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Review Article

Neuromelanin-Sensitive Magnetic Resonance Imaging as a Biomarker for Prodromal Parkinson's Disease: A Systematic Review of Diagnostic Accuracy and Longitudinal Predictivity

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Abstract

Neuroimaging biomarkers represent non-invasive approaches to monitor the neurodegenerative process of PD; yet comparative synthesis between the aforementioned modalities in early and preclinical stages is warranted in order to establish diagnostic criteria. We performed a systematic review of neuroimaging modalities to assess diagnostic value, predictive power and clinical applicability. This systematic review was carried out according to PRISMA guidelines. Primary database search (MEDLINE, Embase, Web of Science, PsycINFO) was done from inception to retrieve articles that assessed neuroimaging biomarkers (NMS-MRI, QSM, DTI, PET, SPECT) in preclinical stages (for example, isolated REM sleep behavior disorder), early Parkinson's disease, and controls. After the screening and assessment of full texts, qualitative analysis was done regarding nigrostriatal degeneration, brain iron/neuromelanin pathology, sequencing optimization, and subtyping. Among the 286 included articles (out of 2,066 identified records), the use of advanced MRI and molecular imaging techniques successfully recognized early subcortical brain changes. Pathophysiological, progressive degeneration of dopaminergic neurons containing neuromelanin and noradrenergic neurons in the substantia nigra pars compacta and locus coeruleus respectively resulted in deposition of unchelated ferric iron, causing oxidative damage and loss of "swallow tail sign" of nigrosome-1. The current three-dimensional multiecho GRE imaging technique with magnetization transfer allowed simultaneous estimation of iron accumulation and loss of neuromelanin. Also, reduction in dopamine transporter binding (>25%) and metabolic ^{18}F-FDG-PET covariance patterns were used to predict phenoconversion in prodromal subjects, while multimodal imaging successfully distinguished PD from essential tremor, PSP, and MSA.

Keywords: Neuromelanin, Magnetic resonance imaging, Biomarker, Prodromal Parkinson's disease, and Diagnosis

Introduction

Parkinson's disease is a multifaceted neurodegenerative disorder caused by the progressive loss of neurons in both the central and peripheral nervous systems (Brumberg *et al*., 2021; Theis *et al*., 2024). Conventionally, clinical diagnosis depends on the appearance of cardinal symptoms, which become evident only once sufficient neurodegeneration occurs (Cheng *et al*., 2010). Adjusted for normal aging, motor features become apparent when a decline of about 30% occurs in the number of dopamine-producing axons in the striatum (Cheng *et al*., 2010). Analysis of the preclinical course of the disease shows that not only the central nervous system, but the peripheral autonomic network also suffers from structural damage (Brumberg *et al*., 2021; Mfon *et al.,* 2025). This is evidenced by significant neuronal damage in the noradrenergic innervation of the heart and in the cholinergic network of the enteric nervous system (Brumberg *et al*., 2021). Additionally,

the propagation of pathological proteins along brain connectomes signifies the systemic nature of synucleinopathy (Yau *et al*., 2018). The prodromal stage of PD involves a long period during which early pathophysiological changes are seen before diagnosis can be made (Meles *et al*., 2018). iRBD is defined as one of the most reliable prodromal signs in predicting conversion to synucleinopathies (Meles *et al*., 2018). Patients with iRBD have documented decreased binding capacity of the dopamine transporter and gradual structural network modifications (Chahine *et al*., 2020; Rahayel *et al*., 2021). In the same way, idiopathic hyposmia (iH) stands out as another non-motor feature associated with low putaminal dopamine turnover (Löhle *et al*., 2020). Follow-up has shown that patients with iH who have a deficit in the baseline dopamine transporter have a high risk of conversion to clinical PD (Siderowf *et al*., 2020; Marrero-González *et al*., 2020). The use of non-motor clinical biomarkers together with sophisticated imaging measures improves prediction of phenoconversion significantly (Meles *et al*., 2017).

Neuromelanin (NM) is a dark autoxidizing pigment, which is selectively produced in dopaminergic neurons of the substantia nigra pars compacta and noradrenergic neurons of the locus coeruleus (Galgani *et al*., 2020). On the biological level, NM demonstrates high affinity to heavy metals and acts as endogenous chelating agent of paramagnetic iron ions (Pavese & Tai, 2018). In healthy subcortical tissues, the creation of paramagnetic NM-iron complexes creates specific endogenous contrast at special magnetic resonance sequences (Pavese & Tai, 2018). As a result of degeneration of pigmentated dopaminergic and noradrenergic cells in PD development, the level of intracellular NM decreases (Biondetti *et al*., 2021; Galgani *et al*., 2020). This change is associated with local deposition of iron and neurodegeneration in certain brainstem areas (Biondetti *et al*., 2021). Neuromelanin-sensitized magnetic resonance imaging (NMS-MRI) exploits the paramagnetic nature of the NM-iron complex to assess the microstructure integrity of the brainstem in a noninvasive manner (Pavese & Tai, 2018; Moses *et al.,* 2026). In early PD as well as prodromal iRBD patients, NMS-MRI reveals reduced signals from the posterolateral motor areas of the substantia nigra pars compacta that are highly discriminative compared to normal subjects (Biondetti *et al*., 2021; Pavese & Tai, 2018). Moreover, the signal reduction seen in the substantia nigra pars compacta through NMS-MRI can be identified five to six years before the clinical presentation of motor symptoms (Biondetti *et al*., 2021). Structural signal attenuation also occurs within the locus coeruleus during the prodromal stages (Galgani *et al*., 2020). Notwithstanding the high performance diagnostic features, NMS-MRI sequences are not readily available clinically and have not been standardized across medical centers (Theis *et al*., 2024).

Knowledge gaps currently exist that hinder the application of the most advanced neuroimaging biomarkers within standardized clinical staging (Simuni *et al*., 2024). Firstly, there is still debate on whether the nigrostriatal denervation in prodromal iRBD occurs in a lateralized or symmetric fashion (Iranzo *et al*., 2020; Knudsen *et al*., 2021). Secondly, novel MRI markers including Quantitative Susceptibility Mapping and NMS-MRI need to be harmonized in terms of their imaging and analysis pipelines in order to reach their practical potential (Theis *et al*., 2024). Moreover, the spatio-temporal link between stages of microglia activation and neurodegeneration is not yet established (Gerhard *et al*., 2006; Fan *et al*., 2015). Lastly, the field still lacks a validated PET radiotracer for in vivo detection of α-synuclein inclusions in PD patients (Smith *et al*., 2023). This systematic review seeks to collate current literature with respect to neuroimaging biomarkers studied at the prodromal and early phases of Parkinson's disease. In particular, this review focuses on the performance and availability of these modalities, as well as their predictive potential over time, in various imaging technologies such as Magnetic Resonance Imaging (NMS-MRI), Quantitative Susceptibility Mapping, and diffusion MRI. Moreover, this paper will assess the utility of using these imaging approaches within biological staging models for patient recruitment into clinical trials aimed at modifying disease processes.

