LUMEN ET VIRTUS
ISSN: 2177-2789

APPLICATIONS OF FUNCTIONAL MAGNETIC RESONANCE IMAGING IN THE EARLY DIAGNOSIS OF PARKINSON DISEASE: A SYSTEMATIC REVIEW

APLICAÇÕES DA RESSONÂNCIA MAGNÉTICA FUNCIONAL NO DIAGNÓSTICO PRECOCE DA DOENÇA DE PARKINSON: UMA REVISÃO SISTEMÁTICA

APLICACIONES DE LA RESONANCIA MAGNÉTICA FUNCIONAL EN EL DIAGNÓSTICO PRECOZ DE LA ENFERMEDAD DE PARKINSON: UNA REVISIÓN SISTEMÁTICA

https://doi.org/10.56238/levv16n53-098

Submission date: 09/23/2025 **Publication date:** 10/23/2025

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ABSTRACT

Introduction: Parkinson disease (PD) is a progressive neurodegenerative disorder characterized by motor and non-motor symptoms that typically emerge after extensive dopaminergic neuronal loss. Functional magnetic resonance imaging (fMRI) has emerged as a powerful tool for identifying early neural dysfunctions preceding overt clinical manifestations.

Objective: To systematically evaluate the evidence regarding the diagnostic utility of fMRI in detecting early or prodromal Parkinson disease, highlighting the main paradigms, analytical methods, and biomarkers associated with altered brain connectivity and activity patterns.

Methods: Searches were conducted in PubMed, Scopus, Web of Science, Cochrane Library, LILACS, ClinicalTrials.gov, and ICTRP. Studies published from 2019 to 2025 investigating the use of task-based or resting-state fMRI in early, prodromal, or de novo PD were included. Data extraction followed PRISMA guidelines. Methodological quality was assessed with the Newcastle-Ottawa Scale for observational studies and QUADAS-2 for diagnostic accuracy.

Results and Discussion: 24 studies met the eligibility criteria. Altered functional connectivity was consistently observed within the basal ganglia–thalamocortical circuit, default mode network, and cerebellar regions. Machine-learning models using fMRI-based biomarkers achieved diagnostic accuracies between 82 % and 95 % in distinguishing early PD from

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healthy controls. However, heterogeneity of acquisition parameters and analytic pipelines limited direct comparability across studies.

Conclusion: fMRI provides sensitive markers of early neuronal dysfunction in Parkinson disease and holds promise as a non-invasive adjunct to clinical and molecular biomarkers. Standardization of protocols and longitudinal validation are required before routine clinical implementation.

Keywords: Parkinson Disease. Magnetic Resonance Imaging. Biomarkers. Neural Networks.

RESUMO

Introdução: A doença de Parkinson (DP) é uma doença neurodegenerativa progressiva caracterizada por sintomas motores e não motores que tipicamente surgem após extensa perda neuronal dopaminérgica. A ressonância magnética funcional (RMf) surgiu como uma ferramenta poderosa para identificar disfunções neurais precoces que precedem manifestações clínicas evidentes.

Objetivo: Avaliar sistematicamente as evidências sobre a utilidade diagnóstica da RMf na detecção da doença de Parkinson precoce ou prodrômica, destacando os principais paradigmas, métodos analíticos e biomarcadores associados a padrões alterados de conectividade e atividade cerebral.

Métodos: As buscas foram realizadas nas bases de dados PubMed, Scopus, Web of Science, Biblioteca Cochrane, LILACS, ClinicalTrials.gov e ICTRP. Foram incluídos estudos publicados de 2019 a 2025 que investigaram o uso de RMf baseada em tarefas ou em estado de repouso na DP precoce, prodrômica ou de novo. A extração de dados seguiu as diretrizes PRISMA. A qualidade metodológica foi avaliada com a Escala Newcastle-Ottawa para estudos observacionais e o QUADAS-2 para acurácia diagnóstica.

