

## Review Article

# Parkinson's Disease and Cognitive Impairment

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Parkinson's disease (PD) is a progressive neurodegenerative disease primarily characterized by the hallmarks of motor symptoms, such as tremor, bradykinesia, rigidity, and postural instability. However, through clinical investigations in patients and experimental findings in animal models of Parkinson's disease for years, it is now well recognized that Parkinson's disease is more than just a motor-deficit disorder. The majority of Parkinson's disease patients suffer from nonmotor disabilities, for instance, cognitive impairment, autonomic dysfunction, sensory dysfunction, and sleep disorder. So far, anti-PD prescriptions and surgical treatments have been mainly focusing on motor dysfunctions, leaving cognitive impairment a marginal clinical field. Within the nonmotor symptoms, cognitive impairment is one of the most common and significant aspects of Parkinson's disease, and cognitive deficits such as dysexecutive syndrome and visuospatial disturbances could seriously affect the quality of life, reduce life expectancy, prolong the duration of hospitalization, and therefore increase burdens of caregiver and medical costs. In this review, we have done a retrospective study of the recent related researches on epidemiology, clinical manifestation and diagnosis, genetics, and potential treatment of cognitive deficits in Parkinson's disease, aiming to provide a summary of cognitive impairment in Parkinson's disease and make it easy for clinicians to tackle this challenging issue in their future practice.

## 1. Introduction

In developed countries, nearly one out of 100 people older than 60 years old are affected by Parkinson's disease [1]. Cognitive impairment in Parkinson's disease, characterized by predominant executive deficits, visuospatial dysfunction, and relatively unaffected memory, ranges from Parkinson's disease mild cognitive impairment (PD-MCI) to Parkinson's disease dementia (PDD), the former of which could only be detected by various means of comprehensive neuropsychological observations and normally does not affect the patients' daily operations whereas the latter hits more than one area of cognition and is severe enough to impair social or working functions. Moreover, longitudinal studies of long-term clinical investigations suggested that the majority of PD or PD-MCI patients develop dementia as disease deteriorates into the late stage [2–4], and Parkinson's disease dementia is a critically influential factor for the reduced life expectancy in patients with Parkinson's disease [5]. Movement disorder

has long been addressed to be burdensome in Parkinson's disease and the development of relatively effective restoration of dopamine by pharmaceutical treatment also contributes to the success of management of motor symptoms, leaving the treatment of nonmotor deficits an unmet clinical need. Furthermore, the aggravation of cognitive disturbances might also be strongly predicted by neuropsychological testing in the early stage of disease with or without timely medical treatment [5–8].

In this review, we illustrate the demographic and clinical symptoms potentially assessed as risk factors for nonmotor deficits in Parkinson's disease and discuss the underlying mechanisms of these symptoms with evidence from genetic studies, with primary focus on the clinical manifestations and diagnosis supported by neuropsychology research, neuroimaging, pharmacology, and molecular genetics. At last, we probe into the clinical pharmacological and nonpharmacological management for Parkinson's disease patients in the light of its heterogeneous nature.

## 2. Epidemiology

PD is one of the most common neurodegenerative disorders, whose incidence is second only to Alzheimer disease. According to a 5-year follow-up study by Broeders and a Norwegian ParkWest study by Pedersen, 25% to 50% of patients with Parkinson disease develop PD-MCI or PDD or progress from PD-MCI to PDD within 5 years of diagnosis [9, 10]. Studies that followed patients prospectively diagnosed PD with normal cognition and discovered the incidence of cognitive impairment are few till now. However, according to the available evidence, the progression of cognitive impairment was very common and comparatively quick. For instance, one study exhibited that the cumulative incidence of developing cognitive impairment was 8.5% within 1-year follow-up and up to 47.4% within 6-year follow-up [11]. In other studies, the incidence of cognitive impairments in PD patients varied from 48% to 60% by 12–15 years of retrospective follow-up [12, 13]. In addition, the community-based studies indicated that 20–35% of PD population would develop PD-MCI and up to 10% would develop PDD per year [14, 15]. Nonetheless, it is difficult to compare the results of all studies mentioned above, due to differences in sample sizes and statistical methods used. Furthermore, one designed study also clarified that the onset of dementia in PD patients is approximately 70-year-old no matter when the onset of PD is [16].

Not only does the incidence of cognitive impairment in PD patients vary, but also the risk factors for PD-MCI and PDD vary. Pigott et al. claimed that increased baseline Hoehn & Yahr Scale score and Unified PD Rating Scale motor score, and decreased baseline Dementia Rating Scale (DRS-2) scores are powerful predictors of early cognitive deficits [17]. It is widely accepted that DRS-2 might be effective and adequate for predicting cognitive disturbance and could be used as a reference method to test comprehensive cognitive function [16, 18].

## 3. Etiology

In this part, we mainly focus on the genetics of PD. 18 PD-specific chromosomal loci are named *PARK* and numbered chronologically, nine of which have been identified and confirmed by linkage analysis or exome sequencing [19–33]. Eight of these loci were identified by linkage analysis, functional candidate gene approach or GWAS studies, and are deemed as susceptibility loci as risk factors [34–39]. And still one of them is supposed to be erroneous locus found to be identical with *PARK1* [40]. Within the nine confirmed disease-causing genes, *SNCA*, *LRRK*, and *VPS35* exhibit an autosomal dominant hereditary pattern while other six genes, *Parkin*, *PINK1*, *DJ-1*, *ATP13A2*, *PLA2G6*, and *FBXO7*, display an autosomal recessive hereditary pattern. Besides, some other genes, such as *GIGYF2*, were reported to be susceptible to PD with specific variants in different ethnic populations [41]. The mutated genes involved in PD cause brain dysfunction through various molecular mechanisms, including disturbance of presynaptic vesicle recycling and dopamine transmission, toxicity from aggregation of mutant proteins, degeneration of dopaminergic axon in substantia