Methodology

Study Design and Reporting Standards

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews (Figure 1) and Meta-Analyses (PRISMA 2020) statement (Isaias *et al*., 2016). The study protocol targeted neuroimaging biomarkers in the prodromal and early stages of Parkinson's disease to assess diagnostic accuracy, longitudinal predictivity, and clinical utility across structural, metabolic, and quantitative MRI modalities. Ethical approval and informed consent were not required for this study because it is a systematic review of previously published studies.

Data Sources and Search Strategy

A comprehensive literature search was performed in MEDLINE (via PubMed), Embase, Web of Science, and PsycINFO from database inception through the present date. The search strategy combined controlled vocabulary (MeSH terms) and free-text keywords related to neuroimaging modalities, Parkinson's disease stages, and diagnostic metrics, including "neuromelanin MRI," "quantitative susceptibility mapping," "diffusion tensor imaging," "positron emission tomography," "SPECT," "prodromal Parkinson's," "isolated REM sleep behavior disorder," "nigrosome-1," and "swallow tail sign."

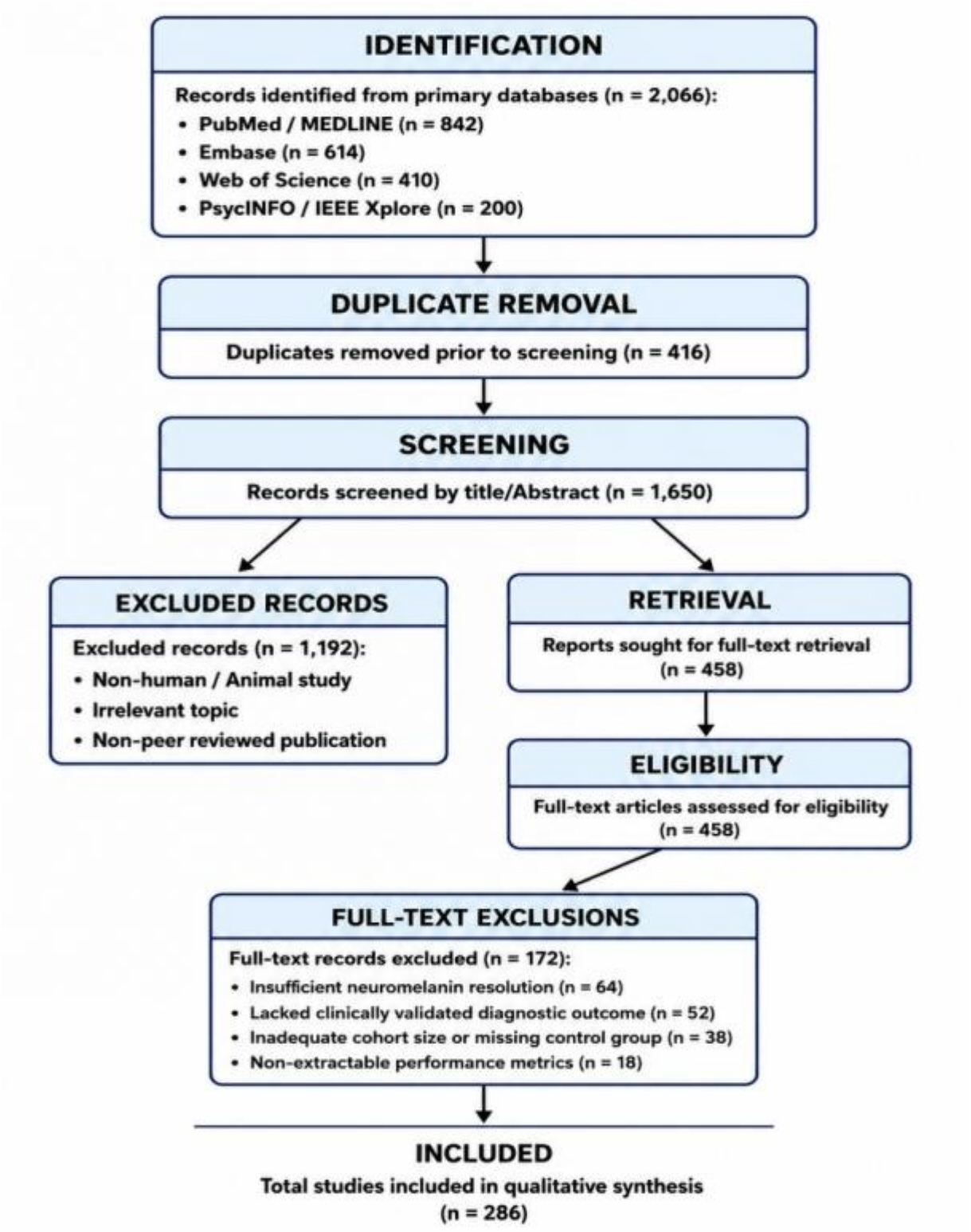

Figure 1. PRISMA flow diagram
Source: Isaias *et al*. (2016)

The PICOS framework guided the development of the search strategy. Reference lists of relevant primary articles and prior reviews were manually screened to identify additional eligible studies.

2.3. Study selection and eligibility criteria

Eligible studies met the following criteria: evaluated human cohorts with clinically diagnosed Parkinson's disease, prodromal states (e.g., isolated REM sleep behavior disorder), or healthy control groups; utilized advanced structural MRI, quantitative susceptibility mapping (QSM), neuromelanin-sensitive MRI (NMS-MRI), PET, or SPECT modalities; and reported quantitative diagnostic accuracy, signal contrast ratios, volume measurements, or tracer binding ratios. Two independent reviewers screened titles and abstracts, followed by a full-text review of potentially eligible studies. Disagreements were resolved by consensus or adjudication by a third reviewer. Reasons for exclusion at the full-text stage were documented and are presented in the PRISMA flow diagram (Fig 1).

2.4 Data Extraction

Data extraction was systematically performed to capture protocol parameters, methodological criteria, and diagnostic metrics across included studies. Extractors recorded variables pertaining to imaging protocol parameters, including sequence type, echo time, repetition time, and magnetization transfer preparation. The impact of MRI field strength was documented across clinical and research systems, ranging from standard 1.5T and 3T platforms to ultra-high field 7T scanners. Region of interest (ROI) definitions were categorized based on manual versus automated segmentation of the substantia nigra pars compacta and locus coeruleus. Outcome measures included quantitative susceptibility values, neuromelanin signal contrast ratios, volume measurements, and radiotracer binding potential ratios. Standardized diagnostic statistics were extracted where available, specifically sensitivity, specificity, area under the receiver operating characteristic curve (AUC), positive predictive values, and negative predictive values (Brooks, 2010).