Resultados e Discussão: 24 estudos preencheram os critérios de elegibilidade. Conectividade funcional alterada foi consistentemente observada no circuito gânglios da base-tálamo-cortical, na rede de modo padrão e nas regiões cerebelares. Modelos de aprendizado de máquina utilizando biomarcadores baseados em fMRI alcançaram precisões diagnósticas entre 82% e 95% na distinção entre pacientes com DP em estágio inicial e controles saudáveis. No entanto, a heterogeneidade dos parâmetros de aquisição e dos pipelines analíticos limitou a comparabilidade direta entre os estudos.

Conclusão: A fMRI fornece marcadores sensíveis de disfunção neuronal precoce na doença de Parkinson e é promissora como um complemento não invasivo aos biomarcadores clínicos e moleculares. A padronização de protocolos e a validação longitudinal são necessárias antes da implementação clínica de rotina.

Palavras-chave: Doença de Parkinson. Ressonância Magnética. Biomarcadores. Redes Neurais.

RESUMEN

Introducción: La enfermedad de Parkinson (EP) es un trastorno neurodegenerativo progresivo que se caracteriza por síntomas motores y no motores que suelen aparecer tras una pérdida neuronal dopaminérgica extensa. La resonancia magnética funcional (RMf) se ha convertido en una herramienta eficaz para identificar disfunciones neuronales tempranas que preceden a manifestaciones clínicas evidentes.

Objetivo: Evaluar sistemáticamente la evidencia sobre la utilidad diagnóstica de la RMf en la detección de la enfermedad de Parkinson temprana o prodrómica, destacando los principales paradigmas, métodos analíticos y biomarcadores asociados con alteraciones de la conectividad cerebral y los patrones de actividad.

Métodos: Se realizaron búsquedas en PubMed, Scopus, Web of Science, Cochrane Library, LILACS, ClinicalTrials.gov e ICTRP. Se incluyeron estudios publicados entre 2019 y 2025 que investigaron el uso de la RMf basada en tareas o en estado de reposo en la EP temprana, prodrómica o de novo. La extracción de datos se realizó siguiendo las directrices PRISMA. La calidad metodológica se evaluó con la Escala Newcastle-Ottawa para estudios observacionales y con QUADAS-2 para la precisión diagnóstica.

Resultados y discusión: Veinticuatro estudios cumplieron los criterios de elegibilidad. Se observó una alteración de la conectividad funcional de forma consistente en el circuito ganglio-tálamo-cortical basal, la red neuronal por defecto y las regiones cerebelosas. Los modelos de aprendizaje automático que utilizan biomarcadores basados en fMRI alcanzaron una precisión diagnóstica de entre el 82 % y el 95 % al distinguir la EP temprana de los controles sanos. Sin embargo, la heterogeneidad de los parámetros de adquisición y los procesos analíticos limitó la comparabilidad directa entre los estudios.

Conclusión: La fMRI proporciona marcadores sensibles de disfunción neuronal temprana en la enfermedad de Parkinson y es prometedora como complemento no invasivo a los biomarcadores clínicos y moleculares. Se requiere la estandarización de protocolos y la validación longitudinal antes de su implementación clínica rutinaria.

Palabras clave: Enfermedad de Parkinson. Resonancia Magnética. Biomarcadores. Redes Neuronales.

1 INTRODUCTION

Parkinson disease (PD) is the second most prevalent neurodegenerative disorder worldwide, affecting approximately ten million individuals and imposing a growing socioeconomic burden[1]. Neurodegeneration in PD primarily involves dopaminergic neurons of the substantia nigra pars compacta, leading to impaired basal ganglia function and progressive motor dysfunction[1]. Traditional diagnosis relies on clinical symptoms that appear only after more than 50 % of dopaminergic terminals are lost[2].

The early diagnosis of PD remains a major challenge because the prodromal phase may last years before motor signs emerge[2]. Non-motor symptoms such as hyposmia, constipation, and REM sleep behavior disorder can precede motor dysfunction, but lack specificity[3]. Therefore, the development of imaging biomarkers capable of detecting early neuronal dysfunction represents a crucial goal for disease modification strategies[3].

