Cognitive functioning in Parkinson's disease

- A splice-switching antisense oligonucleotide targeting APP reduces accumulation of alpha-synuclein in a mouse model of Parkinson's disease
- Online Occupational Therapy as a Rehabilitation Intervention for Parkinson's Disease: A Systematized Review
- Modulating Cognition-Linked Histone Acetyltransferases (HATs) as a Therapeutic Strategy for Neurodegenerative Diseases: Recent Advances and Future Trends
- Neurotoxic Effects of Pesticides: Implications for Neurodegenerative and Neurobehavioral Disorders
- Meta-Analysis of Exercise Effects on Cognition in Persons with Parkinson's Disease
- Regional free-water diffusion is more strongly related to neuroinflammation than neurodegeneration
- Resting-state Alpha Reactivity Is Reduced in Parkinson's Disease and Associated With Gait Variability
- Unveiling mysteries of aging: the potential of melatonin in preventing neurodegenerative diseases in older adults

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Parkinson's disease (PD) is a neurodegenerative disorder primarily characterized by motor symptoms, such as tremor, bradykinesia, and rigidity. However, cognitive impairment is a common non-motor symptom that can significantly impact quality of life. Cognitive dysfunction in PD ranges from mild cognitive impairment (MCI) to more severe forms, such as Parkinson’s disease dementia (PDD).

Cognitive Domains Affected in PD Executive Function:

Commonly impaired even in early stages. Includes difficulties with planning, problem-solving, multitasking, and maintaining mental flexibility. May manifest as an inability to adapt to new rules or situations. Attention:

Sustained attention and the ability to shift focus may be reduced. Often linked to deficits in processing speed and mental fatigue. Memory:

Memory impairments are typically less severe compared to Alzheimer’s disease. Problems with retrieval (rather than storage) are more common. Recognition memory often remains intact. Visuospatial Abilities:

Difficulty in perceiving spatial relationships and navigating environments. Impaired perception of depth or visual patterns. Language:

Generally preserved in early stages but may show subtle deficits in word finding or fluency. Processing Speed:

Slower cognitive processing is a hallmark of PD-related cognitive impairment. Pathophysiology of Cognitive Impairment in PD Dopaminergic Dysfunction:

Decline in dopamine levels affects the fronto-striatal circuits, leading to executive dysfunction. Cholinergic System Involvement:

Loss of acetylcholine is more pronounced in PDD, contributing to attention and memory issues. Lewy Body Pathology:

Accumulation of alpha-synuclein in cortical and subcortical regions impacts cognitive networks. Other Neurotransmitter Systems:

Serotonergic and noradrenergic deficits may also play roles. Risk Factors for Cognitive Decline in PD Older age at disease onset. Longer disease duration. Severe motor symptoms. Presence of REM sleep behavior disorder. Apathy or depression. Genetic factors (e.g., mutations in GBA or LRRK2 genes). Clinical Assessment Screening Tools: Montreal Cognitive Assessment (MoCA) Mini-Mental State Examination (MMSE) PD-Cognitive Rating Scale (PD-CRS) Detailed Neuropsychological Evaluation: Required for diagnosing MCI or PDD. Assesses executive function, attention, memory, visuospatial skills, and language. Management of Cognitive Impairment in PD Non-Pharmacological Approaches:

Cognitive Training: Targeting specific domains such as memory or attention. Physical Exercise: Aerobic and resistance training improve overall brain health. Occupational Therapy: To adapt to functional limitations. Pharmacological Treatments:

Cholinesterase Inhibitors (e.g., rivastigmine): Approved for PDD. Dopaminergic Therapies: Careful adjustment to avoid worsening cognitive symptoms. Adjunctive Therapies: Consideration of antidepressants or anxiolytics if mood disorders are present. Supportive Care:

Psychoeducation for patients and caregivers. Multidisciplinary teams to address motor and cognitive symptoms holistically. Prognosis Cognitive impairment progresses over time in PD, with some patients developing dementia. Early identification and interventions can help slow progression and improve quality of life.

White matter is associated with cognitive function in PD and the alterations may occur before the symptoms of the disease. Previous diffusion tensor imaging (DTI) studies lacked specificity to characterize the concrete contributions of distinct white matter tissue properties. This may lead to inconsistent conclusions about the alteration of white matter microstructure. Here, we used neurite orientation dispersion and density imaging (NODDI) and the white matter fiber clustering method to uncover local white matter microstructures in PD with mild cognitive impairment (PD-MCI). This study included 23 PD-MCI and 20 PD with normal cognition (PD-NC) and 21 healthy controls (HC). To probe specific and fine-grained differences, metrics of NODDI and DTI in white matter fiber clusters were evaluated using along-tract analysis. Our results showed that PD-MCI patients had significantly lower neurite density index (NDI) and orientation dispersion index (ODI) in white matter fiber clusters in the prefrontal region. Correlation analysis and receiver operating characteristic (ROC) analysis revealed that the diagnostic performance of NODDI-derived metrics in the cingulum bundle (2 clusters) and thalamic-frontal (2 clusters) were superior to DTI metrics. Our study provides a more specific insight to uncover local white matter abnormalities in PD-MCI, which benefit understanding the underlying mechanism of cognitive decline in PD and predicting the disease in advance [1)].

