Reframing Parkinson's disease: From motor circuitry to somato-cognitive network dysfunction

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INTRODUCTION

Parkinson's disease (PD) is typically framed as a movement disorder, yet the clinical reality extends far beyond motor impairment. Patients frequently contend with autonomic, sleep, affective, and cognitive disturbances, symptoms that can fluctuate with attention, task demands and therapeutic state. This multidomain, context-sensitive phenotype exposes the limitations of classical cortico-basal ganglia motor models, which, while adept at explaining effector-specific motor signs like tremor and bradykinesia, offer little traction on the disorder's cross-domain heterogeneity.[1] This conceptual gap carries direct clinical consequences, as therapeutic benefit varies widely and optimizing interventions such as deep-brain stimulation (DBS) remains an inexact science, even when anatomical targets are ostensibly similar.[2] Such variability suggests that individual differences in network-level coupling may shape both symptom expression and treatment outcomes. The somato-cognitive action network (SCAN), a recently characterized distributed system that integrates bodily action with cognitive and autonomic control, offers a timely framework for revisiting PD pathophysiology.[3] In a landmark study, Ren and colleagues test the relevance of SCAN to PD using large-scale multimodal and multi-intervention evidence.[4] They report that PD-relevant subcortical targets preferentially couple to this network and that effective interventions consistently reduce SCAN-subcortical hyperconnectivity. The work is clinically generative, offering a compelling network-based lens through which to reinterpret the pathophysiology and treatment of PD. To situate this conceptual advance within the broader trajectory of PD research, Figure 1 traces the historical paradigm shifts from effector-specific basal ganglia motor models and early connectomic analysis to the current SCAN framework and illustrates the multimodal technical pipeline that enables SCAN-guided precision intervention.

OBSTACLES

Traditional models of PD have been shaped by an effector-centric view, attributing core motor symptoms to dopaminergic degeneration within discrete cortico-basal ganglia motor loops. While this framework has proven invaluable for understanding tremor and bradykinesia, its explanatory reach is increasingly strained.

First, PD is characterized by a broad clinical spectrum that encompasses autonomic dysfunction, cognitive decline, and affective disturbances, manifestations that are not readily accommodated by models privileging effector-specific motor circuitry. Second, motor symptoms in PD are profoundly modulated by cognitive and emotional context, and fluctuations driven by attention, motivation, and task demands point to mechanisms beyond impaired motor execution. Finally, these conceptual limitations translate into clinical uncertainty. Although neuromodulatory therapies such as DBS can be highly effective, their network-level mechanisms remain incompletely understood, and target selection continues to rely largely on anatomical heuristics rather than functionally defined circuits. Addressing these gaps requires a framework that can unify the disorder's diverse clinical features under a common network-level account.

KEY ADVANCES

Against this backdrop, Ren and colleagues advance a network-based reinterpretation of PD centered on SCAN. A key conceptual advance is that SCAN provides functional specificity for action control rather than simple motor execution. Classical cortico-basal ganglia models and effector-specific motor maps are well suited to explain impairment in limb-specific movement execution, but they are less able to account for symptoms that depend on whole-body coordination, arousal, autonomic state, motivation, and cognitive context. By contrast, SCAN is positioned as a distributed action-control network that links bodily movement with cognitive preparation and physiological regulation. This distinction is particularly relevant to PD, in which gait instability, freezing, impaired action initiation, cognitive-motor interference, and autonomic symptoms often cannot be reduced to dysfunction of a single motor effector. Using large-scale resting-state functional MRI datasets, they first delineate SCAN as a reproducible cortical network and systematically characterize its connectivity with PD-relevant subcortical nuclei. Rather than preferentially coupling to effector-specific motor regions, these subcortical structures show robust and convergent connectivity with SCAN, directly challenging expectations derived from classical motor circuit models.