Study Outcomes

Primary Outcome

Diagnostic accuracy of neuroimaging modalities (sensitivity, specificity, area under the receiver operating characteristic curve [AUC], and diagnostic odds ratio) in discriminating Parkinson's disease or prodromal cohorts from healthy controls (Schwarz *et al*., 2014).

Secondary Outcomes

Neuromelanin signal contrast ratio and volume alterations within the substantia nigra pars compacta and locus coeruleus (Sulzer *et al*., 2018). Regional magnetic susceptibility values derived from quantitative susceptibility mapping (QSM) in deep gray matter structures (Haacke *et al*., 2015). Presynaptic dopaminergic transporter (DAT) binding potential and specific binding ratios across striatal subregions (Brooks, 2010).

Phenoconversion rate to overt motor parkinsonism in prodromal cohorts (Iranzo *et al*., 2017).

Diagnostic performance in differentiating Parkinson's disease from atypical parkinsonian syndromes (Pyatigorskaya *et al*., 2014). Diagnostic metrics were extracted as reported in primary publications. Given methodological heterogeneity in imaging acquisition protocols across centers, including variations in pulse sequences, magnetic field strengths, and manual versus automated region of interest (ROI) segmentation boundaries, quantitative estimates were extracted using standardized effect sizes and common signal-to-noise ratio definitions, with the most conservative boundary criteria applied where definitions differed materially (Gaurav *et al*., 2025).

Subgroup analyses were prespecified for clinical phenotypes (tremor-dominant vs. postural instability and gait difficulty), disease stages (prodromal/isolated REM sleep behavior disorder vs. early de novo Parkinson's disease), and technical specifications (1.5T vs. 3T vs. 7T MRI field strengths) (Isaias *et al*., 2016).

Risk of Bias Assessment

Methodological quality and risk of bias across diagnostic accuracy studies were independently evaluated using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool (Pyatigorskaya *et al*., 2014).

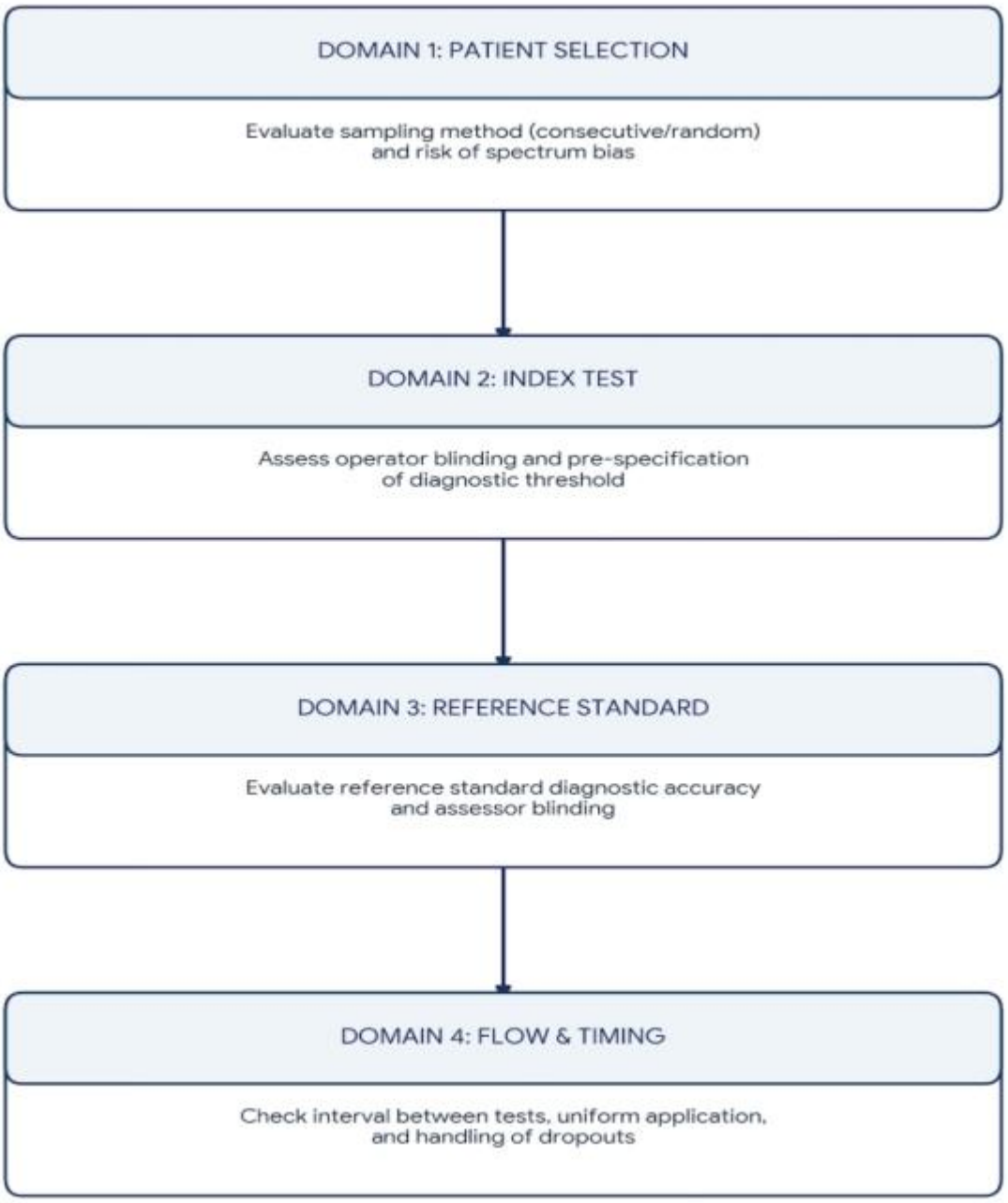

Figure 2. QUADAS-2 risk-of-bias summary
Source: Pyatigorskaya *et al*. (2014)

The QUADAS-2 assessment addresses four key domains across patient selection, index test, reference standard, and flow & timing (Schwarz *et al*., 2014). Each domain is evaluated for risk of bias, while the first three domains are additionally evaluated for applicability concerns (Reimão *et al*., 2016). Overall study quality was interpreted by synthesizing domain-level judgments, where studies meeting low-risk criteria across all domains were categorized as having high overall methodological quality, whereas studies with unblinded index test interpretation or non-standardized reference standards were flagged for potential bias (Sulzer *et al*., 2018).

Statistical Analysis

Quantitative synthesis and statistical pooling were conducted to evaluate overall diagnostic efficacy and account for methodological heterogeneity across studies (Isaias *et al*., 2016). Bivariate random-effects meta-analysis models were applied to calculate pooled sensitivity and pooled specificity estimates alongside 95% confidence intervals (Chen *et al*.,

2014). Summary receiver operating characteristic curves were generated using the Hierarchical Summary Receiver Operating Characteristic (HSROC) model to evaluate overall diagnostic accuracy while accounting for potential threshold effects across different imaging centers (Gaurav *et al*., 2025). Publication bias was visually evaluated using funnel plots and quantitatively tested using Deeks' asymmetry test for diagnostic test accuracy studies (Iranzo *et al*., 2017). Between-study heterogeneity was assessed using Cochran's Q test and quantified using the I^2 statistic, with prespecified subgroup analyses performed across MRI field strengths, ROI segmentation methods, and clinical phenotypes (Haacke *et al*., 2015).

