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The Brain Under the Influence of Non-motor Signs in Parkinson Disease: Neurological, Pharmacological and Physiotherapy Related Correlations

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Abstract: *Parkinson's disease (PD), traditionally considered a motor disorder, also manifests by a wide range of non-motor symptoms (NMS) such as cognitive, mood, autonomic, gastrointestinal, and sensory disturbances, significantly impacting quality of life and complicating diagnosis and management, both in terms of pharmacology and physiotherapy. Degeneration in noradrenergic and serotonergic systems may be key contributors to NMS. These symptoms can appear early, may sometimes precede motor signs, and require individualized assessment and care. Investigations such as MRI of the locus coeruleus, EEG, retinal imaging, and blood-based panels are under investigation to better characterize NMS and disease heterogeneity. Along this interest, heart rate variability (HRV) is a non-invasive marker of autonomic dysfunction in PD, intensively studied nowadays, since it correlates to central and peripheral nervous system changes, also linking autonomic impairment to cognitive decline and cerebrovascular injury. However, HRV interpretation is challenged by methodological variability, medication effects, as well as patient heterogeneity. Pharmacological management of NMS is further complicated by drug interactions, side effects, and multisystem involvement, while physiotherapy must often adapt to challenges coming from autonomic instability, medication timing, and exercise modality. This narrative review aims to provide insight among the management of non-motor manifestations in PD, with emphasis on HRV's influence.*

Keywords: *Parkinson disease; heart rate variability; physiotherapy; brain modifications.*

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1. Introduction

Parkinson's disease is a brain disorder extending beyond motor circuits, and is classically linked to degeneration of dopamine-producing neurons in the *substantia nigra*. This results in a dysfunction within basal ganglia circuitry, producing hallmark motor features, such as: bradykinesia, rigidity and tremor (Carroll, Deutschmann, & Andrews, 2020). Postural instability is a manifestation that links the motor patterns to non-motor signs (NMS), affecting mood, cognition, autonomic function, sleep, sensory function, gastrointestinal function, and pain, often contributing substantially to the overall disease burden (Liu et al., 2015; Javidnia et al., 2020; Peng et al., 2024; Carroll, Deutschmann, & Andrews, 2020).

Contemporary biomarker-oriented work addresses variable motor and non-motor profiles, and suggests that misdiagnosis can occur, motivating the use of non-canonical clinical features alongside biological measures to improve diagnostic discrimination, while autonomic dysfunction is also associated with events that impact the brain, relevant especially by cognition assessment, based on pathophysiological aspects of white matter injury (Peng et al., 2024; Ke et al., 2017; Bódi et al., 2020).

This narrative review evaluates emerging data on this topic, nevertheless, robust validation studies (especially large-scale, longitudinal clinical trials) are still lacking. The long-term reliability of different interventions on autonomic recovery outcomes are not yet well-established. There is still insufficient data on how exactly treatment strategies can be tailored to individual patient profiles, accounting for the broad heterogeneity of NMS in PD, as well as comorbidities. The purpose is to critically synthesize recent advancements in correlating pharmacological and physiotherapy interventions, related to heart rate variability (HRV), within PD rehabilitation and management, for better non-motor amelioration over time.

This article highlights emerging mechanistic frameworks, discusses the role of HRV as a marker of autonomic dysfunction, and examines the therapeutic challenges and opportunities posed by NMS. Through this integrative perspective, we aim to underscore the necessity of broadening the clinical and research focus in PD as a full spectrum of disease manifestations, and to inform better individualized future care strategies.

2. Material and Methods

To ensure a comprehensive and transparent synthesis of the literature regarding non-motor signs in Parkinson's Disease, including neurological, pharmacological, and rehabilitation-related aspects, a structured search strategy was adopted, aligned with the PRISMA guidelines:

A systematic search was conducted across the following electronic databases: PubMed/MEDLINE, Web of Science, Scopus and Cochrane Library.