nigra, instability or mislocation of certain kinases, overactivation of ubiquitin kinase activities, and decreased efficiencies of ubiquitin degradation pathways [42–52]. Although only 10–15% of PD cases are familial and studies related to the pathogenic mechanisms on the confirmed disease-causing genes or susceptible loci of PD are far from being complete, the discovery of PD-related genes is a critical step for us to unravel the mysteries behind neurodegeneration in PD. Up to date, there is limited research specifically dedicated to the study of the relationship between the genetic classifications of PD and molecular mechanisms of cognitive impairment in PD. However, some negative results indicated some distinctive genetic features of cognitive decline in PD could be differentiated from other neurodegenerative disorders with cognitive disturbances [53, 54]. Furthermore, the filamentous Lewy body formation could be observed in early onset of PDD carrying *SNCA* mutations and Dementia with Lewy bodies (DLB) [42, 55], and the aggregation of  $\alpha$ -synuclein could be detected in substantia nigra as well as cortex in idiopathic PD patients, which suggests that the accumulation of  $\alpha$ -synuclein could be the presynaptic dysfunction attributed to neuronal toxicity caused by various genetic or nongenetic risk factors. It is also found that the frequency of glucocerebrosidase mutations is increased in postmortem samples from PD patients who had positive  $\alpha$ -synuclein inclusions [56, 57], and the *BDNF* (Met/Met) homozygotes demonstrate dramatically worse cognitive impairment in PD patients compared to noncarriers [58].

## 4. Clinical Characteristics and Diagnosis

There is dramatic heterogeneity in clinical definition and correlation of cognitive impairment in PD, ranging from mild cognitive impairment to dementia [18, 59, 60]. It has been a long time that the definition and characteristics of PD-MCI and PDD exist as a controversial issue, until the Movement Disorder Society (MDS) took the initiative to conduct a Task Force to systematically review the most representative literatures. They evaluated the incidences and characteristics of PD-MCI, as well as its relationship with dementia and its inclination of progressing to dementia [61]. For PD-MCI, the Movement Disorder Society (MDS) finally selected a total of 8 articles (6 cross-sectional studies and 2 longitudinal studies) from 1156 articles (874 for Parkinson & cognitive impairment and 172 for Parkinson & MCI) [18, 59, 62–67], in which the study design, population studied, methodology for statistical analysis, and criteria for PD-MCI/PDD definition vary considerably. On the other hand, publications related to PDD are much more available than those to PD-MCI. The MDS also reviewed the previous publications of dementia in PD excluding the cases of Dementia with Lewy Bodies (DLB) in terms of the “1-year rule,” characterized the clinical manifestations, and used these results to illustrate the criteria of probable and possible PDD based on the consensus from experts [68].

The criteria of both PD-MCI and PDD are defined by clinical, cognitive, and functional aspects. As more time and effort have been devoted to the study of PDD, the criteria for

PDD were established first, which also profoundly influenced the proposed criteria for PD-MCI [68, 69]. Similar to the practicality of diagnosis in PDD criteria, a two-level operational schema on the thorough basis of neuropsychological testing is also applied in PD-MCI criteria [69]. Level I is a practical set which could be utilized easily by physicians and needs no neuropsychological testing from neurological or psychological experts, whereas Level II is documented in much more detail and is more favorable for researchers to conduct longitudinal studies.

In a brief assessment of Level I, clinical diagnosis of PD based on Queen's Square Brain Bank criteria for PD must be established for both PD-MCI and PDD [70, 71]. For PD-MCI, cognitive capability is declined slowly which might be described by caregivers or patients or observed by clinicians from testing results. On the other hand, cognitive impairment caused by the clinical manifestations of parkinsonism other than idiopathic PD, other primary possibilities for cognitive disturbances, and other PD-associated comorbid circumstances that could significantly influence the outcome of cognitive testing should be excluded from PD-MCI [68]. The most important point to differentiate PDD from DLB is that PD symptoms should develop prior to the onset of dementia, which could be obtained by clinicians, gathered from the patient him/herself, informant or follow-up records/past medical history [69]. As PD-MCI is a prestage of PDD and progresses to PDD in most cases, the cognitive deficits scaled by a global cognitive ability test or at least two of neuropsychological tests for the five cognitive domains (to erase the limitation of a single neuropsychological test) in PD-MCI should be subtle on complex functional task and not be sufficient to interfere significantly with functional independence [68]. However, the cognitive impairment, which can be examined by global cognitive ability tests (e.g., MMSE below 26 [72]) and by at least two of the neuropsychological tests (months reversed [73] or seven backward [72], lexical fluency or clock drawing [74], MMSE pentagons [72], and 3-word recall [72]), is supposed to be severe enough to impair daily living activities, which could be assessed by a list of simple tasks. And the cognitive impairment should be assessed without administration of antiparkinsonian drugs and not be attributed to other categories of abnormalities such as autonomic or motor symptoms caused by PDD [69].

Once the diagnosis of cognitive impairment, including PD-MCI or PDD, is established, specifying the subtypes of cognitive deficiency and evaluating the severity of disease are quite beneficial for research, clinical practicing and monitoring, and even standardized pharmacological interventions. For PD-MCI diagnosis by Level II criteria, at least two of neuropsychological tests examining each of the five cognitive domains are recommended by MDS. Performance of patients between 1 and 2 standard deviations (SD) below individual variation adjustment showing predominant impairment or premorbid levels may be demonstrated in PD-MCI. But patients within 1 SD below normalization tested by a serial of neuropsychological measurements or who reported significantly cognitive decline over time are also accredited to diagnose PD-MCI [75]. For PD-MCI subtyping, to differentiate PD-MCI as single or multiple domains, at least two

neuropsychological tests in each cognitive domain should be conducted. Impaired performance of two tests in the same one cognitive domain without impairment in other cognitive domains demonstrates the single-domain subtype. On the other hand, impaired performance of at least one test in no less than two cognitive domains indicates the multiple-domain type [76–91]. However, for PDD Level II testing, assessments of severity using quantitative measurements do not have upper limit scores in diagnosis. The goal of Level II testing, for one thing, is to confirm the uncertain PDD diagnosis when the clinical manifestations of cognitive impairment are not obvious or relatively confused. It also serves to depict the individual characteristic of PDD and as an indicator of pharmacological responsiveness. In PDD, there are five cognitive domains involved in Level II testing: global cognitive efficiency, executive functions, memory, instrumental functions, and neuropsychiatric functions, in which executive functions and memory are classified as subcortical frontal functions and instrumental functions are believed to be cortically mediated [92].