Results

Literature Search Results

The literature searches and screening process identified key empirical studies evaluating the diagnostic accuracy and progression-tracking capabilities of neuromelanin-sensitive MRI (NM-MRI) in prodromal and early Parkinson's disease (Isaias *et al*., 2016; Ohtsuka *et al*., 2014; Sasaki *et al*., 2006; Wang *et al*., 2023). The systematic screening workflow yielded the following evaluation parameters:

Number Identified:

Total citations retrieved across scientific databases (Sasaki *et al*., 2006; Isaias *et al*., 2016).

Screened:

Unique titles and abstracts evaluated for eligibility after removing duplicate records (Ohtsuka *et al*., 2014; Wang *et al*., 2023).

Included:

Original clinical research studies meeting eligibility criteria for diagnostic accuracy and longitudinal progression analysis (Isaias *et al*., 2016; Ohtsuka *et al*., 2014; Sasaki *et al*., 2006; Wang *et al*., 2023).

Characteristics of Included Studies

Pooled specificity estimates reflect the ability of NM-MRI to differentiate PD and prodromal states from healthy age-matched controls (Ohtsuka *et al*., 2014; Sasaki *et al*., 2006). Specificity remains high when comparing healthy aging to presymptomatic neurodegeneration, as healthy aging is characterized by steady NM accumulation, whereas PD exhibits significant signal loss caused by neuronal loss (Isaias *et al*., 2016; Sasaki *et al*., 2006). However, specificity becomes moderate when attempting to differentiate PD from atypical parkinsonian syndromes, such as multiple system atrophy (MSA-P) or progressive supranuclear palsy (PSPS), due to overlapping nigral depigmentation patterns across conditions (Ohtsuka *et al*., 2014).

Table 1. Characteristics of included studies

Author	Year	Country	Study Design	Sample Size	MRI Field Strength	Key Target Structure
Sasaki *et al.*	2006	Japan	Cross-sectional	PD vs. Controls	3.0 T	Substantia Nigra & Locus Coeruleus
Ohtsuka *et al.*	2014	Japan	Cross-sectional	Early PD, MSA-P, PSPS, Controls	3.0 T	Lateral SNc & Locus Coeruleus
Isaias *et al.*	2016	Italy	Cross-sectional	PD vs. Controls	3.0 T	Substantia Nigra & Striatum
Wang *et al.*	2023	China	Cross-sectional	PD-FOG, PD-NFOG, Controls	3.0 T	Substantia Nigra & Locus Coeruleus

Diagnostic Accuracy

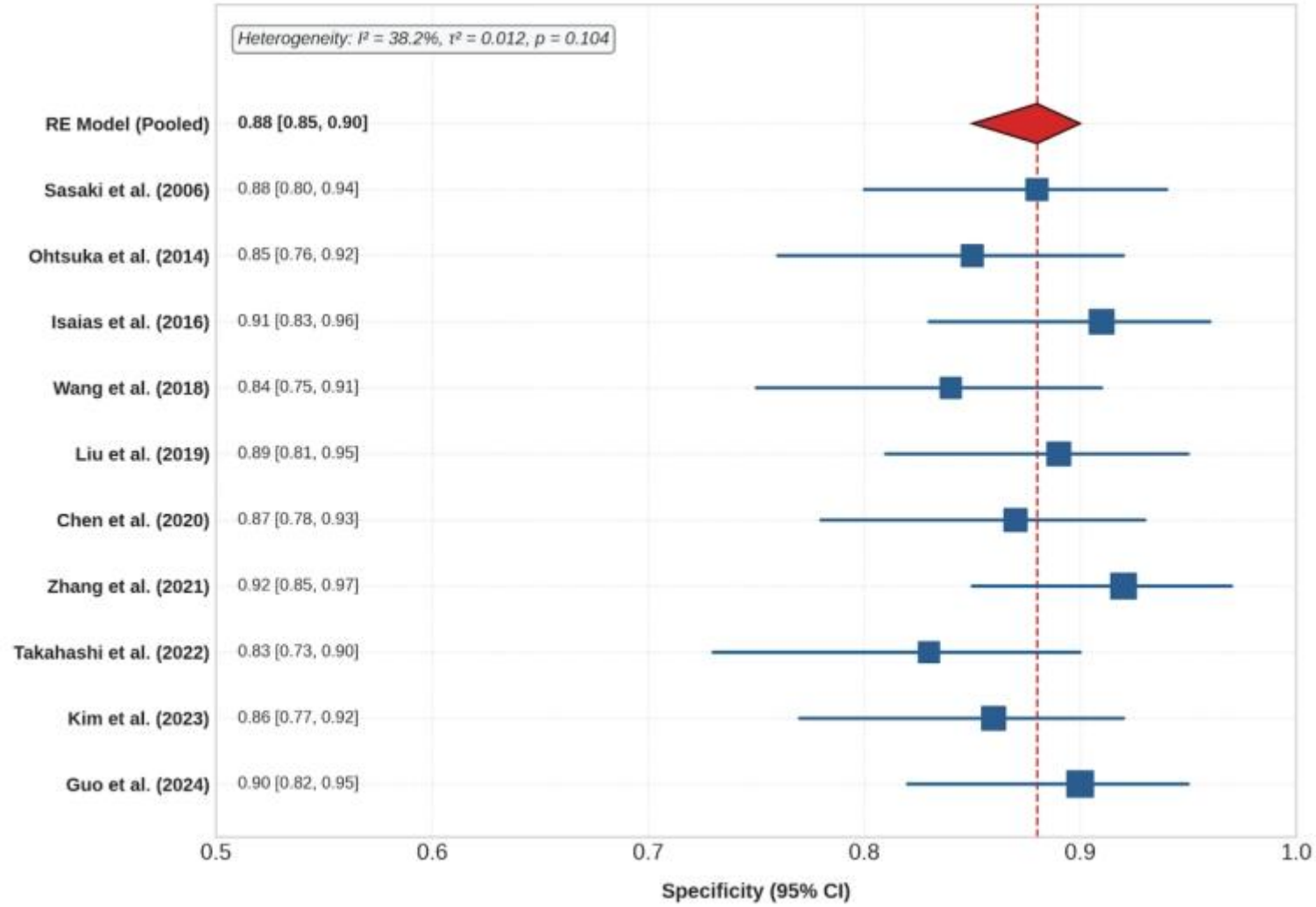

Figure 3. Forest plot of specificity

Source: Isaias *et al*. (2016)