Functional magnetic resonance imaging (fMRI) allows in-vivo mapping of neuronal activity through blood-oxygen-level-dependent (BOLD) signal fluctuations[4]. Unlike structural MRI, which detects macroscopic atrophy, fMRI can reveal alterations in brain connectivity and network efficiency that precede volumetric loss[4]. Resting-state and task-based paradigms have shown disrupted synchronization between the basal ganglia and cortical motor areas in PD patients even at early stages[5].

In recent years, advances in acquisition speed, noise reduction, and multiband sequences have improved the sensitivity of fMRI for detecting subtle neural changes[5]. Studies using independent component analysis (ICA) and graph-theoretical models demonstrated decreased connectivity in the putamen and supplementary motor area of patients with de novo PD[6]. These findings suggest that fMRI may serve as a biomarker for early neuronal dysfunction before clinical conversion[6].

Machine-learning techniques, including support vector machines and convolutional neural networks, have further enhanced the diagnostic potential of fMRI[7]. When trained on large datasets, these models can distinguish PD patients from healthy controls based on spatial patterns of BOLD activity[7]. Integration of fMRI with other modalities such as diffusion tensor imaging (DTI) and PET has been proposed to increase diagnostic accuracy[8].

Nevertheless, challenges persist regarding reproducibility and cross-site variability[8]. Differences in preprocessing pipelines, scanner field strengths, and sample sizes hinder meta-analytic synthesis[9]. Moreover, comorbidities, medication status, and motion artifacts may confound BOLD-based measurements[9]. Addressing these limitations is essential for the translation of fMRI from research settings to clinical application[10].

The identification of early biomarkers is particularly important given the recent development of neuroprotective and disease-modifying therapies targeting α-synuclein aggregation[10]. Reliable imaging markers could enable earlier intervention and patient stratification for clinical trials[11]. Thus, reviewing the current evidence on fMRI in early PD is timely and clinically relevant[11].

2 OBJECTIVES

The main objective of this systematic review is to evaluate the diagnostic value of functional magnetic resonance imaging (fMRI) in the early detection of Parkinson disease (PD), with emphasis on resting-state and task-based paradigms. Secondary objectives include: (1) identifying the most frequently altered neural networks in early PD; (2) analyzing the diagnostic performance and reproducibility of fMRI biomarkers compared to conventional and molecular imaging techniques; (3) assessing the methodological quality and heterogeneity of published studies; and (4) discussing the clinical implications and future perspectives for incorporating fMRI-based metrics into diagnostic.

3 METHODOLOGY

This systematic review followed the **Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)** guidelines to ensure transparency and reproducibility. Comprehensive searches were conducted in **PubMed/MEDLINE, Scopus, Web of Science, Cochrane Library, LILACS, ClinicalTrials.gov**, and the **WHO International Clinical Trials Registry Platform (ICTRP)**. The search strategy included the following keywords and MeSH terms combined with Boolean operators: *("Parkinson disease" OR "Parkinsonism") AND ("functional MRI" OR "resting-state fMRI" OR "BOLD") AND ("early diagnosis" OR "prodromal" OR "de novo")*. The time window was restricted to studies published between **January 2019 and October 2025**.

Eligible studies included human participants diagnosed with early or de novo PD (disease duration ≤3 years) or individuals at prodromal risk, such as those with REM sleep behavior disorder or genetic mutations associated with PD. Both **task-based and resting-state fMRI** designs were accepted. Exclusion criteria were studies involving advanced PD, animal models without human validation, or lacking diagnostic or connectivity outcomes. In cases where fewer than ten eligible studies were available for a subtheme, the time window was expanded to include up to ten years of literature. No language restriction was applied.

4 RESULTS

67 full-text articles were reviewed in detail, and 24 studies met all inclusion criteria for qualitative synthesis. Common reasons for exclusion included advanced PD samples, non-functional MRI methods, or lack of diagnostic relevance.

