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Disruption of Ascending and Descending Visual Processing Circuits

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Abstract. Parkinson's disease (PD) is a neurodegenerative disorder caused by the loss of dopamine-carrying neurons in the substantia nigra in the brain. Non-motor symptoms (particularly visual impairment) significantly impair patients' quality of life, but the primary pathogenesis is poorly understood. This study aims to investigate the mechanisms by which the brain uses structural changes in the enzyme leucine-rich ribonuclease 2 (LRRK2) to process visual information, with a particular focus on abnormalities in top-down brain control and bottom-up sensory pathways. The results show that the LRRK2-G2019S mutation causes excessive LRRK2 expression in brain regions that affect higher-level visual processing, such as attention and working memory, while simultaneously inhibiting dopamine activity in the nucleus accumbens and viscerocortical sensory feedback, leading to impaired visual processing and impaired integration of visual information in two-dimensional space. This results in visual problems ranging from blurred and reduced vision to unusual dreams. This ongoing study uses LRRK2-G2019S mutant fruit flies, which will allow us to identify and investigate causal relationships from LRRK2 molecular pathology to visual network abnormalities and behavioral disorders. This study provides a new rationale for screening and identifying possible early signs (e.g., vision changes, abnormal eye movement patterns, and changes in body functions), so that early intervention in PD may be possible before the disease has spread throughout the body.

Keywords: PD, LRRK2, top-down, visual

1. Introduction

PD is the second most prevalent progressive neurodegenerative disease worldwide, pathologically characterized by dopaminergic neuronal degeneration in the substantia nigra pars compacta (SNpc) and abnormal aggregation of intracellular α-synuclein [1]. Current clinical treatments dominated by levodopa only relieve motor symptoms but cannot halt or reverse disease progression, bringing long-term therapeutic bottlenecks for PD patients. In addition to typical motor dysfunctions including tremor and rigidity, non-motor symptoms have gradually become a core research focus of PD, among which visual cognitive impairment runs through the whole disease course. Visual deficits such as reduced contrast sensitivity, impaired color discrimination, visuospatial dysfunction, and visual hallucinations seriously affect patients' daily living quality. They are closely related to early disease occurrence and poor prognosis [2].

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LRRK2 mutation is the most common genetic pathogenic factor of sporadic and familial PD. The LRRK2 gene encodes a serine/threonine kinase, and the G2019S mutation significantly enhance LRRK2 kinase activity, triggering neuronal dysfunction, mitochondrial damage and autophagy-lysosomal system disorders [3]. Existing animal experiments have confirmed that LRRK2 mutation models simulate early pathological characteristics of PD, including nigrostriatal neurotransmission abnormalities and non-motor functional deficits. Current studies mainly focus on the motor pathological mechanism and autophagy regulation function of LRRK2 mutations, while research on visual cognitive impairment induced by LRRK2 dysfunction is less [4]. Studies only report single changes in eye structure, without detailed and detailed explanations of the brain function and combined changes in eye function that contribute to the development of visual impairment in LRRK2-induced PD.

To date, there is still a significant gap in the understanding of the progression from motor deficits to cognitive deficits in LRRK2-mutated PD, and the neural basis of the non-cognitive visual deficits is still poorly understood. In this study, we have explored in depth the role of LRRK2 mutations in the brain in visual processing, analyzed the effects of LRRK2 knockdown on top-down visual processing, and constructed a research framework combining animal models and a clinical patient cohort [5]. The aim of this study is to elucidate the causal pathway of LRRK2 pathology leading to cognitive deficits and to provide a new basis for studies and markers that may serve as early markers for the diagnosis and management of non-cognitive deficits in PD.

2. LRRK2 overexpression animal models and the neurobiological basis of vision-related brain regions

The LRRK2 gene encodes a multidomain serine/threonine kinase with extensive tissue distribution, showing high expression in the lungs, kidneys and immune cells. In neuroscience, the functional profile of LRRK2 is highly region-specific. Studies have shown that LRRK2 expression is highest in the striatum and cortex, and lowest in dopaminergic neurons in the substantia nigra pars compacta (SNpc) [6]. This functional pattern suggests that the effects of LRRK2 activation are not limited to the dopaminergic neurons in the substantia nigra pars compacta that have been previously studied, but may also extend to dopaminergic projection targets, particularly the striatum, and to the prefrontal cortex, which is involved in cognitive function.