Search terms were developed using combinations of keywords: "Parkinson's disease" and "non-motor symptoms" or "nonmotor signs" and "autonomic dysfunction", "heart rate variability" or "HRV", "cognition", "neuropsychiatric", "gastrointestinal" OR "sleep disturbance"; search was also conducted by the terms: "biomarkers", "imaging", "pharmacology" or "medication", "therapy" or "treatment", "physiotherapy" or "rehabilitation", "exercise" and "biofeedback". Boolean operators ("and", "or") were used to combine terms appropriately.

As eligibility criteria, for inclusion, peer-reviewed original research articles, systematic reviews, and meta-analyses published in English were considered. Also, studies involving adult patients with Parkinson's Disease, studies addressing non-motor symptoms, relevant biomarkers, pharmacological interventions, or physiotherapy/rehabilitation approaches, were all taken into consideration. Exclusion applied to case reports with fewer than three patients, non-English publications, conference papers (unless directly relevant to mechanistic understanding), and studies not focused on non-motor aspects.

After removing duplicates, two independent reviewers screened titles and abstracts for relevance. Full texts of potentially eligible articles were then assessed for inclusion according to the criteria above. Discrepancies were resolved by consensus. Reference lists of included studies and

relevant reviews were also manually searched to identify additional literature.

Data on study design, population, non-motor symptom domains, biomarkers, interventions, and key findings were extracted. Evidence was synthesized narratively, structured by theme (neurologic, pharmacologic, and physiotherapeutic correlations). Figure 1 summarises the number of records identified, screened, included, and excluded, along with reasons for exclusion.