Table 1

Summary of studies included in the review

Reference	Population / Intervention / Comparison	Outcomes	Main conclusions
1. Tahmasian M et al., 2019, *Hum Brain Mapp*	45 de novo PD vs. 45 controls; resting-state fMRI	Basal ganglia connectivity	Reduced striatal–motor connectivity distinguishes early PD.
2. Berman BD et al., 2020, *Neuroimage Clin*	60 early PD vs. 50 controls; motor task fMRI	SMA and M1 activation	Decreased task-related activity correlates with UPDRS scores.
3. Li Q et al., 2020, *Brain Imaging Behav*	55 PD vs. 55 controls; resting-state	Default mode network	Reduced connectivity in DMN regions predicts disease duration.
4. Chen Y et al., 2021, *Front Neurosci*	40 prodromal PD (RBD) vs. 40 controls	Functional network homogeneity	Altered connectivity in limbic and olfactory networks in RBD.
5. Rizzo G et al., 2021, *Neuroimage Clin*	52 early PD; independent component analysis	Salience network	Reduced insular connectivity differentiates PD from controls.
6. Tahmasian M et al., 2021, *Mov Disord*	70 PD (de novo); longitudinal	Resting-state dynamics	Progressive disruption of thalamocortical network over 12 months.
7. Wu T et al., 2021, *Brain Commun*	48 PD vs. 48 controls; motor imagery task	SMA–putamen coupling	Decreased coupling linked to motor performance deficits.
8. Zhang J et al., 2021, *Front Neurol*	60 early PD; graph theory analysis	Global efficiency	Network efficiency reduction predicts motor symptom severity.
9. Gao L et al., 2022, *Brain Imaging Behav*	58 PD vs. 58 controls; multimodal fMRI + DTI	Combined metrics	Fusion of modalities improves diagnostic accuracy to 92 %.
10. Zheng J et al., 2022, *Neuroimage*	70 early PD; dynamic connectivity	Basal ganglia–cortical loops	Temporal instability predicts motor symptom progression.
11. Singh A et al., 2022, *Mov Disord*	35 LRRK2 carriers; resting-state	Preclinical biomarker	Altered frontostriatal connectivity before symptom onset.

Reference	Population / Intervention / Comparison	Outcomes	Main conclusions
12. Tang C et al., 2022, *Front Hum Neurosci*	64 early PD; machine-learning model	Diagnostic performance	SVM model achieved 90 % accuracy for early PD classification.
13. Liu J et al., 2023, *Neuroimage Clin*	50 PD; cerebellar connectivity	Motor network	Increased cerebellar–frontal coupling compensates basal ganglia loss.
14. Luo W et al., 2023, *Front Aging Neurosci*	42 PD vs. 42 controls; olfactory fMRI task	Olfactory bulb activation	Reduced activation predicts hyposmia severity.
15. Chou KH et al., 2023, *Hum Brain Mapp*	70 early PD; network-based statistics	Cortical hub disruption	Decreased connectivity in posterior cingulate and precuneus.
16. Li Y et al., 2023, *Eur Radiol*	60 PD; DLPFC activation task	Cognitive task fMRI	Diminished prefrontal activation in early cognitive impairment.
17. Park J et al., 2024, *Brain Commun*	55 early PD; seed-to-voxel	Sensorimotor network	Reduced coupling between putamen and SMA.
18. Zhao X et al., 2024, *Front Neurol*	50 early PD; longitudinal fMRI	Network progression	Decline in default mode network correlates with cognitive decline.
19. Kim H et al., 2024, *Magn Reson Imaging*	80 PD vs. 80 controls; 7T fMRI	Spatial resolution	7T improves sensitivity for subthalamic nucleus activation.
20. Xu Q et al., 2024, *Neuroimage Clin*	45 early PD; task-based fMRI	Executive function	Decreased frontoparietal activation predicts working memory deficit.
21. Gao Y et al., 2024, *Front Neurosci*	60 PD; deep-learning fMRI classifier	Diagnostic model	CNN achieved 95 % accuracy distinguishing PD vs. controls.
22. Li S et al., 2025, *Neurobiol Aging*	62 early PD; resting-state	Connectivity trajectories	Network alterations progress faster in younger-onset PD.
23. Zhang W et al., 2025, *J Magn Reson Imaging*	50 early PD; graph metrics	Network clustering	Decreased clustering coefficient in basal ganglia network.
24. Silva R et al., 2025, *Front Hum Neurosci*	58 early PD; combined fMRI and PET	Metabolic correlation	fMRI-PET coupling improves differentiation of early PD.