At the patient level, SCAN-subcortical connectivity is markedly elevated in PD relative to healthy controls, and this hyperconnectivity correlates consistently with motor severity as well as cognitive and affective measures. These findings position SCAN as a candidate network-level pathological signature, suggesting that PD-related dysfunction is expressed primarily within a distributed action-control network rather than isolated effector representations. Importantly, this account is reinforced by convergent interventional evidence. Across pharmacological treatment, DBS, and non-invasive brain stimulation, clinical improvement is accompanied by a reduction in SCAN-subcortical coupling. Moreover, in a randomized trial, network-guided stimulation targeting SCAN yields greater symptomatic benefit compared with conventional M1-based approaches. Together, these findings move the field from anatomical heuristics toward a functionally defined, network-guided framework for understanding and treating PD.

LIMITATIONS

Notwithstanding the study's conceptual innovation and the breadth of convergent evidence, several unresolved issues merit closer consideration. First, SCAN hyperconnectivity should be interpreted in the context of a broader and sometimes heterogeneous literature on PD network dysfunction. Prior studies have reported both increased and reduced cortico-subcortical connectivity, with discrepancies likely shaped by disease stage, medication status, symptom subtype, and analytic procedures. These divergent findings do not necessarily refute the SCAN framework, but they suggest that SCAN dysfunction may evolve dynamically across the disease course. Hyperconnectivity may reflect a compensatory or maladaptive state in some stages, whereas later neurodegeneration may lead to weakening or fragmentation of specific network interactions. The SCAN model should therefore be tested longitudinally as a stage-sensitive framework rather than a fixed signature of PD.

The mechanistic status of SCAN hyperconnectivity also remains uncertain. Its reduction after DBS, medication, and TMS indicates state sensitivity, but does not determine whether it represents a primary pathogenic driver, a compensatory reorganization, or a downstream consequence of dopaminer-

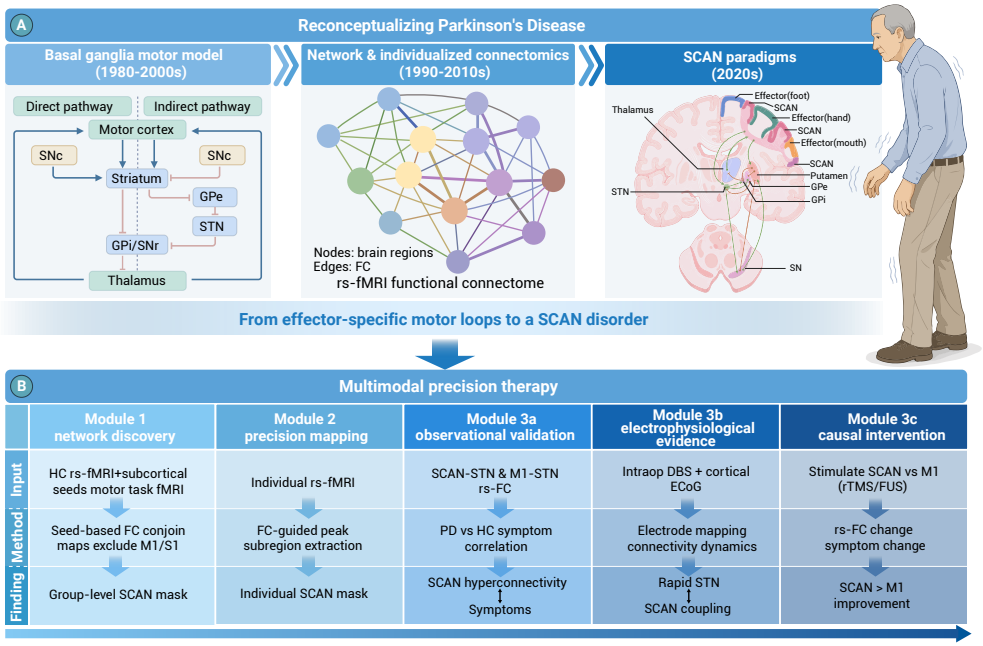

Figure 1. Reconceptualizing Parkinson's disease from effector-specific motor loops to SCAN disorder (A) Historical evolution of pathophysiological models: from classical basal ganglia motor circuits, through connectomic analyses, to the current SCAN-based framework. (B) Multimodal technical pipeline for SCAN-guided precision intervention, integrating individualized functional mapping with targeted neuromodulation.