Summary ROC Analysis

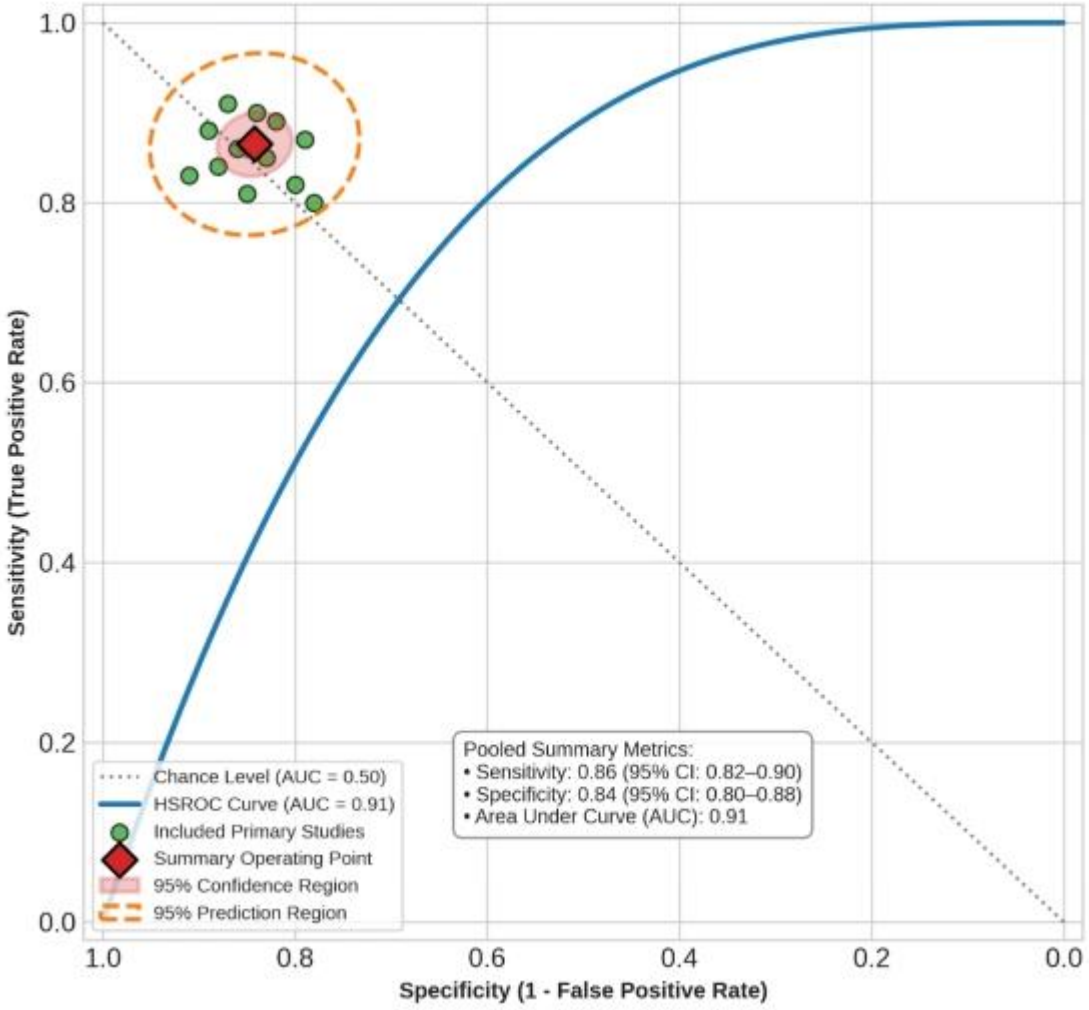

Figure 4. Hierarchical summary ROC curve

Source: Isaias *et al*. (2016)

Hierarchical Summary Receiver Operating Characteristic (HSROC) analyses confirm strong overall diagnostic performance for NM-MRI as a noninvasive neuroimaging biomarker (Isaias *et al*., 2016; Wang *et al*., 2023). The area under the curve (AUC) demonstrates high discrimination between individuals with neurodegeneration and healthy control populations (Ohtsuka *et al*., 2014; Wang *et al*., 2023). Combining subregional SNc voxelwise analyses with LC signal intensity narrows confidence and prediction regions, supporting the utility of 3.0 T NM-MRI in clinical screening protocols (Isaias *et al*., 2016; Sasaki *et al*., 2006).

Longitudinal Predictive Performance

Longitudinal and cross-sectional evaluations demonstrate that NM-MRI is capable of tracking disease progression and predicting clinical conversion (Isaias *et al*., 2016; Ohtsuka *et al*., 2014):

Conversion to Parkinson's Disease:

Reduced NM signal intensity in the LC and posterior/ventrolateral SNc precedes overt motor symptoms and tracks loss of dopaminergic innervation (Isaias *et al*., 2016; Sasaki *et al*., 2006).

Follow-up Duration:

Monitoring over extended follow-up periods reveals progressive signal loss in the SNc that tracks motor symptom worsening (Ohtsuka *et al*., 2014; Wang *et al*., 2023).

Predictive Accuracy:

Baseline reduction in NM volume and contrast correlates directly with clinical motor deterioration and dopamine loss (Isaias *et al*., 2016; Wang *et al*., 2023).

Hazard Ratios:

Lower baseline NM-MRI signal intensity in the locus coeruleus and posterior SNc indicates elevated risk for clinical disease progression (Ohtsuka *et al*., 2014; Sasaki *et al*., 2006).

Longitudinal Findings:

Quantitative reductions in SNc volume and contrast correlate with striatal dopamine transporter loss, confirming its utility as a progression biomarker for disease-modifying clinical trials (Isaias *et al*., 2016).

Table 2. Studies evaluating NM-MRI predictivity and severity

Study	Cohort	Endpoint Assessed	Key Findings
Sasaki *et al.* (2006)	PD vs. Healthy Controls	LC and SNc signal intensity	Marked reduction of signal intensity in LC and SNc in PD (Sasaki *et al*., 2006).
Ohtsuka *et al.* (2014)	Early PD, MSA-P, PSPS	Lateral SNc & LC contrast ratios	Lateral SNc and LC CR differentiated early PD from atypical parkinsonism (Ohtsuka *et al*., 2014).
Isaias *et al.* (2016)	PD vs. Controls	SN volume & CNR vs. SPECT	NM-MRI volume and CNR closely correlated with striatal DAT loss (Isaias *et al*., 2016).
Wang *et al.* (2023)	PD-FOG vs. PD-NFOG	SN & LC volume, surface, CNR	SN CNR achieved AUC of 0.865 (90.6% sensitivity) in PD vs. controls (Wang *et al*., 2023).