5 RESULTS AND DISCUSSION

Functional magnetic resonance imaging (fMRI) has demonstrated growing reliability as a biomarker for early Parkinson disease (PD), allowing the detection of functional network disruption before the onset of major motor symptoms[13]. The majority of included studies

employed resting-state paradigms to investigate basal ganglia–thalamocortical circuitry, revealing decreased functional connectivity between the striatum and motor cortices[13]. Tahmasian et al. (2019) showed that striatal–motor connectivity reduction was evident even in de novo PD, correlating with disease severity[14].

Task-based paradigms also revealed significant abnormalities, particularly in the supplementary motor area (SMA) and primary motor cortex (M1)[14]. Berman et al. (2020) demonstrated reduced activation in SMA and M1 during movement execution, with signal amplitude inversely correlated to Unified Parkinson Disease Rating Scale (UPDRS) motor scores[15]. This relationship underscores that fMRI is capable not only of distinguishing early PD from controls but also of quantifying disease progression[15].

Resting-state analyses frequently identified abnormalities in the default mode network (DMN), which regulates self-referential cognition and executive control[16]. Li et al. (2020) observed decreased DMN connectivity that significantly predicted disease duration and non-motor symptom burden[16]. These alterations suggest that fMRI may capture early dysfunction in cognitive networks before measurable deficits arise in neuropsychological testing[17].

Evidence from prodromal PD populations, such as individuals with REM sleep behavior disorder (RBD), supports the hypothesis that network abnormalities precede motor onset[17]. Chen et al. (2021) found that patients with RBD displayed decreased limbic and olfactory connectivity, regions previously implicated in early α-synuclein pathology[18]. These findings align with Braak's staging hypothesis and reinforce fMRI's sensitivity to preclinical neural dysfunction[18].

Network-level studies using independent component analysis (ICA) and graph-theoretical models further elucidated the topological reorganization in early PD[19]. Rizzo et al. (2021) identified reduced integration within the salience network, particularly the insular cortex, which may explain the impaired detection of salient stimuli observed in PD patients[19]. Similarly, Zhang et al. (2021) reported decreased global efficiency and disrupted small-world properties in functional brain networks[20]. Such metrics highlight the progressive disconnection among cortical and subcortical hubs involved in motor planning and execution[20].

Multimodal imaging combining fMRI with diffusion tensor imaging (DTI) or positron emission tomography (PET) has enhanced diagnostic power[21]. Gao et al. (2022) demonstrated that integrating functional and structural features increased accuracy for early PD classification up to 92 %[21]. These hybrid approaches leverage the complementary information of microstructural and metabolic integrity, supporting their translation into precision medicine frameworks[22].

Dynamic connectivity analyses revealed that temporal variability within basal ganglia–cortical loops is an early indicator of progression[22]. Zheng et al. (2022) observed instability in network states correlating with longitudinal deterioration of motor scores[23]. This evidence emphasizes that static connectivity measures may underestimate the dynamic nature of PD-related alterations[23].

Genetic and preclinical cohorts also contribute to understanding early neurofunctional changes[24]. Singh et al. (2022) evaluated asymptomatic carriers of *LRRK2* mutations, showing reduced frontostriatal coupling even before symptom onset[24]. These results underscore the potential of fMRI for identifying individuals at high risk for conversion, which may facilitate inclusion in preventive trials[25].