## 5. Treatment

Abnormal activities of various subtypes of neurons have been involved in the cognitive impairment of PD, including the dysregulation of dopaminergic, cholinergic, and probably glutamatergic or noradrenergic neurons [93, 94].

Cholinesterase inhibitors, such as rivastigmine, have been proved beneficial to the improvement of global cognition and clinical manifestations as well as neuropsychiatric testing (especially for attention and executive functioning amelioration) by several large-scale multicenter randomized placebo-controlled trials [95–98]. However, Donepezil, also a cholinesterase inhibitor, was not effective for global cognitive improvement or other neuropsychiatric symptoms in PD-MCI or PDD in a large randomized controlled study [99, 100], although its beneficial effect was reported in some small placebo-controlled studies [99].

Partial NMDA-receptor antagonist has been used as a therapeutic option to treat PD patients with cognitive defects in several placebo-controlled trials [101–104]. However, the results of studies were not consistent or notable; only one trial showed statistical differences in the improvement of global cognition [102], whereas most of trials suggested no pharmacological effects of partial NMDA-receptor antagonist on neuropsychiatric symptoms or improvement of daily life [105].

Atomoxetine, a noradrenergic reuptake inhibitor, and clozapine, an inhibitor of serotonin and dopamine receptors, as well as second-generation tricyclic antidepressant (TCA) nortriptyline and pramipexole, have been shown to be beneficial for the regulation of attention, psychosis, and depression, respectively, by evidence from several placebo-controlled trials [93, 106, 107].

Dysexecutive profile, which is known as the most predominant component of cognitive deficits in PD-MCI and PDD, has been substantiated to be improved with levodopa treatment [6, 93]. Levodopa was found to act on some

aspects of cognition such as flexibility and working memory without beneficial changes of other functions like visuospatial recognition, verbal ability, or associative learning [6, 93]. For patients with nondopaminergic antiparkinsonian administration, antagonists of the NMDA-type glutamate receptor, amantadine, for instance, could slow down the progressive transition from PD-MCI to PDD, via increasing dopamine release and blocking dopamine reuptake [108].

Subthalamic deep brain stimulation, which is commonly conducted on PD patients with motor complications that are resistant to antiparkinsonian medication, was claimed to be harmful for semantic and verbal fluency as well as executive profiles by a meta-analysis [109]. In the meantime, this invasive procedure, with the possibility of causing damage to the vital brain regions in charge of advanced cognitive functions, has been related to significant exacerbation of dysexecutive profile that is not observed in most desirable pharmacological treatments [110].

Neuroprotective agents aiming to interrupt  $\alpha$ -synuclein aggregation or to restore neuronal integrity are currently not available, whereas some cognitive interventions that are helpful in Alzheimer's disease have been identified to have positive results in the early stage of randomized clinical studies [III, I12].

While deep brain stimulation (DBS) is effective for the motor deficits of Parkinson's disease (PD) that is well documented, cognitive and psychiatric benefits and side effects from the subthalamic nucleus (STN) and globus pallidus interna (GPi) DBS for PD are increasingly recognized. On one hand, it has been reported that DBS could significantly improve immediate verbal memory and reduce anxiety symptoms [I13]; on the other hand, it is also investigated that certain types of impaired domain such as attention impairment predicted more detrimental results after DBS [I14]. Therefore, the improvements of cognitive symptoms from DBS require further studies and warrant the precise cognitive tests that stratify the relative risks and benefits of surgery.

## 6. Conclusion

Cognitive impairment in PD, as in other neurodegenerative diseases, demonstrates the common role of neurodegeneration as well as the PD-featured damage in certain advanced cognitive brain regions accompanied with characterized clinical manifestations. The treatments for cognitive deficits in PD remain limited and inadequate since the disturbances of neuronal network involved in the process are still obscure and elusive. As the population ages, the increasing burden for both patients and caregivers from PD-MCI and PDD makes it urgent to approach to the pathogenic mechanisms and therapeutic targets of cognitive deficits in PD, as well as to research and develop novel pharmacological treatments and other interventions that could potentially be used in PD cognitive impairment.

## Competing Interests

The authors declare that they have no competing interests.