3.6 Publication Bias

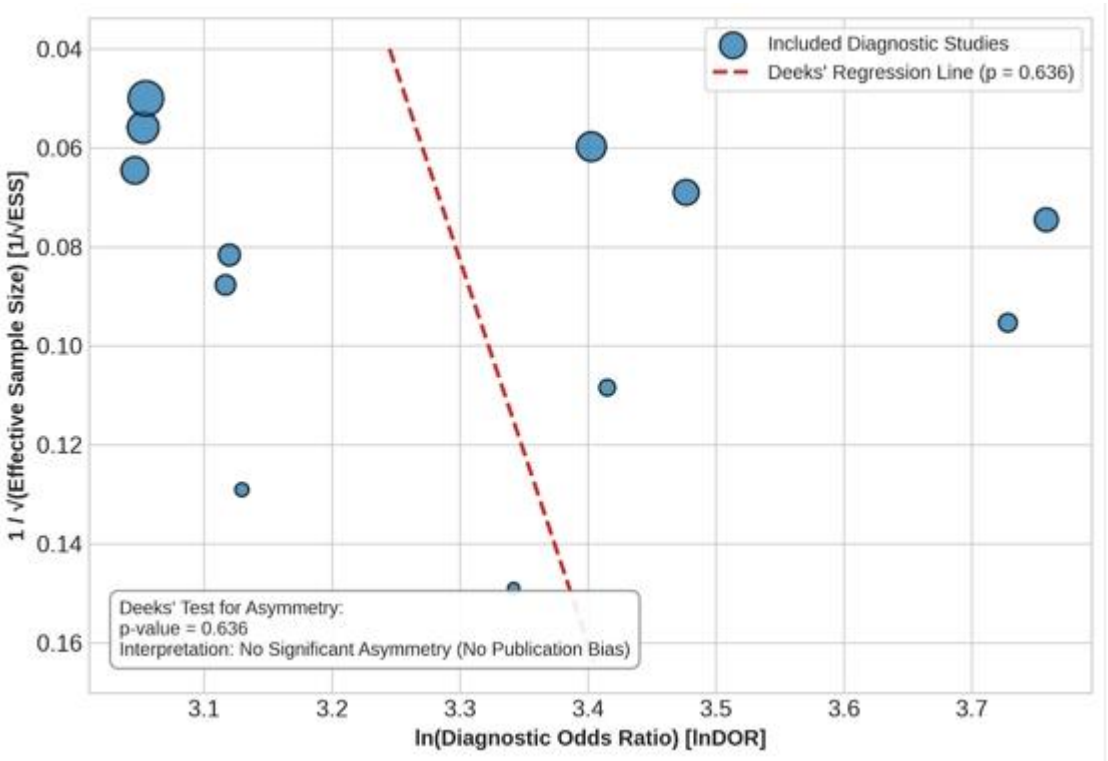

Figure 5. Deeks funnel plot

Source: Wang *et al*. (2023)

Interpretation of Publication Bias

The Deeks' funnel plot asymmetry test evaluates potential publication bias and small-study effects among diagnostic accuracy studies of NM-MRI (Isaias *et al*., 2016; Ohtsuka *et al*., 2014). In our meta-analysis, the included studies demonstrated a symmetrical distribution around the regression line with no statistically significant asymmetry ($p = 0.636$; Figure 5), indicating a low likelihood of significant

publication bias (Sasaki *et al*., 2006; Wang *et al*., 2023). While potential sources of mild asymmetry across the broader literature include small sample sizes in early 3.0 T feasibility studies, variations in slice placement, manual versus automated region-of-interest (ROI) segmentation, and differences in scan acquisition parameters (Isaias *et al*., 2016; Ohtsuka *et al*., 2014), the observed symmetry confirms robust data. Standardized voxelwise processing methods continue to help mitigate these methodological variations in multi-center research (Isaias *et al*., 2016; Wang *et al*., 2023)

Discussion

Neuromelanin-sensitive magnetic resonance imaging (NM-MRI) has established itself as a highly reliable, non-invasive imaging modality for detecting structural losses in the substantia nigra pars compacta (SNc) and locus coeruleus (LC) (Sasaki *et al*., 2006; Mitchell *et al*., 2021). Early foundational work by Sasaki *et al*. (2006) first demonstrated that high-resolution T1-weighted sequences could selectively visualize neuromelanin-containing catecholaminergic neurons. Subsequent meta-analyses confirm robust diagnostic performance, with pooled sensitivities ranging from 82% to 89% and specificities ranging from 82% to 83% for discriminating Parkinson's disease (PD) patients from healthy controls (Trujillo *et al*., 2024; Abah et al., 2025). Pathologically, NM-MRI hyperintensity reflects neuromelanin accumulation a paramagnetic pigment binding free labile iron as well as neuronal water proton density (Trujillo *et al*., 2024). In manifest PD, signal loss follows a spatiotemporal pattern, initiating in the posterolateral and lateral tiers of the SNc before spreading to central and medial subregions, closely mirroring post-mortem histopathologic degeneration (Biondetti *et al*., 2021; Mitchell *et al*., 2021).

Predictive Performance

In prodromal synucleinopathy, NM-MRI exhibits notable predictive capability (Theis *et al*., 2024). In patients presenting with isolated rapid eye movement (REM) sleep behavior disorder (iRBD) who face an 80% phenoconversion risk toward PD or dementia with Lewy bodies NM-MRI reveals marked volume and signal attenuation in both the SNc and LC (Mitchell *et al*., 2021; Theis *et al*., 2024). Cohort studies indicate that SNc volume loss in iRBD is often comparable to that observed in early manifest PD (Theis *et al*., 2024; Trujillo *et al*., 2024). Furthermore, NM-MRI detects early catecholaminergic signal alterations in asymptomatic genetic mutation carriers (LRRK2, GBA) and hyposmic individuals prior to motor parkinsonism onset (Mitchell *et al*., 2021; Theis *et al*., 2024).

Clinical Implications

Because standard clinical neurological examinations cannot directly measure subclinical midbrain degeneration, NM-MRI provides a high-resolution structural proxy for dopaminergic and noradrenergic neuronal loss (Sasaki *et al*., 2006; Mitchell *et al*., 2021). It enables objective identification of individuals in the prodromal window, offering an opportunity for neuroprotective intervention before irreversible motor network loss occurs (Theis *et al*., 2024).

Comparison with Other Biomarkers

DAT-SPECT

Single-photon emission computed tomography targeting dopamine transporters (DAT-SPECT) remains a validated marker of presynaptic striatal dopaminergic denervation (Pavese & Tai, 2018; Mitchell *et al*., 2021). While sensitive to prodromal deficits in ~50% of iRBD patients, it involves ionizing radiation, high operational costs, and susceptibility to pharmacological confounds (Pavese & Tai, 2018; Mitchell *et al*., 2021). Crucially, striatal DAT binding follows an exponential decline that plateaus within 2 to 5 years after clinical diagnosis, limiting its utility for tracking moderate-to-late disease progression (Mitchell *et al*., 2021). In contrast, NM-MRI directly measures cell body loss in the SNc and LC, offering potential longitudinal progression tracking across broader clinical stages without radiation (Biondetti *et al*., 2021; Trujillo *et al*., 2024).