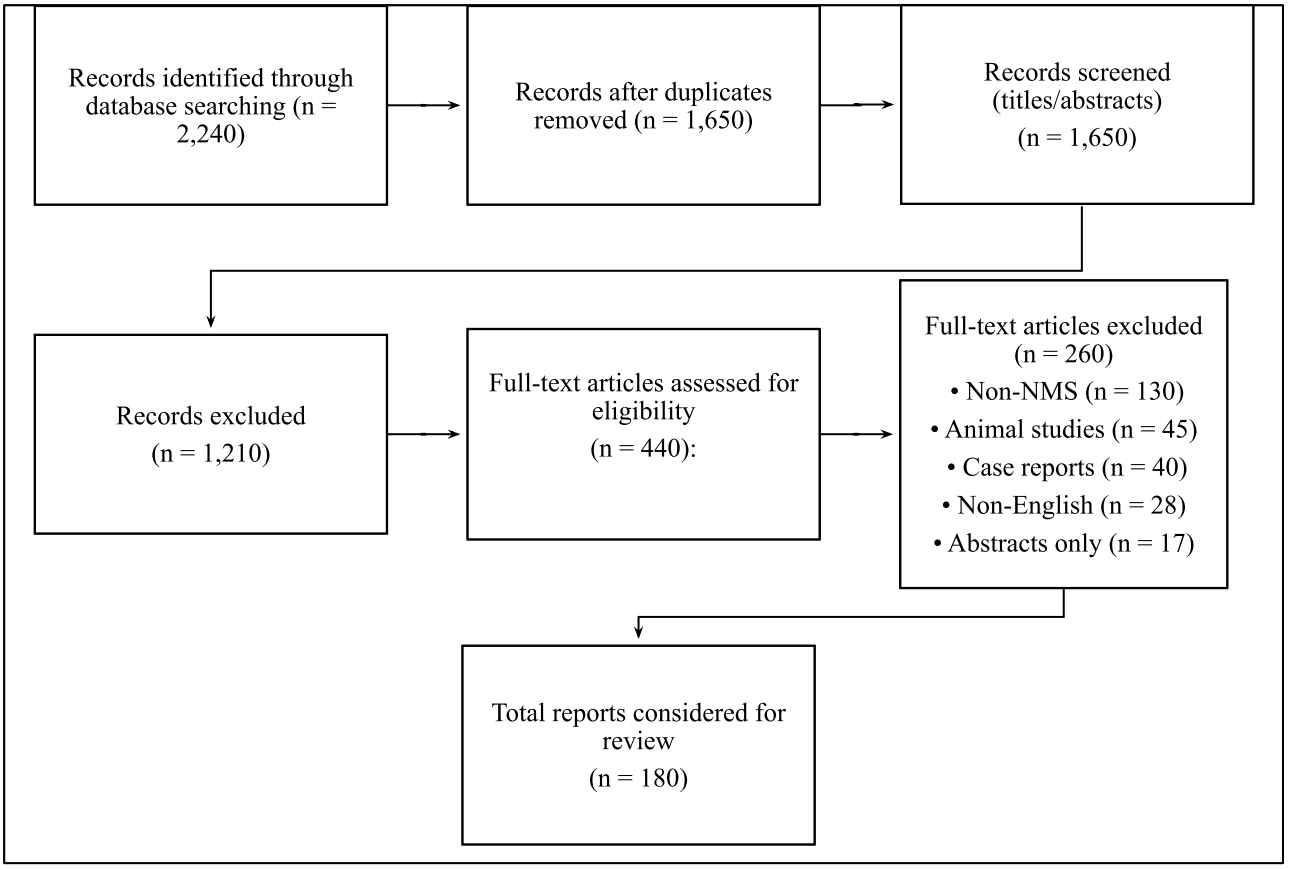

Figure 1. Flowchart of the literature search and selection process

3. Brain Substrates Implicated in Non-motor Signs

3.1. Noradrenergic locus coeruleus degeneration and serotonergic involvement in non-motor dysfunction

Recent studies highlight that degeneration of noradrenergic neurons in the locus coeruleus, visible using specialized MRI, is closely linked to non-motor symptoms (NMS) in Parkinson's disease, supporting the role of non-dopaminergic brainstem systems alongside classic dopamine-related pathways. Preclinical models further suggest that disturbances in neurotransmitters like serotonin also contribute to NMS, particularly mood and anxiety symptoms, indicating that multiple systems beyond dopamine are involved (Madelung et al., 2022; Carroll, Deutschmann, & Andrews, 2020).

Preclinical modelling further supports multi-neurotransmitter contributions to NMS. In MPTP-induced PD mouse models, anxious-like behavioural changes are investigated in relation to impairment of the 5-hydroxytryptamine (serotonin) system, linking affective symptoms to non-dopaminergic neurotransmission disturbances in parkinsonian states (Xia et al., 2018). While such animal findings cannot be directly equated to human PD phenomenology, they reinforce

mechanistic plausibility that anxiety and related NMS may be mediated by neurotransmitter systems beyond dopamine (Xia et al., 2018; Madelung et al., 2022).

3.2. Non-motor signs in PD: domains, early presentation, and individual differences

Cross-sectional analysis of newly diagnosed, untreated PD within the Parkinson's Progression Markers Initiative (PPMI) demonstrates that NMS can be quantified using validated instruments across sleep, olfactory, neurobehavioural, autonomic, and neuropsychological domains. The same study's design, contrasting early PD vs controls, supports the view that NMS may be present very early in the disease course and can contribute to differentiating PD from healthy aging when systematically assessed (Liu et al., 2015).

Consistent with early NMS burden, PPMI-based assessment of pharmacotherapy use for NMS shows that symptomatic treatment for common NMS is frequent among newly diagnosed participants, and that treatment for some NMS (notably depression) can antedate the formal PD diagnosis, implying that NMS may appear and be treated before motor diagnosis in a substantial subset (Javidnia et al., 2020).

Within early PD patients, potential sex differences in NMS have been specifically investigated in a large PPMI cohort, indicating that NMS heterogeneity may be partly structured by sex-related factors (biological and/or psychosocial) (Liu et al., 2015). This heterogeneity aligns with broader biomarker work emphasising clinically heterogeneous PD phenotypes incorporating both motor and non-motor variability (Peng et al., 2024).

