Early Parkinson's: Targeting LRRK2 could preserve synaptic function

Written by The Life Science Feed Editorial Team · Published 13 August 2026 · Edited by Mara Voss

> Parkinson's disease (PD) manifests through debilitating motor and non-motor symptoms, primarily driven by the degeneration of dopamine-producing neurons in the substantia nigra pars compacta. But increasing evidence suggests that synapse dysfunction precedes this neuronal loss by years, making early synaptic alterations an important, yet poorly understood, area of research. A new study published in eLife now offers a deeper understanding of LRRK2's role in this early synaptic pathology.1

KEY TAKEAWAYS

- The Pivot: LRRK2 directly modulates synaptic actin cytoskeleton dynamics, a key mechanism in BDNF-dependent synaptic function.
- The Data: Loss of LRRK2 impairs BDNF signaling and alters postsynaptic density architecture, affecting maturation and spontaneous synaptic activity in human iPSC-derived neurons.1
- The Action: Targeting LRRK2-mediated actin remodeling could offer a novel therapeutic strategy for early Parkinson's disease.

Parkinson's disease is not merely a motor disorder; its multisystemic nature means non-motor symptoms often emerge years before the classic tremors and rigidity. The prevailing hypothesis is that synaptic dysfunction, a subtle disruption in neuronal communication, represents one of the earliest pathological events in PD. Understanding these initial changes is paramount for developing interventions that could delay or even prevent the progression to overt neurodegeneration.1 Giulia Tombesi and colleagues integrated a comprehensive approach, combining literature meta-analysis, multi-omics, biochemical assays, advanced imaging, and electrophysiological measurements. They utilized both Lrrk2 mouse models and human iPSC-derived neurons lacking LRRK2 to dissect the protein's function. This multi-pronged strategy allowed for a robust investigation across different biological systems, providing a detailed picture of LRRK2's cellular roles.1

LRRK2's Relationship with BDNF and Actin

The investigators first demonstrated that brain-derived neurotrophic factor (BDNF), a vital neurotrophin involved in neuronal survival and plasticity, activates LRRK2 in differentiated SH-SY5Y cells and primary mouse neurons. This activation was not a passive event; it actively reshaped the LRRK2 interactome, steering it towards a network of proteins intimately involved in actin cytoskeleton regulation. This finding immediately pointed to a novel mechanistic link between LRRK2 and synaptic structural plasticity.1

Gene-ontology analyses further solidified this connection. Examining both literature-curated LRRK2 interactors and the phospho-proteome from striatal tissues with elevated LRRK2 activity, the researchers consistently highlighted

synapse-actin remodeling as a major affected pathway. This convergence of evidence from diverse analytical methods strongly implicated LRRK2 in the dynamic regulation of synaptic structure, a process fundamental to healthy neuronal communication.1

The actin cytoskeleton is a dynamic scaffold within neurons, essential for maintaining synaptic architecture, regulating neurotransmitter release, and shaping dendritic spines. Disruptions in actin dynamics are increasingly recognized as contributors to various neurological disorders, including PD. The identification of LRRK2 as a modulator of this system provides a direct link between a known PD-associated protein and an important cellular process.1

Structural and Functional Consequences of LRRK2 Loss

Loss of LRRK2 significantly impaired BDNF signaling, a pathway vital for synaptic health and neuronal resilience. This impairment was not merely a biochemical observation; it translated into tangible alterations in postsynaptic density architecture. The postsynaptic density (PSD) is a complex protein network beneath the postsynaptic membrane, essential for receiving and integrating synaptic signals. Its structural integrity directly impacts synaptic efficacy.1

In young Lrrk2 knockout mice, the investigators observed structural alterations in dendritic protrusions. Dendritic protrusions, particularly dendritic spines, are the primary sites of excitatory synaptic input in the brain. Their morphology and density are highly plastic and directly correlate with synaptic strength and learning. The fact that these structural alterations normalized with age in the mouse models presents an interesting temporal dynamic, suggesting potential compensatory mechanisms or age-dependent roles for LRRK2.1

But the implications extended beyond structural changes. In human iPSC-derived neurons, LRRK2 knockout affected neuronal maturation and, importantly, the BDNF-dependent regulation of spontaneous synaptic activity. Spontaneous synaptic activity reflects the baseline level of communication between neurons, essential for network function and plasticity. Its disruption indicates a fundamental impairment in neuronal circuit function. The use of human iPSC-derived neurons provides a highly relevant model for studying human disease mechanisms, circumventing some limitations of purely animal models.1

The study's findings suggest that LRRK2 acts as an important regulator in BDNF-dependent synaptic modulation. This modulation occurs through its influence on the synaptic actin cytoskeleton, identifying this as a convergent site for LRRK2-associated pathophysiological processes in Parkinson's disease. The precise mechanisms by which LRRK2 interacts with specific actin-binding proteins or signaling pathways to exert its effects warrant further investigation. Understanding these molecular details could unlock specific targets for therapeutic intervention.1