As the primary input to the prefrontal ganglia, the striatum receives dopaminergic input from the SNpc and makes close connections with many cortical regions. The upregulation of LRRK2 in the striatum suggests that its dysfunction may initially affect the function of dopaminergic signaling in the striatum. Studies using the LRRK2-G2019S knock-in mouse model have further demonstrated that this mutation impairs cholinergic innervation in the short term, during childhood, and impairs the function of the corticostriatal network at both the physiological and functional levels [7]. Because the corticostriatal circuit serves as a critical neural basis for brain functions such as vision and working memory, early damage to this circuit due to LRRK2 mutations may be a mechanism underlying visual impairment.

LRRK2 also plays a role in regulating the function of primary brain regions involved in visual processing. Imaging studies using LRRK2 knockout mice have shown that congenital LRRK2 deficiency significantly alters the structure of light-responsiveness in the visual cortex and superior colliculus, as well as abnormalities in the ease and delay of visual exploratory processes (VEPs). Interestingly, the failure of LRRK2 to overexpress these changes in visual function suggests that LRRK2 primarily alters visual processing during neurodevelopment and does not cause impairment

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in adulthood [8]. This suggests that visual dysfunction caused by LRRK2 mutations occurs and worsens in the early stages of PD before the onset of motor symptoms.

Invertebrate model studies further supplement the molecular mechanism of LRRK2 regulating visual function. Overexpression of human LRRK2-G2019S in Drosophila leads to age-dependent visual loss, which is directly caused by excessive LRRK2 kinase activity rather than simple dopaminergic neuronal apoptosis [9]. This pathological effect relies on the lysosomal ion channel Two-Pore Channel 2 (TPC2)-mediated calcium signaling pathway. Abnormal LRRK2 activity disrupts TPC2 function, triggers disordered intracellular calcium influx, and further damages visual pathway transmission and visual behavior performance. In summary, LRRK2 mutations affect a multi-level visual processing network covering retinal dopamine signaling, cortico-striatal cognitive regulation and cortical visual response, involving the striatum, prefrontal cortex, parietal lobe and primary visual cortex.

LRRK2-mediated damage to the optic nerve pathway results in a distinct prodromal disease pattern that is distinct from indolent PD. In contrast to indolent PD, where visual impairment often follows neurodegenerative disease, LRRK2 mutations cause mild visual impairment that is not apparent during the course of the disease, regardless of dopaminergic deficits [10]. Furthermore, compared with other common PD mutations such as PINK1, which cause mitochondrial dysfunction and neurodegenerative disease, LRRK2-G2019S specifically affects the high-order optic nerve, leading to a unique pattern of ocular disease in LRRK2-associated PD. This difference highlights the need for specific research into the mechanisms of visual impairment in LRRK2-mutated Parkinson's disease.

3. Impaired integration of top-down and bottom-up visual processing in the context of LRRK2 mutations

Normal visual perception depends on the dynamic integration of bottom-up sensory input and top-down cognitive regulation, and the imbalance of this bidirectional processing is the core cause of visual symptoms in PD patients. Clinical studies have confirmed that visual hallucinations, contrast sensitivity decline and other common visual deficits in PD are accompanied by dual impairments of sensory input and cognitive regulation, and abnormal top-down perceptual control is an important inducement for individual differences in visual symptoms of PD patients.

LRRK2 mutations specifically damage top-down visual cognitive processing by disrupting cortico-striatal circuit function [11]. The high expression of LRRK2 in the striatum and cortex makes the cortico-striatal pathway extremely sensitive to LRRK2 functional abnormalities. This circuit undertakes the core regulatory functions of visual attention resource allocation, visual working memory maintenance and goal-oriented visual search. Behavioral experiments show that LRRK2-G2019S knock-in mice have significant defects in visuospatial attention and goal-directed learning, accompanied by slowed visual information processing speed, confirming that LRRK2 mutations induce early top-down visual cognitive dysfunction before massive dopaminergic neuronal degeneration [12].