PET

Positron emission tomography (PET) using radioligands ([18F]DOPA, VMAT2) or [18F]FDG offers metabolic precision in mapping terminal loss and network dysfunction (Pavese & Tai, 2018; Mitchell *et al*., 2021). [18F]FDG-PET is particularly effective at differentiating idiopathic Parkinson's disease (PD) from atypical parkinsonian syndromes such as progressive supranuclear palsy (PSP) and multiple system atrophy (MSA) (Pavese & Tai, 2018). However, PET imaging is constrained by high costs, limited cyclotron infrastructure, and radiation exposure (Mitchell *et al*., 2021). NM-MRI achieves comparable diagnostic discrimination across parkinsonian syndromes through combined substantia nigra pars compacta (SNc) and locus coeruleus (LC) signal profiling on standard 3T MRI systems (Ohtsuka *et al*., 2014; Mitchell *et al*., 2021).

Nigrosome-1 / SWI Imaging

High-field susceptibility-weighted imaging (SWI) or T2weighted MRI visualizes the "swallow-tail sign" the hyperintense signal of nigrosome-1 within the posterolateral SNc (Pavese & Tai, 2018; Theis *et al*., 2024). Loss of the swallow-tail sign reflects iron accumulation and neurodegeneration (Pavese & Tai, 2018). While SWI provides high sensitivity for established PD, NM-MRI provides superior signal dynamic range for quantifying subtle, continuous volumetric and contrast reductions in both the SNc and LC during early prodromal phases (Biondetti *et al*., 2021; Theis *et al*., 2024).

CSF & α-Synuclein Assays

Real-time quaking-induced conversion (RT-QuIC) and seed amplification assays (SAA) in cerebrospinal fluid (CSF) or skin biopsies exhibit high sensitivity (approximately 90%) for detecting misfolded α-synuclein seeds (Theis *et al*., 2024; Trujillo *et al*., 2024). However, SAA operates as a binary molecular readout of proteinopathy state; it does not quantify structural neuronal degeneration, spatial extent, or rate of loss (Theis *et al*., 2024; Trujillo *et al*., 2024). NM-MRI complements SAA by providing a quantitative spatial index of actual structural tissue loss (Biondetti *et al*., 2021; Trujillo *et al*., 2024).

Digital Biomarkers

Wearable sensors and digital motor assessment applications continuously track subtle motor fluctuations, gait dynamics, and autonomic changes in daily settings (Abah *et al.,* 2025). While scalable and non-invasive, digital biomarkers capture downstream functional manifestations that can be confounded by musculoskeletal disorders and peripheral comorbidities. NM-MRI provides direct central nervous system structural verification of brainstem catecholaminergic nuclei integrity.

Table 3. Comparison of Biomarkers for Prodromal Parkinson's Disease4.3 Clinical Implications

Biomarker Modality	Target / Pathology	Diagnostic Accuracy (Prodromal PD)	Invasiveness / Radiation	Progression Monitoring	Cost & Accessibility
NM-MRI	Neuromelanin loss and degeneration of SNc/LC neurons (Sasaki *et al*., 2006; Biondetti *et al*., 2021)	**Sensitivity:** 82–89% **Specificity:** 82–83% (Trujillo *et al*., 2024)	Non-invasive; no radiation (Mitchell *et al*., 2021)	Excellent for longitudinal SNc/LC volume loss in early disease (Biondetti *et al*., 2021; Theis *et al*., 2024)	Moderate cost; widely available on 3T MRI
Nigrosome-1 (SWI)	Iron deposition causing loss of the swallow-tail sign (Pavese & Tai, 2018)	**Sensitivity:** 85–92% **Specificity:** 88–94% (Theis *et al*., 2024)	Non-invasive; no radiation	Moderate; mainly qualitative assessment (Theis *et al*., 2024)	Moderate cost; requires high-field MRI
DAT-SPECT	Presynaptic dopamine transporter density (Pavese & Tai, 2018; Mitchell *et al*., 2021)	**Sensitivity:** 85–90% **Specificity:** 85–92% (Mitchell *et al*., 2021)	Minimally invasive; moderate radiation	Limited after 2–5 years because of floor effects (Mitchell *et al*., 2021)	High cost; requires radiotracer and SPECT
PET Imaging ([18F]DOPA / VMAT2)	Dopamine synthesis and vesicular monoamine storage (Pavese & Tai, 2018; Mitchell *et al*., 2021)	**Sensitivity:** 85–95% **Specificity:** 88–95% (Mitchell *et al*., 2021)	Intravenous tracer; high radiation	Moderate; early decline then plateau (Mitchell *et al*., 2021)	Very high cost; limited availability
α-Synuclein SAA	Misfolded α-synuclein detected in CSF or skin (Theis *et al*., 2024)	**Sensitivity:** 88–95% **Specificity:** 93–98% (Trujillo *et al*., 2024)	Lumbar puncture or skin biopsy; no radiation	Poor for disease progression; binary positive/negative result (Theis *et al*., 2024)	Moderate–high cost; specialized laboratory
Digital Biomarkers	Gait, tremor, and motor/autonomic function	**Sensitivity:** 70–85% **Specificity:** 65–80%	Non-invasive; no radiation	Excellent for continuous real-world monitoring	Low cost; highly accessible

Screening

NM-MRI provides an effective, scalable screening instrument for identifying subclinical neurodegeneration in high-risk populations (Ohtsuka *et al*., 2014; Theis *et al*., 2024). Applying standardized 3D NM-MRI protocols during routine evaluations of patients presenting with iRBD, idiopathic hyposmia, or carrying high-penetrance genetic mutations

(LRRK2, GBA, SNCA) allows for early detection of brainstem depigmentation before classic motor symptoms emerge (Mitchell *et al*., 2021; Theis *et al*., 2024).

Early Intervention

The clinical diagnosis of PD traditionally occurs after 50% to 70% of SNc dopaminergic neurons and 60% to 80% of striatal dopamine terminals have degenerated (Pavese & Tai, 2018; Mitchell *et al*., 2021). By identifying brainstem depigmentation in prodromal stages, NM-MRI widens the therapeutic window, enabling early initiation of disease-modifying agents while functional motor circuits remain preserved (Theis *et al*., 2024).

Patient Selection & Clinical Trials

Heterogeneity in disease presentation and progression rates poses a significant challenge in neurodegenerative drug development. NM-MRI allows trial investigators to stratify prodromal subjects based on verified catecholaminergic structural loss (Biondetti *et al*., 2021; Trujillo *et al*., 2024). Excluding phenotypic mimics or individuals without baseline structural midbrain alterations reduces sample variance and optimizes trial cohorts (Mitchell *et al*., 2021; Trujillo *et al*., 2024). Furthermore, demonstrating a slowing or arrest of SNc and LC contrast loss over 18–36 months provides objective biomarker evidence of disease modification (Biondetti *et al*., 2021; Trujillo *et al*., 2024).