gic and broader neurodegeneration. Disease heterogeneity presents a related challenge. The available analyses do not yet establish whether SCAN abnormalities are shared across tremor-dominant, akinetic-rigid, postural instability and gait disorder, or cognitively affected phenotypes, which may involve distinct cortical and subcortical network configurations. The relationship between SCAN dysfunction and α-synuclein pathology also remains unresolved. It is unclear whether SCAN topology shapes pathological propagation, whether α-synuclein burden disrupts SCAN integrity, or whether both are secondary to broader circuit vulnerability. In addition, individual SCAN boundaries may vary substantially, and the stability of personalized SCAN mapping across sessions, disease stages, and imaging protocols remains insufficiently characterized. Finally, although associations between SCAN connectivity and clinical measures were statistically significant, effect sizes were modest. Whether SCAN metrics can predict individual disease progression or treatment response therefore remains a critical question.

FUTURE DIRECTIONS

Future work should move from demonstrating SCAN involvement in PD to testing SCAN-specific mechanisms and interventions. A first priority is to determine whether distinct SCAN nodes support different symptom dimensions. The superior, middle, and inferior SCAN regions may not be interchangeable, and their connectivity with STN, GPi, VIM, putamen, or brainstem structures could map onto axial impairment, tremor, bradykinesia, freezing of gait, autonomic dysfunction, or cognitive-motor interference. Such work would transform SCAN from a global network label into a symptom-resolved therapeutic map.

A second direction is to use individualized SCAN connectivity for intervention design. For DBS and MRgFUS, patient-specific subcortical SCAN representations could be compared with conventional anatomical targets to test whether SCAN-guided targeting improves motor and non-motor outcomes. For TMS, algorithms that optimize coil placement over personalized SCAN nodes should be evaluated for dose-response relationships, symptom specificity, and durability. A related strategy is to test combined cortical and subcortical modulation. Pairing cortical SCAN stimulation with STN or GPi DBS may allow clinicians to tune the broader action-control network rather than a single node.

Direct evidence linking SCAN topology to α-synuclein deposition is currently lacking. Mechanistically, future studies should integrate functional imaging, diffusion MRI, electrophysiology, and molecular pathology to ask whether SCAN structural connectivity predicts the spatiotemporal spread of α-synuclein pathology, and whether baseline SCAN functional integrity predicts later regional vulnerability or clinical decline.[5] These studies would directly address whether SCAN is a driver, substrate, or consequence of PD progression. Finally, translation will require scalable implementation. Automated SCAN mapping, harmonized acquisition protocols, and clinically interpretable connectivity reports will be needed before SCAN-guided decision-making can enter routine practice.

CONCLUSIONS

Taken together, this work reframes PD as a disorder of a distributed somato-cognitive action network, rather than a condition confined to effector-specific motor circuitry. By defining SCAN independently of disease status and demonstrating its selective involvement across patient cohorts and interventional contexts, the study establishes a coherent network-level account that links heterogeneous motor and non-motor symptoms to a shared functional substrate. A central strength of this framework lies in its integration of observational, electrophysiological, and interventional evidence, which collectively supports SCAN as both a pathological signature and a modifiable target. At the same time, the clinical impact of this perspective will depend on further clarification of its mechanistic basis, temporal sensitivity across disease stages, and predictive value at the individual level. If these challenges can be addressed, a network-guided approach centered on SCAN has the potential to reshape both the conceptualization and treatment of PD, offering a principled pathway toward more precise and personalized neuromodulation strategies.

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AUTHOR CONTRIBUTIONS

All authors contributed to the manuscript and approved the final version.

DECLARATION OF INTERESTS

The authors declare no competing interests.