The insula, consisting of functionally diverse subdivisions, plays a significant role in Parkinson's disease (PD)-related cognitive disorders. However, the functional connectivity (FC) patterns of insular

subdivisions in PD remain unclear. The aim of Pan et al. is to investigate the changes in FC patterns of insular subdivisions and their relationships with cognitive domains. Three groups of participants were recruited in this study, including PD patients with mild cognitive impairment (PD-MCI, n = 25), PD patients with normal cognition (PD-NC, n = 13), and healthy controls (HCs, n = 17). Resting-state functional magnetic resonance imaging (rs-fMRI) was used to investigate the FC in insular subdivisions of the three groups. Moreover, all participants underwent a neuropsychological battery to assess cognition so that the relationship between altered FC and cognitive performance could be elucidated. Compared with the PD-NC group, the PD-MCI group exhibited increased FC between the left dorsal anterior insular (dAI) and the right superior parietal gyrus (SPG), and altered FC was negatively correlated with memory and executive function. Compared with the HC group, the PD-MCI group showed significantly increased FC between the right dAI and the right median cingulate and paracingulate gyri (DCG), and altered FC was positively related to attention/working memory, visuospatial function, and language. The findings highlighted the different abnormal FC patterns of insular subdivisions in PD patients with different cognitive abilities. Furthermore, dysfunction of the dAI may partly contribute to the decline in executive function and memory in early drug-naïve PD patients [2)].

Personality in Parkinson's disease

During the course of Parkinson's disease (PD), personality dimensions can change in parallel with the development of motor fluctuations, either due to the evolution of the disease and/or dopaminergic treatments [3)].

Observational studies

A study attempted to elucidate whether deep brain stimulation for Parkinson's disease alters the functional connectivity pattern of cognitive networks.

The study obtained fMRI and cognitive scale data from 37 PD patients before and after the DBS surgery. Seed-based FC analysis helped demonstrate the FC changes of the default mode network (DMN), executive control network (ECN), and dorsal attention network (DAN).

PD patients indicated significant network connectivity decline in DMN [such as in right precuneus, left angular gyrus, and left middle frontal gyrus (MFG)], ECN [such as in left inferior parietal gyrus, left MFG, and left supplementary motor area (SMA)], and DAN [such as in left inferior frontal gyrus and left MFG] post-DBS surgery. The phonemic fluency score was positively associated with the FC value of the right precuneus and left angular gyrus in DMN before DBS.

The general reduction in FC in the major cognitive networks after DBS surgery depicted the presence of the corresponding network reorganization. Further research can help explore the mechanism of impaired cognitive function post-DBS [4)]

This study provides meaningful insights into the effects of DBS on cognitive network connectivity in PD, highlighting significant FC declines in major networks during the microlesion period. However, the small sample size, absence of a control group, and limited cognitive assessments constrain its conclusions. Further research with more robust designs and longer follow-ups is essential to deepen

our understanding of DBS-induced cognitive changes and their clinical implications.

1)
Zhang C, Yuan Y, Sang T, Yu L, Yu Y, Liu X, Zhou W, Zeng Q, Wang J, Peng G, Feng Y. Local white matter abnormalities in Parkinson's disease with mild cognitive impairment: Assessed with neurite orientation dispersion and density imaging. J Neurosci Res. 2023 Feb 28. doi: 10.1002/jnr.25179. Epub ahead of print. PMID: 36854050.
2)
Pan C, Ren J, Li L, Li Y, Xu J, Xue C, Hu G, Yu M, Chen Y, Zhang L, Zhang W, Hu X, Sun Y, Liu W, Chen J. Differential functional connectivity of insular subdivisions in de novo Parkinson's disease with mild cognitive impairment. Brain Imaging Behav. 2021 Mar 26. doi: 10.1007/s11682-021-00471-2. Epub ahead of print. PMID: 33770371.
3)
Boussac M, Arbus C, Dupouy J, Harroch E, Rousseau V, Croiset A, Ory-Magne F, Rascol O, Moreau C, Rolland AS, Maltête D, Rouaud T, Meyer M, Drapier S, Giordana B, Anheim M, Hainque E, Jarraya B, Benatru I, Auzou N, Belamri L, Tir M, Marques AR, Thobois S, Eusebio A, Corvol JC, Devos D, Brefel-Courbon C; PREDI-STIM study group. Personality dimensions of patients can change during the course of parkinson's disease. PLoS One. 2021 Jan 7;16(1):e0245142. doi: 10.1371/journal.pone.0245142. PMID: 33411732.
4)
Luo B, Zou Y, Yan J, Sun J, Wei X, Chang L, Lu Y, Zhao L, Dong W, Qiu C, Yan J, Zhang Y, Zhang W. Altered Cognitive Networks Connectivity in Parkinson's Disease During the Microlesion Period After Deep Brain Stimulation. CNS Neurosci Ther. 2024 Dec;30(12):e70184. doi: 10.1111/cns.70184. PMID: 39722165.