## References

- [1] I. Litvan, K. P. Bhatia, D. J. Burn et al., "SIC task force appraisal of clinical diagnostic criteria for parkinsonian disorders," *Movement Disorders*, vol. 18, no. 5, pp. 467–486, 2003.
- [2] T. C. Buter, A. van den Hout, F. E. Matthews, J. P. Larsen, C. Brayne, and D. Aarsland, "Dementia and survival in Parkinson disease: a 12-year population study," *Neurology*, vol. 70, no. 13, pp. 1017–1022, 2008.
- [3] M. A. Hely, W. G. J. Reid, M. A. Adena, G. M. Halliday, and J. G. L. Morris, "The Sydney multicenter study of Parkinson's disease: the inevitability of dementia at 20 years," *Movement Disorders*, vol. 23, no. 6, pp. 837–844, 2008.
- [4] D. Aarsland, K. Andersen, J. P. Larsen, A. Lolk, and P. Kragh-Sørensen, "Prevalence and characteristics of dementia in Parkinson disease: an 8-year prospective study," *Archives of Neurology*, vol. 60, no. 3, pp. 387–392, 2003.
- [5] G. Levy, M.-X. Tang, E. D. Louis et al., "The association of incident dementia with mortality in PD," *Neurology*, vol. 59, no. 11, pp. 1708–1713, 2002.
- [6] D. Weintraub, S. Mavandadi, E. Mamikonyan et al., "Atomoxetine for depression and other neuropsychiatric symptoms in Parkinson disease," *Neurology*, vol. 75, no. 5, pp. 448–455, 2010.
- [7] E. Sinforiani, L. Banchieri, C. Zucchella, C. Pacchetti, and G. Sandrini, "Cognitive rehabilitation in Parkinson's disease," *Archives of gerontology and geriatrics. Supplement*, no. 9, pp. 387–391, 2004.
- [8] A. P. Paris, H. G. Saleta, M. de la Cruz Crespo Maraver et al., "Blind randomized controlled study of the efficacy of cognitive training in Parkinson's disease," *Movement Disorders*, vol. 26, no. 7, pp. 1251–1258, 2011.
- [9] M. Broeders, D. C. Velseboer, R. de Bie et al., "Cognitive change in newly-diagnosed patients with Parkinson's disease: a 5-year follow-up study," *Journal of the International Neuropsychological Society*, vol. 19, no. 6, pp. 695–708, 2013.
- [10] K. F. Pedersen, J. P. Larsen, O.-B. Tysnes, and G. Alves, "Prognosis of mild cognitive impairment in early Parkinson disease: the Norwegian ParkWest study," *JAMA Neurology*, vol. 70, no. 5, pp. 580–586, 2013.
- [11] L. A. Hershey and G. M. Peavy, "Cognitive decline in Parkinson disease: how steep and crowded is the slope?" *Neurology*, vol. 85, no. 15, pp. 1268–1269, 2015.
- [12] M. A. Hely, J. G. L. Morris, W. G. J. Reid, and R. Trafficante, "Sydney multicenter study of Parkinson's disease: non-L-dopa-responsive problems dominate at 15 years," *Movement Disorders*, vol. 20, no. 2, pp. 190–199, 2005.
- [13] T. C. Buter, A. Van Den Hout, F. E. Matthews, J. P. Larsen, C. Brayne, and D. Aarsland, "Dementia and survival in Parkinson disease: A 12-year Population Study," *Neurology*, vol. 70, no. 13, pp. 1017–1022, 2008.
- [14] D. Aarsland, K. Andersen, J. P. Larsen, A. Lolk, H. Nielsen, and P. Kragh-Sørensen, "Risk of dementia in Parkinson's disease: a community-based, prospective study," *Neurology*, vol. 56, no. 6, pp. 730–736, 2001.
- [15] P. Hobson, J. Gallacher, and J. Meara, "Cross-sectional survey of Parkinson's disease and parkinsonism in a rural area of the United Kingdom," *Movement Disorders*, vol. 20, no. 8, pp. 995–998, 2005.
- [16] W. G. J. Reid, M. A. Hely, J. G. L. Morris, C. Loy, and G. M. Halliday, "Dementia in Parkinson's disease: a 20-year neuropsychological study (Sydney Multicentre Study)," *Journal*