Methodological Rigor and Future Directions

The strength of this study lies in its multi-omics approach, which allowed for a comprehensive and unbiased identification of LRRK2's interactors and downstream effectors. The integration of literature meta-analysis with experimental data provided a robust framework for validating their findings. The use of both mouse models and human iPSC-derived neurons offers complementary insights, bridging the gap between animal physiology and human disease pathology.1

The electrophysiological measurements, specifically the assessment of spontaneous synaptic activity, provided functional evidence for the observed structural changes. This correlation between structural and functional deficits strengthens the argument for LRRK2's direct involvement in synaptic health. The detailed imaging of postsynaptic density architecture and dendritic protrusions offered high-resolution insights into the morphological consequences of

LRRK2 loss.1

Still, the study primarily focused on the loss of LRRK2 function. Many PD-associated LRRK2 mutations lead to a gain of function, specifically increased kinase activity. Future research needs to explore how hyperactive LRRK2, rather than its absence, impacts BDNF signaling and actin dynamics. This distinction is important for developing targeted therapies that either inhibit or modulate LRRK2 activity in a disease-relevant context. The age-dependent normalization of dendritic protrusion alterations in mice also raises questions about the long-term consequences of LRRK2 dysfunction and potential compensatory mechanisms in the aging brain.1

The study's focus on early synaptic alterations aligns with the growing understanding that PD pathology begins years before motor symptoms appear. This early window offers a significant opportunity for disease modification. If LRRK2-mediated actin remodeling is indeed a convergent site for PD pathophysiology, then interventions aimed at stabilizing or restoring synaptic actin dynamics could represent a novel therapeutic avenue. This could involve small molecules that modulate LRRK2 kinase activity or compounds that directly target actin regulatory proteins. Clinicians looking for a concise neurology reference might find the Oxford Handbook of Neurology (2nd ed) useful for quick consultation on movement disorders and other neurological conditions.1

The precise role of BDNF in this pathway also warrants further exploration. Can exogenous BDNF or BDNF mimetics rescue the synaptic deficits observed in LRRK2 knockout models? Such experiments would provide further validation for the proposed mechanism and potentially identify additional therapeutic strategies. The complexity of BDNF signaling and its pleiotropic effects means that careful consideration of delivery and specificity would be necessary for any clinical application.1

The study did not examine the specific LRRK2 substrates involved in actin regulation. Identifying these direct targets would provide a more granular understanding of the molecular cascade and offer highly specific drug development opportunities. For instance, if LRRK2 phosphorylates a particular actin-binding protein, then inhibiting that phosphorylation event could be a therapeutic strategy. The relationship between LRRK2 and other PD-related genes, such as alpha-synuclein, also remains an open question. Synaptic dysfunction is a common theme across various neurodegenerative diseases, and understanding how different genetic factors converge on this process is important.1

The use of iPSC-derived neurons, while powerful, still represents an in vitro model. The complexity of the human brain, with its intricate neuronal networks and glial interactions, cannot be fully replicated in a dish. Future studies will need to validate these findings in more complex ex vivo or in vivo human models, such as organoids or post-mortem brain tissue from PD patients with LRRK2 mutations. This would provide stronger evidence for the clinical relevance of the observed mechanisms.1

The study provides compelling evidence that LRRK2 is a key player in maintaining synaptic function through its regulation of actin cytoskeletal dynamics. This mechanism is activated by BDNF, and its disruption leads to structural and functional synaptic deficits. These findings open new avenues for understanding early Parkinson's disease pathology and developing targeted interventions. The next step involves translating these mechanistic insights into tangible therapeutic strategies that can be tested in clinical trials, focusing on early-stage PD patients.1

CLINICAL IMPLICATIONS

The direct link between LRRK2 and synaptic actin dynamics offers a fresh perspective on Parkinson's disease pathogenesis. For years, the focus has been on neuronal loss, but this work reinforces the idea that synaptic dysfunction is an earlier, and potentially more tractable, target. Clinicians should consider that interventions aimed at preserving synaptic integrity might hold more promise for early disease modification than strategies solely focused on preventing neuronal death.

This research provides a mechanistic rationale for exploring therapies that modulate LRRK2 activity, not just in the context of its kinase function, but specifically in its role in actin remodeling. If LRRK2's influence on the actin cytoskeleton is indeed a convergent point for PD pathology, then targeting this pathway could offer a broad therapeutic benefit, even for patients without known LRRK2 mutations. The challenge will be developing compounds that selectively modulate this specific function without disrupting other essential cellular processes.

The finding that BDNF activates LRRK2 and that LRRK2 loss impairs BDNF signaling suggests that BDNF-enhancing strategies could be beneficial. But delivering neurotrophic factors to the brain effectively and safely remains a significant hurdle. This study highlights the need for more sophisticated delivery methods or indirect modulators of BDNF pathways, which could be combined with LRRK2-targeted therapies for a synergistic effect.

This work highlights the complexity of Parkinson's disease and the need to move beyond single-target approaches. Understanding the intricate relationship between genetic factors like LRRK2, neurotrophic support, and fundamental cellular processes like actin dynamics will be important for developing truly effective, disease-modifying treatments. The field needs to focus on these upstream events to truly impact the trajectory of this debilitating condition.

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