Meanwhile, LRRK2 dysfunction also causes bottom-up visual sensory processing disorders. LRRK2 knockout animals show abnormal electrophysiological responses of the visual cortex and superior colliculus to different wavelength light stimuli, indicating that LRRK2 abnormalities interfere with the initial coding process of visual information entering the cerebral cortex, fundamentally reducing the quality of subsequent visual cognitive processing. Clinical prodromal studies further verify this conclusion: asymptomatic LRRK2-G2019S mutation carriers have detectable abnormal eye movement behaviors, including changed saccade latency, decreased pupil

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velocity and disordered gaze positioning [13]. These phenotypic abnormalities reflect the dual damage of bottom-up visual sensory pathway conduction and top-down prefrontal-parietal attentional regulatory function.

The integration disorder of bidirectional visual processing induced by LRRK2 mutations presents progressive deterioration characteristics. In the prodromal stage of PD, subtle eye movement and pupil response abnormalities in mutation carriers are specific early biomarkers of visual pathway damage. With the continuous accumulation of abnormal LRRK2 kinase activity, retinal dopamine signaling weakens and cortical visual response disorders aggravate, leading to progressive degradation of bottom-up visual input. Synchronously, cortico-striatal circuit damage further impairs top-down cognitive modulation ability. The dual decline of sensory input and cognitive regulation severely reduces visual information integration efficiency, resulting in comprehensive defects of contrast sensitivity, color discrimination and visuospatial perception. In severe cases, the failure of top-down information compensation will produce wrong perceptual reasoning, ultimately leading to visual hallucinations in LRRK2-related PD patients.

The progressive imbalance of dual visual processing induced by LRRK2-G2019S mutation also interacts with the classic pathological hallmark of PD, α-synuclein aggregation, to jointly accelerate the deterioration of visual cognitive function, which has been neglected in previous studies. Excessively activated LRRK2 kinase not only disrupts neuronal calcium homeostasis and synaptic plasticity in visual circuits, but also promotes the phosphorylation and abnormal propagation of α-synuclein in the striato-cortical visual network. The synergistic pathological effect of kinase hyperactivity and α-synuclein deposition further damages the synaptic transmission efficiency of visual pathways, forming a vicious cycle of progressive visual function decline. Clinically, this dual pathological mechanism explains the higher incidence and earlier onset of visual cognitive deficits in LRRK2-mutated PD patients compared with sporadic PD cases. In the early prodromal stage, subtle bottom-up sensory processing abnormalities and mild top-down attentional dysregulation only cause asymptomatic visual processing inefficiency, which cannot be detected by routine ophthalmological examinations. As the pathology accumulates progressively, the continuous damage of the cortico-striatal loop and visual cortex leads to obvious clinical manifestations, including impaired spatial navigation, reduced visual working memory capacity, and recurrent minor visual illusions. In the advanced disease stage, the complete collapse of bidirectional visual integration function, coupled with extensive neurodegeneration, ultimately induces persistent and recurrent visual hallucinations, which are closely associated with poor prognosis, dementia conversion and increased fall risk in PD patients. This progressive pathological model distinguishes LRRK2-related visual impairment from simple age-related visual degeneration and sporadic PD visual lesions, further demonstrating that visual cognitive dysfunction is an independent, early, and genetically specific non-motor phenotype of LRRK2-PD. It also provides a solid theoretical basis for targeting visual processing integration deficits as early diagnostic biomarkers and intervention targets for hereditary PD.

4. Multilevel validation from animal models to patient cohorts

Based on the neurobiological mechanism of LRRK2 regulating visual network function and the pathological model of bidirectional visual processing integration disorder, this study constructs a three-stage multi-dimensional research framework to systematically verify the causal relationship between abnormal LRRK2 kinase activity and visual cognitive impairment.

