently, cortical loops are affected differently across individuals.

According to the Dual Syndrome Hypothesis, there are two distinct clinical presentations of cognitive impairment in PD: 1) A mild deficit with executive dysfunction, stemming from depleted dopamine-dependent channels; and 2) A profile of more pervasive deficits that involves additional neurotransmitters and progression to dementia. The first subgroup, a dopaminergically-mediated profile, presents with impairment in the fronto-striatal loop connecting the basal ganglia with the pre-frontal cortex. This compromised pathway most commonly results in MCI with executive function deficits impacting rule shifting, planning, attentional set shifting, and working memory [111]. It is most strongly aligned with the tremor-dominant motor profile of PD. The second subgroup largely implicates cholinergic pathways and presents more commonly with early deficits in visuospatial functioning, verbal and visual memory, and semantic fluency, as well as an akinetic-rigid motor profile. With more posterior and temporal involvement, this subgroup is more commonly associated with progression to dementia [113-118].

The Dual Syndrome Hypothesis provides more than just a cluster of symptoms that are modulated by dopamine. From their longitudinal studies, the authors have been able to identify predictors for development of dementia [111,112]. That is, impaired semantic fluency and pentagon copying at baseline were found to be significant predictors of the development of global cognitive decline 3.5 years post-diagnosis. Additionally, a non-tremor dominant motor presentation at baseline was significantly correlated with global cognitive decline [119,120]. Ultimately, the Dual Syndrome Hypothesis provides evidence that distinct cognitive profiles can be dissociated in the early stages of the disease and serves as a comprehensive framework for understanding cognitive heterogeneity.

Clinical implications

As this review has highlighted, cognitive impairment in PD is heterogeneous and complex. Rehabilitation professionals thus face a unique and challenging task of bridging a systems-level understanding with personalized recommendations. Models of cognitive impairment have clinical utility in this process as they provide insight to possible patterns of cognitive impairment, rate of cognitive decline, relationship to motor profiles, and medication effects. Moreover, these models offer testable predictions for translational and clinical researchers.

When viewed through a clinical lens, these models represent an important part of the evidence-based triad [121]. They can serve as a catalyst for theoretically motivated and evidence-based decisions surrounding evaluation and management. The models reviewed in this tutorial approach cognitive heterogeneity from different perspectives, collectively describing the complex milieu of factors that influence cognition in this population. Thus, the clinical implications per model vary. For example, a clinician familiar with Braak's model may note their patient's report of decreased olfaction, constipation, dizziness, and sleep issues and make a referral to the neurologist to assess risk of Parkinson's disease. A clinician familiar with the Go/NoGo model may have a deeper understanding of why errorless learning approaches may be particularly effective for patients with PD, and choose to use them to teach safe transfer or swallowing strategies, while being mindful of model predications regarding medication influence. A clinician versed in the Dopamine Overdose Hypothesis may recognize why some aspects of their patient's cognition began to decline with the start of a new dopamine supplementation medication, while other aspects of cognition started improving. Finally, a clinician informed of the Dual-Syndrome Hypothesis may recognize the elevated risk of dementia for their newly diagnosed patient with PD who has deficits in visuospatial function and semantic fluency, as well as early indications of postural instability, compared to their patient with PD with an early tremor-dominant profile and mild dysexecutive syndrome. Thus, for a holistic view of cognitive heterogeneity, clinicians can endeavor to recognize patterns that align with a given model and may subsequently shape evaluation and management decisions. Table 2 provides a summary of the models reviewed and specific clinical implications per model.

All models should be considered along with individual differences, such as contextual and environmental factors described in biopsychosocial models [122]. Cultural differences and personal factors, such as level of resilience, will also color the clinical picture [123,124]. Additionally, comorbidities are frequent in PD and have been demonstrated to predict mortality [125] and

influence cognition [126]. Diabetes, vascular disease, and psychiatric conditions such as depression are concomitant issues that are typically unaccounted for in theoretical models but should be considered during clinical interpretation. The disease path or presentation of PD may be modified as the result of comorbidities, particularly as an individual ages.

Conclusions and Recommendations

The aim of this review was to shed light on the historically overlooked and overshadowed cognitive challenges associated with PD. No single framework can explain every nuance of cognitive heterogeneity, just as one clinical recommendation does not generalize to all individuals. Highlighting models of cognitive impairment in PD magnifies the pronounced cognitive heterogeneity and provides a framework for theoretically-motivated research. Ideally, future research on cognitive decline in PD would examine contrasting predictions based on competing theories. This review also attempted to bridge empirically supported frameworks of cognitive impairment with clinical practice. It is our hope that patterns of cognitive decline in individual patients may be better understood when viewed through the lens of one or more of the theories described here. Ultimately, theoretically grounded research, combined with sharpened clinical perspective, may lead to improved behavioral treatments for the cognitive challenges faced by individuals with PD.

Clinical Message

- Understanding current perspectives of cognitive decline in PD can have an important influence on clinical practice.
- Theoretical models can explain medication effects, rates of cognitive decline, and cognitive sub groupings in PD.
- Interprofessional communication can be improved with a shared understanding of the complexities and heterogeneity of cognitive decline in PD.

Author Contributions

KB: Conceptual design; literature searches; drafted and revised portions of article; DS: Literature searches; drafted and revised portions of the article; created tables; KS: Conceptual design; drafted and revised portions of the article.

Declaration of Conflicting Interests

Authors KB and DS declare no potential conflicts of interest with respect to research, authorship or publication of this article. Author KS is a member of the NINDS/NICHD NeuroRehab Common Data Elements working group and has no other potential conflicts of interest.

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