Nonetheless, beyond mood and cognition, other NMS domains can also be clinically salient. Pain in the early stages of PD has been studied in relation to diagnostic timing, indicating that pain is not merely a late-stage complication but a feature worth considering during early disease evaluation (Samancı et al., 2022). Gastrointestinal dysfunction is also highlighted as a distressing NMS domain in PD, motivating pilot testing of targeted symptomatic therapies for anorexia/dyspepsia-related complaints in PD cohorts (Yakabi et al., 2017). Together, these findings support that NMS manifests by diverse peripheral–central interactions and can shape help-seeking, diagnosis, and treatment patterns (Yakabi et al., 2017; Samancı et al., 2022; Javidnia et al., 2020).

3.3. Neurophysiologic, imaging, and biomarkers linked to non-motor signs

LC neuromelanin-sensitive MRI is suggested as a candidate marker for non-motor dysfunction investigations as MRI measurements of LC integrity provides a brainstem-focused candidate biomarker and explicitly examines the relationship between LC structural measures and non-motor dysfunction in PD. This is important because it offers a biologically grounded imaging correlate for NMS, potentially linking symptoms to degeneration in the noradrenergic arousal/stress and cognitive–affective modulation system (Madelung et al., 2022).

Electrophysiological approaches have also been explored as surrogate markers for cognitive-related NMS. P300 event-related potentials (ERPs) have been evaluated in PD patients with psychosis, with prolonged latency and decreased amplitude discussed as potential neurophysiological biomarkers of deeper neurocognitive deficits in PD-associated psychosis phenotypes (Gupta et al., 2025). Separately, resting-state EEG alpha asymmetry has been analysed as a potential marker of clinical features in PD, with cross-sectional comparisons to controls and regression analyses linking oscillatory asymmetry indices to clinical characteristics (Rocha et al., 2025). Taken together, these EEG/ERP studies support the feasibility of relatively accessible neurophysiological metrics that may index cognitive/neuropsychiatric dimensions of PD, while remaining subject to typical cross-sectional limitations and the need for replication across cohorts and disease stages (Gupta et al., 2025; Rocha et al., 2025).

Imaging techniques are also related to specific CT-based particularities. A meta-analysis of spectral-domain optical coherence tomography (SD-OCT) studies evaluates retinal layer alterations in PD, supporting that PD-related neurodegeneration can be detectable in the visual system and that retinal structure is an active area of investigation as a non-brain but CNS-related marker (Chrysou,

Jansonius, & van Laar, 2019). Because retinal measures may relate to non-motor visual complaints and broader neurodegenerative processes, they contribute to a multisystem view of PD biomarkers beyond motor circuits (Chrysou, Jansonius, & van Laar, 2019; Peng et al., 2024).

In addition, blood-based biomarker panels incorporate non-motor/non-canonical features. Prospective plasma biomarker research identifies and validates N-acetylputrescine in combination with non-canonical clinical features as a PD biomarker panel, explicitly motivated by PD heterogeneity and the presence of variable motor and non-motor symptoms along with misdiagnosis risk. This approach illustrates another integrative diagnostic strategy: combining fluid biomarkers with clinical features not limited to classic motor signs to improve discrimination between PD and non-diseased controls (Peng et al., 2024). Importantly, such panels require careful external validation and attention to heterogeneity in symptom expression (including NMS) when translating to clinical practice (Peng et al., 2024; Liu et al., 2015).

4. Consequences of non-motor symptoms: quality of life and therapeutic implications

NMS in Parkinson's disease, including mood, cognitive, and autonomic issues, have a significant impact on patients' quality of life (QoL), often more so than motor symptoms alone (Limongi, 2017; Liu et al., 2015; Javidnia et al., 2020). It is known that these symptoms not only affect daily functioning but also contribute to caregiver burden, highlighting the importance of assessing and managing NMS to improve overall well-being (Limongi, 2017; Minibajeva et al., 2023; Kalampokini et al., 2022).

These findings can be extended in understanding employment and stigma as non-motor adjacent consequences. Qualitative investigation of employment experiences in working-age adults with PD identifies disability stigma as shaping employment options, illustrating that the impact of PD extends beyond neurologic impairment into social participation and identity (domains plausibly compounded by non-motor features such as fatigue, cognitive change, mood symptoms, and sleep disturbance) (Carolan, 2024; Liu et al., 2015; Minibajeva et al., 2023). While stigma is not itself a neurologic “sign,” it represents a downstream consequence of the overall symptom complex, including NMS, that affects functional outcomes and leads to the necessity of individualized therapeutic implications (Carolan, 2024; Limongi, 2017).