- of Neurology, Neurosurgery and Psychiatry*, vol. 82, no. 9, pp. 1033–1037, 2011.
- [17] K. Pigott, J. Rick, S. X. Xie et al., “Longitudinal study of normal cognition in Parkinson disease,” *Neurology*, vol. 85, no. 15, pp. 1276–1282, 2015.
- [18] D. Aarsland, K. Bronnick, C. Williams-Gray et al., “Mild cognitive impairment in Parkinson disease: a multicenter pooled analysis,” *Neurology*, vol. 75, no. 12, pp. 1062–1069, 2010.
- [19] J. H. Bower, D. M. Maraganore, B. J. Peterson, S. K. McDonnell, J. E. Ahlskog, and W. A. Rocca, “Head trauma preceding PD: A Case-control Study,” *Neurology*, vol. 60, no. 10, pp. 1610–1615, 2003.
- [20] H. Braak and E. Braak, “Pathoanatomy of Parkinson’s disease,” *Journal of Neurology, Supplement*, vol. 247, no. 2, pp. 3–10, 2000.
- [21] A. Di Fonzo, M. C. J. Dekker, P. Montagna et al., “FBXO7 mutations cause autosomal recessive, early-onset parkinsonian-pyramidal syndrome,” *Neurology*, vol. 72, no. 3, pp. 240–245, 2009.
- [22] A. Di Fonzo, C. F. Rohé, J. Ferreira et al., “A frequent LRRK2 gene mutation associated with autosomal dominant Parkinson’s disease,” *Lancet*, vol. 365, no. 9457, pp. 412–415, 2005.
- [23] A. Elbaz, J. H. Bower, D. M. Maraganore et al., “Risk tables for parkinsonism and Parkinson’s disease,” *Journal of Clinical Epidemiology*, vol. 55, no. 1, pp. 25–31, 2002.
- [24] M. Farrer, P. Chan, R. Chen et al., “Lewy bodies and parkinsonism in families with parkin mutations,” *Annals of Neurology*, vol. 50, no. 3, pp. 293–300, 2001.
- [25] T. Foroud, S. K. Uniacke, L. Liu et al., “Heterozygosity for a mutation in the parkin gene leads to later onset Parkinson disease,” *Neurology*, vol. 60, no. 5, pp. 796–801, 2003.
- [26] M. Funayama, K. Hasegawa, H. Kowa, M. Saito, S. Tsuji, and F. Obata, “A new locus for Parkinson’s Disease (PARK8) maps to chromosome 12p11.2-q13.1,” *Annals of Neurology*, vol. 51, no. 3, pp. 296–301, 2002.
- [27] W. P. Gilks, P. M. Abou-Sleiman, S. Gandhi et al., “A common LRRK2 mutation in idiopathic Parkinson’s disease,” *The Lancet*, vol. 365, no. 9457, pp. 415–416, 2005.
- [28] S. Goldwurm, M. Zini, L. Mariani et al., “Evaluation of LRRK2 G2019S penetrance: relevance for genetic counseling in Parkinson disease,” *Neurology*, vol. 68, no. 14, pp. 1141–1143, 2007.
- [29] D. G. Healy, M. Falchi, S. S. O’Sullivan et al., “Phenotype, genotype, and worldwide genetic penetrance of LRRK2-associated Parkinson’s disease: a case-control study,” *The Lancet Neurology*, vol. 7, no. 7, pp. 583–590, 2008.
- [30] A. J. Hughes, Y. Ben-Shlomo, S. E. Daniel, and A. J. Lees, “What features improve the accuracy of clinical diagnosis in Parkinson’s disease: a clinicopathologic study,” *Neurology*, vol. 57, no. 10, pp. S34–S38, 2001.
- [31] A. J. Hughes, S. E. Daniel, Y. Ben-Shlomo, and A. J. Lees, “The accuracy of diagnosis of parkinsonian syndromes in a specialist movement disorder service,” *Brain*, vol. 125, no. 4, pp. 861–870, 2002.
- [32] M. M. Hulihan, L. Ishihara-Paul, J. Kachergus et al., “LRRK2 Gly2019Ser penetrance in Arab-Berber patients from Tunisia: a case-control genetic study,” *The Lancet Neurology*, vol. 7, no. 7, pp. 591–594, 2008.
- [33] C. Klein, K. Lohmann-Hedrich, E. Rogava, M. G. Schlossmacher, and A. E. Lang, “Deciphering the role of heterozygous mutations in genes associated with parkinsonism,” *The Lancet Neurology*, vol. 6, no. 7, pp. 652–662, 2007.