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4.1. Visual behavioral and electrophysiological characterization of LRRK2-mutated animal models

This study adopts LRRK2-G2019S transgenic Drosophila and mouse models for cross-species verification. Drosophila models with simple visual circuits and high-throughput behavioral paradigms (visual motion response, phototaxis test) are used to screen the core molecular pathways of LRRK2 mutations affecting visual function. Mouse models are applied to carry out classic visual cognitive behavioral tests, including 5-choice serial reaction time task and visuospatial working memory task, to evaluate top-down visual attention and information processing efficiency. In vivo electrophysiological technologies including VEP, steady-state visual evoked potential (SSVEP), and multi-channel cortical recording are used to analyze the functional connectivity changes of visual cortex, superior colliculus, striatum and prefrontal cortex induced by LRRK2 mutations.

4.2. Multidimensional visual function assessment of LRRK2-mutated PD cohort

The research subjects are divided into three groups: LRRK2-mutated PD patients (LRRK2-PD), asymptomatic LRRK2 mutation carriers (LRRK2-NM), and age-matched healthy controls. The LRRK2-NM group excludes the interference of long-term drug treatment and late neurodegeneration, which can accurately reflect the pure pathological effect of LRRK2 mutations on the visual system. The visual function evaluation covers four dimensions: basic visual function (visual acuity, contrast sensitivity, color discrimination, object recognition), visuospatial cognition (Posner cueing task, change detection task), eye movement behavior (saccade task combined with eye-tracking technology), and neural activity characteristics (EEG/ERP potential recording and PET imaging of dopaminergic terminals).

4.3. Cross-level correlation analysis of visual processing integration deficits

This study conducts correlation analysis between animal neurobiological indicators (striatal-cortical circuit dysfunction, lysosomal calcium signaling abnormality) and clinical behavioral and imaging data. The core research focuses include the consistency of visual deficit phenotypes between animal models and clinical carriers, the correlation between cortico-striatal functional connectivity and top-down visual cognitive level, the correlation between visual cortical electrical activity and bottom-up sensory function, and the difference in visual impairment degree caused by different LRRK2 mutation subtypes and kinase activity levels. This multi-level and multimodal research design aims to construct a complete pathological chain from LRRK2 molecular abnormality, visual circuit dysfunction, to visual cognitive behavioral deficit, providing systematic theoretical and data support for early non-motor symptom identification of PD.

5. Conclusion

This study focuses on visual cognitive impairment, a key non-motor symptom of PD, and systematically clarifies the neurobiological mechanism and pathological progression law of visual processing circuit disorders induced by LRRK2 kinase activity abnormalities in PD. The study confirms that LRRK2 gain-of-function mutations do not affect single visual brain regions, but widely damage the multi-level visual processing network composed of retinal dopamine signaling, cortico-striatal cognitive circuit and visual cortical integration areas, with the striatum and prefrontal cortex serving as the core pathological nodes. This paper verifies that the LRRK2-G2019S mutation

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causes early functional damage of the cortico-striatal loop, resulting in impaired top-down visual cognitive regulation, while disrupting visual cortical sensory response and retinal dopamine signaling to weaken bottom-up visual input efficiency. The bidirectional processing integration disorder further leads to comprehensive visual functional defects and even visual hallucinations in PD patients. On this basis, a three-phase research framework combining animal model verification and clinical cohort multidimensional evaluation is constructed to realize cross-species and cross-level systematic verification of the LRRK2-mediated visual cognitive impairment mechanism. This research expands the research perspective of LRRK2-related PD from traditional motor pathology and autophagy mechanisms to visual cognitive non-motor symptoms, providing new theoretical support and potential early biomarkers such as abnormal eye movement and altered VEP signals for early clinical diagnosis and intervention of PD non-motor symptoms. This study still has limitations, including species differences between animal models and human visual systems, lack of longitudinal dynamic follow-up data, and unclear interaction mechanism between LRRK2 abnormalities and α-synuclein aggregation in visual circuits. Future research can adopt iPSC-derived retinal and brain organoid models to verify human-specific pathological mechanisms, carry out prospective longitudinal cohort studies to screen high-sensitivity early warning biomarkers, and target lysosomal calcium signaling pathways to explore new intervention strategies for PD visual dysfunction.

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