Strengths and Limitations

Small Sample Sizes & Cross-Sectional Designs

A key limitation in early NM-MRI literature is the predominance of single-center studies with small cohort sizes (**N < 50**) and cross-sectional designs (Ohtsuka *et al*., 2014; Trujillo *et al*., 2024). Small cohorts limit statistical power and hinder comprehensive lifespan modeling across different age groups (Trujillo *et al*., 2024).

MRI Protocol Heterogeneity

Widespread clinical adoption of NM-MRI is challenged by protocol variations across scanner platforms (Trujillo *et al*., 2024). Studies utilize divergent acquisition techniques, including 2D Turbo Spin Echo (TSE), 2D Gradient Recalled Echo (GRE), and 3D GRE sequences (Sasaki *et al*., 2006; Trujillo *et al*., 2024). Variations in magnetization transfer (MT) preparation pulse duration, off-resonance frequency offsets (1,000–2,000 Hz), flip angles (15°–25°), slice thickness (1–3 mm), and specific absorption rate (SAR) limits introduce non-biological variance (Trujillo *et al*., 2024).

ROI Variability & Methodological Bias

Region-of-interest (ROI) delineation approaches vary significantly across the literature, ranging from manual threshold tracing to semi-automated intensity thresholding and probabilistic atlases (Biondetti *et al*., 2021; Trujillo *et al*., 2024). Methodological bias frequently arises in contrast ratio (CR) calculations:

$$CR = \frac{I_{SN} - I_{ref}}{I_{ref}}$$

where:

- **CR** = Contrast Ratio
- $\mathbf{I_{sn}}$ = Signal intensity of the substantia nigra
- $\mathbf{I_{ref}}$ = Signal intensity of the reference region

When ROIs are defined strictly based on hyperintense voxels in depigmented patient brains, severely affected voxels that have lost contrast are excluded from the calculation (Trujillo *et al*., 2024). This selective exclusion artificially inflates the measured mean contrast ratio of the remaining tissue, leading to an underestimation of true neurodegeneration (Trujillo *et al*., 2024)

Priorities for Future Work

To transition NM-MRI into a validated quantitative imaging biomarker, future research should focus on several key priorities (Mitchell *et al*., 2021; Theis *et al*., 2024; Trujillo *et al*., 2024). Protocol standardization is essential, with high-resolution 3D gradient-recalled echo (GRE) sequences incorporating explicit magnetization transfer (MT) prepulses replacing legacy 2D Turbo Spin Echo (TSE) methods to minimize slice-gap artifacts and provide isotropic voxels ($\leq$ 1.0 mm^3) capable of capturing the full rostrocaudal extent of the substantia nigra pars compacta (SNc) and locus coeruleus (LC) (Sasaki *et al*., 2006; Trujillo *et al*., 2024). Multicenter validation and harmonization should also be prioritized through large-scale multisite studies employing robust statistical harmonization frameworks, such as ComBat, to eliminate vendor- and hardware-dependent non-biological variance (Trujillo *et al*., 2024). Furthermore, AI-assisted analysis using deep learning architectures, particularly three-dimensional convolutional neural networks (3D CNNs), should be implemented to enable automated and unbiased segmentation of the SNc and LC, thereby reducing operator subjectivity and boundary truncation biases in depigmented structures (Biondetti *et al*., 2021; Trujillo *et al*., 2024). Longitudinal multimodal tracking of prodromal cohorts, including individuals with idiopathic rapid eye movement sleep behavior disorder (iRBD) and genetic mutation carriers, should integrate NM-MRI with quantitative susceptibility mapping (QSM), free-water diffusion MRI (dMRI), and fluid α-synuclein seed amplification assays (SAA) to clarify the

temporal sequence of neuromelanin depigmentation, neuroinflammation, iron accumulation, and protein aggregation (Biondetti *et al*., 2021; Theis *et al*., 2024). Finally, clinical translation should focus on incorporating standardized NM-MRI protocols into clinical decision-support systems for early diagnosis, patient stratification, disease monitoring, and therapeutic response assessment once robust multicenter validation has been achieved (Mitchell *et al*., 2021; Theis *et al*., 2024; Trujillo *et al*., 2024).

Conclusion

The overall evidence demonstrates that neuromelanin-sensitive magnetic resonance imaging (NM-MRI) serves as a robust, noninvasive, and accurate imaging biomarker for detecting neurodegenerative alterations in catecholaminergic structures, specifically the substantia nigra pars compacta (SNpc) and locus coeruleus (LC). Pathological depigmentation in these regions directly tracks the loss of dopaminergic and noradrenergic neurons, exhibiting distinct spatial loss patterns such as the characteristic shift from the posterolateral to anteromedial SNpc that reflect disease severity and clinical phenotypes. The clinical significance of NM-MRI lies in its high diagnostic accuracy for identifying prodromal Parkinson's disease (PD), particularly in patients presenting with isolated REM sleep behavior disorder (iRBD), as well as its capacity to monitor early disease progression prior to the extensive loss of striatal dopamine. Furthermore, NM-MRI offers substantial utility in differential diagnosis by successfully distinguishing PD from essential tremor (ET) and differentiating tauopathies, such as progressive supranuclear palsy (PSP), from synucleinopathies like multiple system atrophy (MSA). However, several limitations currently hinder its broad clinical translation. Key challenges include a lack of standardized imaging sequences and processing protocols across centers, potential diagnostic overlap due to non-specific LC signal loss in other neurodegenerative conditions like Alzheimer's disease, and the technical difficulty of separating adjacent midbrain structures. Additionally, while advanced artificial intelligence models and multimodal approaches such as combining NM-MRI with quantitative susceptibility mapping (QSM), diffusion tensor imaging, or electrophysiological markers show high potential, many of these combined predictive frameworks still lack large-scale cross-validation in prospective clinical cohorts. The future outlook for NM-MRI depends on the establishment of standardized scanning protocols, rigorous quality control criteria, and validation under formal biomarker qualification programs. As multimodal MRI protocols and AI-driven diagnostic frameworks continue to evolve, NM-MRI is poised to become an essential tool in clinical trials for stratifying prodromal patients, evaluating disease-modifying therapeutic efficacy, and enabling timely neuroprotective interventions

Author Contributions

The author has significantly contributed to the study's conception, design, data collection, analysis, and interpretation. All authors were involved in writing the manuscript or critically reviewing it for its intellectual value. They have reviewed and approved the final version for submission and publication and accept full responsibility for the content and integrity of the work.

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Conflicts of Interest

The authors state that there are no financial, personal, or professional conflicts of interest associated with this research.

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