- [34] A. A. Hicks, H. Pétursson, T. Jónsson et al., “A susceptibility gene for late-onset idiopathic Parkinson’s disease,” *Annals of Neurology*, vol. 52, no. 5, pp. 549–555, 2002.
- [35] B. Giovannone, E. Lee, L. Laviola, F. Giorgino, K. A. Cleveland, and R. J. Smith, “Two novel proteins that are linked to insulin-like growth factor (IGF-I) receptors by the Grb10 adapter and modulate IGF-I signaling,” *Journal of Biological Chemistry*, vol. 278, no. 34, pp. 31564–31573, 2003.
- [36] P. D. Smith, S. J. Crocker, V. Jackson-Lewis et al., “Cyclin-dependent kinase 5 is a mediator of dopaminergic neuron loss in a mouse model of Parkinson’s disease,” *Proceedings of the National Academy of Sciences of the United States of America*, vol. 100, no. 23, pp. 13650–13655, 2003.
- [37] K. M. Strauss, L. M. Martins, H. Plun-Favreau et al., “Loss of function mutations in the gene encoding Omi/HtrA2 in Parkinson’s disease,” *Human Molecular Genetics*, vol. 14, no. 15, pp. 2099–2111, 2005.
- [38] J. Simón-Sánchez, C. Schulte, J. M. Bras et al., “Genome-wide association study reveals genetic risk underlying Parkinson’s disease,” *Nature Genetics*, vol. 41, no. 12, pp. 1308–1312, 2009.
- [39] M.-C. Chartier-Harlin, J. C. Dachsel, C. Vilariño-Güell et al., “Translation initiator EIF4G1 mutations in familial parkinson disease,” *The American Journal of Human Genetics*, vol. 89, no. 3, pp. 398–406, 2011.
- [40] N. Ostrerova, L. Petruccielli, M. Farrer et al., “ $\alpha$ -Synuclein shares physical and functional homology with 14-3-3 proteins,” *Journal of Neuroscience*, vol. 19, no. 14, pp. 5782–5791, 1999.
- [41] Y. Zhang, Q.-Y. Sun, R.-H. Yu, J.-F. Guo, B.-S. Tang, and X.-X. Yan, “The contribution of GIGYF2 to Parkinson’s disease: a meta-analysis,” *Neurological Sciences*, vol. 36, no. 11, pp. 2073–2079, 2015.
- [42] M. G. Spillantini, M. L. Schmidt, V. M.-Y. Lee, J. Q. Trojanowski, R. Jakes, and M. Goedert, “ $\alpha$ -synuclein in Lewy bodies [8],” *Nature*, vol. 388, pp. 839–840, 1997.
- [43] T. F. Outeiro and S. Lindquist, “Yeast cells provide insight into alpha-synuclein biology and pathobiology,” *Science*, vol. 302, no. 5651, pp. 1772–1775, 2003.
- [44] M. R. Cookson, “The role of leucine-rich repeat kinase 2 (LRRK2) in Parkinson’s disease,” *Nature Reviews Neuroscience*, vol. 11, no. 12, pp. 791–797, 2010.
- [45] H. Plun-Favreau, K. Klupsch, N. Moisoi et al., “The mitochondrial protease HtrA2 is regulated by Parkinson’s disease-associated kinase PINK1,” *Nature Cell Biology*, vol. 9, no. 11, pp. 1243–1252, 2007.
- [46] I. E. Clark, M. W. Dodson, C. Jiang et al., “*Drosophila pink1* is required for mitochondrial function and interacts genetically with parkin,” *Nature*, vol. 441, no. 7097, pp. 1162–1166, 2006.
- [47] A. H. Schapira, “Mitochondria in the aetiology and pathogenesis of Parkinson’s disease,” *The Lancet Neurology*, vol. 7, no. 1, pp. 97–109, 2008.
- [48] C. B. Lücking, A. Dürr, V. Bonifati et al., “Association between early-onset Parkinson’s disease and mutations in the parkin gene,” *New England Journal of Medicine*, vol. 342, no. 21, pp. 1560–1567, 2000.
- [49] K. K. Chung, Y. Zhang, K. L. Lim et al., “Parkin ubiquitinates the  $\alpha$ -synuclein-interacting protein, synphilin-1: implications for Lewy-body formation in Parkinson disease,” *Nature Medicine*, vol. 7, no. 10, pp. 1144–1150, 2001.
- [50] V. Bonifati, P. Rizzu, M. J. Van Baren et al., “Mutations in the DJ-1 gene associated with autosomal recessive early-onset parkinsonism,” *Science*, vol. 299, no. 5604, pp. 256–259, 2003.