Machine-learning models have become increasingly prevalent in fMRI research, providing individualized predictions of disease presence[25]. Tang et al. (2022) developed a support vector machine (SVM) model achieving 90 % classification accuracy in early PD[26]. Similarly, Gao et al. (2024) trained convolutional neural networks (CNNs) that reached diagnostic accuracies exceeding 95 %, outperforming traditional statistical classifiers[26]. These algorithms highlight the potential for automated diagnostic tools using large-scale neuroimaging datasets[27].

Compensatory mechanisms have also been identified, particularly involving the cerebellum[27]. Liu et al. (2023) reported increased cerebellar–frontal coupling that appeared to offset reduced basal ganglia connectivity[28]. This compensatory activation may reflect neural adaptation to dopaminergic loss and underscores the brain's plasticity during the early disease phase[28].

Olfactory fMRI paradigms provide an interesting window into prodromal dysfunction[29]. Luo et al. (2023) demonstrated that diminished olfactory bulb activation correlates strongly with psychophysical hyposmia severity[29]. Given that olfactory impairment is among the earliest symptoms of PD, such findings suggest fMRI may serve as a non-invasive biomarker for identifying at-risk individuals[30].

High-field MRI systems (7 Tesla) have further improved the spatial resolution of basal ganglia and subthalamic nucleus imaging[30]. Kim et al. (2024) reported enhanced sensitivity in detecting subthalamic activation patterns, which may inform surgical targeting for deep brain stimulation[31]. However, accessibility and motion artifacts remain practical limitations for widespread 7T implementation[31].

Longitudinal studies have shown that fMRI connectivity alterations parallel clinical decline[32]. Zhao et al. (2024) observed progressive disruption in the DMN correlating with

worsening cognitive function over 18 months[32]. Such findings strengthen the role of fMRI as a potential biomarker not only for diagnosis but also for monitoring therapeutic response[33].

Despite encouraging results, methodological heterogeneity remains a major barrier[33]. Differences in acquisition protocols, preprocessing pipelines, and network analysis methods limit comparability across studies[34]. Furthermore, small sample sizes and lack of standardized cutoffs contribute to inconsistent diagnostic thresholds[34]. Future research must prioritize multicentric harmonization initiatives to improve reproducibility[35].

6 CONCLUSION

This systematic review demonstrates that functional magnetic resonance imaging (fMRI) provides a highly sensitive, non-invasive approach for detecting early neurofunctional changes in Parkinson disease. The reviewed studies consistently revealed altered functional connectivity within the basal ganglia–thalamocortical circuit, default mode network, and salience network during the prodromal and de novo stages of the disease. These findings highlight that fMRI captures both motor and non-motor network disruptions before clinical symptom onset, supporting its value as an early biomarker for Parkinson disease.

From a clinical perspective, fMRI can serve as a complementary diagnostic tool alongside molecular and structural imaging modalities. The inclusion of resting-state and task-based paradigms allows for a multidimensional assessment of brain function, potentially guiding therapeutic decisions and identifying candidates for disease-modifying interventions. Additionally, machine-learning algorithms trained on large fMRI datasets have achieved impressive diagnostic accuracy, suggesting a near-future application of artificial intelligence in early Parkinsonian screening.

Nevertheless, the available literature remains limited by methodological heterogeneity, small sample sizes, and the absence of standardized preprocessing and analytic frameworks. Differences in scanner field strength, task paradigms, and statistical thresholds compromise cross-study comparability. The scarcity of longitudinal data further limits conclusions regarding the prognostic value of fMRI metrics.

Future research should focus on multicenter collaborations using harmonized acquisition protocols and standardized pipelines. Integrating multimodal imaging (fMRI, DTI, PET) and genetic profiling can enhance diagnostic accuracy and elucidate the mechanistic underpinnings of early Parkinson disease. Longitudinal designs are needed to establish predictive biomarkers of disease progression and therapeutic response.

In conclusion, functional MRI represents a promising frontier for the early diagnosis of Parkinson disease. By combining advanced neuroimaging techniques with computational

analysis and clinical data, the field is moving toward evidence-based, multidisciplinary, and individualized diagnostic strategies that may revolutionize the management of neurodegenerative disorders.

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