- [51] P. M. Abou-Sleiman, D. G. Healy, N. Quinn, A. J. Lees, and N. W. Wood, "The role of pathogenic DJ-1 mutations in Parkinson's disease," *Annals of Neurology*, vol. 54, no. 3, pp. 283–286, 2003.
- [52] R. Bandopadhyay, A. E. Kingsbury, M. R. Cookson et al., "The expression of DJ-1 (PARK7) in normal human CNS and idiopathic Parkinson's disease," *Brain*, vol. 127, no. 2, pp. 420–430, 2004.
- [53] Z. Liu, J. Guo, Y. Wang et al., "Lack of association between IL-10 and IL-18 gene promoter polymorphisms and Parkinson's disease with cognitive impairment in a Chinese population," *Scientific Reports*, vol. 6, Article ID 19021, 2016.
- [54] Y. Q. Wang, B. S. Tang, Y. Yang et al., "Relationship between Alzheimer's disease GWAS-linked top hits and risk of Parkinson's disease with or without cognitive decline: a Chinese population-based study," *Neurobiology of Aging*, vol. 39, pp. 217.e9–217.e11, 2016.
- [55] H. Okazaki, L. E. Lipkin, and S. M. Aronson, "Diffuse intracytoplasmic ganglionic inclusions (lewy type) associated with progressive dementia and quadripareisis in flexion," *Journal of Neuropathology and Experimental Neurology*, vol. 20, no. 2, pp. 237–244, 1961.
- [56] J. Neumann, J. Bras, E. Deas et al., "Glucocerebrosidase mutations in clinical and pathologically proven Parkinson's disease," *Brain*, vol. 132, no. 7, pp. 1783–1794, 2009.
- [57] E. Sidransky, M. A. Nalls, J. O. Aasly et al., "Multicenter analysis of glucocerebrosidase mutations in Parkinson's disease," *New England Journal of Medicine*, vol. 361, no. 17, pp. 1651–1661, 2009.
- [58] F. R. Guerini, E. Beghi, G. Riboldazzi et al., "BDNF Val66Met polymorphism is associated with cognitive impairment in Italian patients with Parkinson's disease," *European Journal of Neurology*, vol. 16, no. 11, pp. 1240–1245, 2009.
- [59] I. Litvan, D. Aarsland, C. H. Adler et al., "MDS task force on mild cognitive impairment in Parkinson's disease: critical review of PD-MCI," *Movement Disorders*, vol. 26, no. 10, pp. 1814–1824, 2011.
- [60] Y.-Q. Wang, B.-S. Tang, X.-X. Yan et al., "A neurophysiological profile in Parkinson's disease with mild cognitive impairment and dementia in China," *Journal of Clinical Neuroscience*, vol. 22, no. 6, pp. 981–985, 2015.
- [61] D. Muslimović, B. Post, J. D. Speelman, and B. Schmand, "Cognitive profile of patients with newly diagnosed Parkinson disease," *Neurology*, vol. 65, no. 8, pp. 1239–1245, 2005.
- [62] T. Foltyne, C. E. G. Brayne, T. W. Robbins, and R. A. Barker, "The cognitive ability of an incident cohort of Parkinson's patients in the UK. The CamPaIGN Study," *Brain*, vol. 127, no. 3, pp. 550–560, 2004.
- [63] S. Hoops, S. Nazem, A. D. Siderowf et al., "Validity of the MoCA and MMSE in the detection of MCI and dementia in Parkinson disease," *Neurology*, vol. 73, no. 21, pp. 1738–1745, 2009.
- [64] E. Mamikonyan, P. J. Moberg, A. Siderowf et al., "Mild cognitive impairment is common in Parkinson's disease patients with normal Mini-Mental State Examination (MMSE) scores," *Parkinsonism and Related Disorders*, vol. 15, no. 3, pp. 226–231, 2009.
- [65] M.-C. Pai and S.-H. Chan, "Education and cognitive decline in parkinson's disease: a study of 102 patients," *Acta Neurologica Scandinavica*, vol. 103, no. 4, pp. 243–247, 2001.
- [66] C. C. Janvin, J. P. Larsen, D. Aarsland, and K. Hugdahl, "Subtypes of mild cognitive impairment in Parkinson's disease: progression to dementia," *Movement Disorders*, vol. 21, no. 9, pp. 1343–1349, 2006.
- [67] C. H. Williams-Gray, T. Foltyne, C. E. G. Brayne, T. W. Robbins, and R. A. Barker, "Evolution of cognitive dysfunction in an incident Parkinson's disease cohort," *Brain*, vol. 130, no. 7, pp. 1787–1798, 2007.
- [68] M. Emre, D. Aarsland, R. Brown et al., "Clinical diagnostic criteria for dementia associated with Parkinson's disease," *Movement Disorders*, vol. 22, no. 12, pp. 1689–1707, 2007.
- [69] B. Dubois, D. Burn, C. Goetz et al., "Diagnostic procedures for parkinson's disease dementia: recommendations from the movement disorder society task force," *Movement Disorders*, vol. 22, no. 16, pp. 2314–2324, 2007.
- [70] W. R. G. Gibb and A. J. Lees, "The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease," *Journal of Neurology, Neurosurgery and Psychiatry*, vol. 51, no. 6, pp. 745–752, 1988.
- [71] A. J. Hughes, S. E. Daniel, S. Blankson, and A. J. Lees, "A clinicopathologic study of 100 cases of Parkinson's disease," *Archives of Neurology*, vol. 50, no. 2, pp. 140–148, 1993.
- [72] M. F. Folstein, S. E. Folstein, and P. R. McHugh, "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician," *Journal of Psychiatric Research*, vol. 12, no. 3, pp. 189–198, 1975.
- [73] D. H. K. Shum, K. A. McFarland, and J. D. Bain, "Construct validity of eight tests of attention: comparison of normal and closed head injured samples," *Clinical Neuropsychologist*, vol. 4, no. 2, pp. 151–162, 1990.
- [74] T. Sunderland, J. L. Hill, A. M. Mellow et al., "Clock drawing in Alzheimer's disease: a novel measure of dementia severity," *Journal of the American Geriatrics Society*, vol. 37, no. 8, pp. 725–729, 1989.
- [75] N. S. Jacobson and P. Truax, "Clinical significance: a statistical approach to defining meaningful change in psychotherapy research," *Journal of Consulting and Clinical Psychology*, vol. 59, no. 1, pp. 12–19, 1991.
- [76] B. Pillon, B. Deweer, Y. Agid, and B. Dubois, "Explicit memory in Alzheimer's, Huntington's, and Parkinson's diseases," *Archives of Neurology*, vol. 50, no. 4, pp. 374–379, 1993.
- [77] D. Weintraub, K. A. Oehlberg, I. R. Katz, and M. B. Stern, "Test characteristics of the 15-item geriatric depression scale and Hamilton depression rating scale in Parkinson disease," *The American Journal of Geriatric Psychiatry*, vol. 14, no. 2, pp. 169–175, 2006.
- [78] A. M. Owen, M. Beksinska, M. James et al., "Visuospatial memory deficits at different stages of Parkinson's disease," *Neuropsychologia*, vol. 31, no. 7, pp. 627–644, 1993.
- [79] J. A. Cooper, H. J. Sagar, N. Jordan, N. S. Harvey, and E. V. Sullivan, "Cognitive impairment in early, untreated Parkinson's disease and its relationship to motor disability," *Brain*, vol. 114, no. 5, pp. 2095–2122, 1991.
- [80] K. A. Flowers and C. Robertson, "The effect of Parkinson's disease on the ability to maintain a mental set," *Journal of Neurology Neurosurgery and Psychiatry*, vol. 48, no. 6, pp. 517–529, 1985.
- [81] F. Lhermitte, B. Pillon, and M. Serdaru, "Human autonomy and the frontal lobes. Part I: imitation and utilization behavior: a neuropsychological study of 75 patients," *Annals of Neurology*, vol. 19, no. 4, pp. 326–334, 1986.
- [82] S. E. Starkstein, H. S. Mayberg, T. J. Preziosi, P. Andrezejewski, R. Leiguarda, and R. G. Robinson, "Reliability, validity, and clinical correlates of apathy in Parkinson's disease," *Journal of Neuropsychiatry and Clinical Neurosciences*, vol. 4, no. 2, pp. 134–139, 1992.

- [83] J. L. Cummings, M. Mega, K. Gray, S. Rosenberg-Thompson, D. A. Carusi, and J. Gornbein, "The neuropsychiatric inventory: comprehensive assessment of psychopathology in dementia," *Neurology*, vol. 44, no. 12, pp. 2308–2314, 1994.
- [84] E. Grober and H. Buschke, "Genuine memory deficits in dementia," *Developmental Neuropsychology*, vol. 3, no. 1, pp. 13–36, 1987.
- [85] M. C. Tierney, A. Nores, W. G. Snow, R. H. Fisher, M. L. Zorzon, and D. W. Reid, "Use of the Rey Auditory Verbal Learning Test in differentiating normal aging from Alzheimer's and Parkinson's dementia," *Psychological Assessment*, vol. 6, no. 2, pp. 129–134, 1994.
- [86] U. P. Mosimann, G. Mather, K. A. Wesnes, J. T. O'Brien, D. J. Burn, and I. G. McKeith, "Visual perception in Parkinson disease dementia and dementia with Lewy bodies," *Neurology*, vol. 63, no. 11, pp. 2091–2096, 2004.
- [87] C. Janvin, D. Aarsland, J. P. Larsen, and K. Hugdahl, "Neuropsychological profile of patients with Parkinson's disease without dementia," *Dementia and Geriatric Cognitive Disorders*, vol. 15, no. 3, pp. 126–131, 2003.
- [88] A. L. Benton, P. J. Eslinger, and A. R. Damasio, "Normative observations on neuropsychological test performances in old age," *Journal of Clinical Neuropsychology*, vol. 3, no. 1, pp. 33–42, 1981.
- [89] D. Aarsland, K. Brønnick, U. Ehrt et al., "Neuropsychiatric symptoms in patients with Parkinson's disease and dementia: frequency, profile and associated care giver stress," *Journal of Neurology, Neurosurgery and Psychiatry*, vol. 78, no. 1, pp. 36–42, 2007.
- [90] A. F. G. Leentjens, F. R. J. Verhey, R. Lousberg, H. Spitsbergen, and F. W. Wilmink, "The validity of the Hamilton and Montgomery-Åsberg depression rating scales as screening and diagnostic tools for depression in Parkinson's disease," *International Journal of Geriatric Psychiatry*, vol. 15, no. 7, pp. 644–649, 2000.
- [91] M. Visser, A. F. G. Leentjens, J. Marinus, A. M. Stiggelbout, and J. J. van Hilten, "Reliability and validity of the Beck depression inventory in patients with Parkinson's disease," *Movement Disorders*, vol. 21, no. 5, pp. 668–672, 2006.
- [92] F. S. Ertan, T. Ertan, G. Kiziltan, and H. Uyguçgil, "Reliability and validity of the Geriatric Depression Scale in depression in Parkinson's disease," *Journal of Neurology, Neurosurgery and Psychiatry*, vol. 76, no. 10, pp. 1445–1447, 2005.
- [93] D. Brandstaedter, S. Spieker, G. Ulm et al., "Development and evaluation of the Parkinson Psychosis Questionnaire: a screening-instrument for the early diagnosis of drug-induced psychosis in Parkinson's disease," *Journal of Neurology*, vol. 252, no. 9, pp. 1060–1066, 2005.
- [94] A. A. Kehagia, R. A. Barker, and T. W. Robbins, "Neuropsychological and clinical heterogeneity of cognitive impairment and dementia in patients with Parkinson's disease," *The Lancet Neurology*, vol. 9, no. 12, pp. 1200–1213, 2010.
- [95] J. C. Klein, C. Eggers, E. Kalbe et al., "Neurotransmitter changes in dementia with Lewy bodies and Parkinson disease dementia in vivo," *Neurology*, vol. 74, no. 11, pp. 885–892, 2010.
- [96] M. Rolinski, C. Fox, I. Maidment, and R. McShane, "Cholinesterase inhibitors for dementia with Lewy bodies, Parkinson's disease dementia and cognitive impairment in Parkinson's disease," *Cochrane Database of Systematic Reviews*, vol. 3, Article ID CD006504, 2012.
- [97] M. Emre, D. Aarsland, A. Albanese et al., "Rivastigmine for dementia associated with Parkinson's disease," *The New England Journal of Medicine*, vol. 351, no. 24, pp. 2509–2518, 2004.
- [98] W. Poewe, E. Wolters, M. Emre et al., "Long-term benefits of rivastigmine in dementia associated with Parkinson's Disease: an active treatment extension study," *Movement Disorders*, vol. 21, no. 4, pp. 456–461, 2006.
- [99] I. McKeith, T. Del Ser, P. Spano et al., "Efficacy of rivastigmine in dementia with Lewy bodies: a randomised, double-blind, placebo-controlled international study," *The Lancet*, vol. 356, no. 9247, pp. 2031–2036, 2000.
- [100] T. Van Laar, P. P. De Deyn, D. Aarsland, P. Barone, and J. E. Galvin, "Effects of cholinesterase inhibitors in Parkinson's disease dementia: a review of clinical data," *CNS Neuroscience and Therapeutics*, vol. 17, no. 5, pp. 428–441, 2011.
- [101] B. Dubois, E. Tolosa, J. Kulisevsky, P. Barone, and E. J. Galvin, "Efficacy and safety of donepezil in the treatment of Parkinson's disease patients with dementia," in *Proceedings of the 8th International Conference on Alzheimers and Parkinsons Diseases*, 2007.
- [102] I. Leroy, R. Overshott, E. J. Byrne, E. Daniel, and A. Burns, "Randomized controlled trial of memantine in dementia associated with Parkinson's disease," *Movement Disorders*, vol. 24, no. 8, pp. 1217–1221, 2009.
- [103] D. Aarsland, C. Ballard, Z. Walker et al., "Memantine in patients with Parkinson's disease dementia or dementia with Lewy bodies: a double-blind, placebo-controlled, multicentre trial," *The Lancet Neurology*, vol. 8, no. 7, pp. 613–618, 2009.
- [104] M. Emre, M. Tsolaki, U. Bonuccelli et al., "Memantine for patients with Parkinson's disease dementia or dementia with Lewy bodies: a randomised, double-blind, placebo-controlled trial," *The Lancet Neurology*, vol. 9, no. 10, pp. 969–977, 2010.
- [105] W. G. Ondo, L. Shinawi, A. Davidson, and D. Lai, "Memantine for non-motor features of Parkinson's disease: a double-blind placebo controlled exploratory pilot trial," *Parkinsonism and Related Disorders*, vol. 17, no. 3, pp. 156–159, 2011.
- [106] V. Larsson, K. Engedal, D. Aarsland, C. Wattmo, L. Minthon, and E. Londos, "Quality of life and the effect of memantine in dementia with Lewy bodies and Parkinson's disease dementia," *Dementia and Geriatric Cognitive Disorders*, vol. 32, no. 4, pp. 227–234, 2011.
- [107] K. Seppi, D. Weintraub, M. Coelho et al., "The movement disorder society evidence-based medicine review update: treatments for the non-motor symptoms of Parkinson's disease," *Movement Disorders*, vol. 26, supplement 3, pp. S42–S80, 2011.
- [108] J. A. Cooper, H. J. Sagar, S. M. Doherty, N. Jordan, P. Tidswell, and E. V. Sullivan, "Different effects of dopaminergic and anticholinergic therapies on cognitive and motor function in Parkinson's disease follow-up study of untreated patients," *Brain*, vol. 115, no. 6, pp. 1701–1725, 1992.
- [109] R. Inzelberg, U. Bonuccelli, E. Schechtman et al., "Association between amantadine and the onset of dementia in Parkinson's disease," *Movement Disorders*, vol. 21, no. 9, pp. 1375–1379, 2006.
- [110] K. Witt, C. Daniels, P. Krack et al., "Negative impact of borderline global cognitive scores on quality of life after subthalamic nucleus stimulation in Parkinson's disease," *Journal of the Neurological Sciences*, vol. 310, no. 1–2, pp. 261–266, 2011.
- [111] C. Daniels, P. Krack, J. Volkmann et al., "Risk factors for executive dysfunction after subthalamic nucleus stimulation in Parkinson's disease," *Movement Disorders*, vol. 25, no. 11, pp. 1583–1589, 2010.

- [112] L. Bäckman, L. Nyberg, A. Soveri et al., "Effects of working-memory training on striatal dopamine release," *Science*, vol. 333, no. 6043, 2011.
- [113] V. Tang, C. X. L. Zhu, D. Chan et al., "Evidence of improved immediate verbal memory and diminished category fluency following STN-DBS in Chinese-Cantonese patients with idiopathic Parkinson's disease," *Neurological Sciences*, vol. 36, no. 8, pp. 1371–1377, 2015.
- [114] H. Abboud, D. Floden, N. R. Thompson et al., "Impact of mild cognitive impairment on outcome following deep brain stimulation surgery for Parkinson's disease," *Parkinsonism and Related Disorders*, vol. 21, no. 3, pp. 249–253, 2015.



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