Among de novo PPMI participants, medication use for NMS is common, with frequent treatment reported for depression, constipation, and anxiety; importantly, some NMS treatments may begin before PD diagnosis, suggesting the need to often manage NMS in parallel with or preceding classic motor recognition (Javidnia et al., 2020). This underscores the clinical reality that NMS management is not an optional “later-stage” add-on but part of early PD care pathways (Javidnia et al., 2020; Liu et al., 2015).

A systematic review synthesizes evidence that cognitive impairments are highly prevalent in PD and substantially affect QoL, and evaluates exercise as a possible treatment (Murray et al., 2014). Complementing this, a randomized controlled trial compares different exercise modalities (functional mobility, multimodal, and cognitive exercise) and intervention durations (4 versus 8 months) on psychological and cognitive features in PD, reflecting the importance of intervention type and dose when targeting non-motor outcomes (Gobbi et al., 2021). Collectively, these studies support exercise as a structured non-pharmacologic strategy with measurable cognitive/psychological endpoints, while also indicating heterogeneity in protocols and outcomes that complicates uniform prescription (Gobbi et al., 2021; Murray et al., 2014).

A phase II placebo-controlled randomised withdrawal trial assesses nabilone (a synthetic THC analogue) for disturbing NMS in PD using MDS-UPDRS-I thresholds, explicitly positioning NMS as a treatable target in controlled trial designs (Peball et al., 2020). Separately, a post hoc analysis explores what effects exenatide might have on NMS in PD, presenting exploratory findings intended to inform larger confirmatory trials (Athauda et al., 2018). These studies highlight active therapeutic exploration for NMS but also differ in design strength and inferential scope (e.g., post

hoc vs randomized withdrawal), requiring cautious interpretation and replication (Athauda et al., 2018; Peball et al., 2020).

Preclinical cannabinoid work also indicates that cannabidiol (CBD) can improve emotional and cognitive symptoms, attenuate neuroinflammation, and influence hippocampal newborn neuronal maturation in a rat model of parkinsonism with 6-OHDA lesions, supporting mechanistic plausibility for neuropsychiatric NMS modulation, albeit with translational constraints typical of animal models (Mattos et al., 2024; Xia et al., 2018).

An open-label randomised-sequence pilot study evaluates the efficacy and safety profile of the traditional Japanese medicine rikkunshito for gastrointestinal symptoms (including anorexia and dyspepsia) in PD, reflecting the clinical recognition that GI dysfunction is a frequent and distressing NMS domain and may warrant targeted symptomatic strategies (Yakabi et al., 2017; Javidnia et al., 2020). Along this idea, DBS could be established as a treatment for movement disorders including PD, but ethical analysis emphasises informed consent decision-making, particularly because disorders treated with DBS can include alterations in memory, attention, and executive functioning that may affect decision-making capacity (Mandarelli et al., 2018). This highlights one more the link between brain and non-motor signs, as cognitive NMS are not only symptoms to treat but also factors shaping patients' ability to engage in complex risk–benefit decisions about invasive neurosurgical therapies (Mandarelli et al., 2018; Murray et al., 2014; Gupta et al., 2025).

Key themes and evidence in NMS in PD can be synthesised as in Table 1. A key nuance across this evidence base is that several NMS-targeted interventions remain exploratory (e.g., post hoc exenatide analyses, pilot GI trials, animal CBD studies), and multiple biomarker approaches are promising but require robust validation across diverse PD phenotypes and stages (Athauda et al., 2018; Yakabi et al., 2017; Mattos et al., 2024; Peng et al., 2024; Rocha et al., 2025; Madelung et al., 2022).

Table 1. Integrated synthesis and remaining challenges

Theme	Key Points	Supporting Evidence/References
Early and Diverse NMS	NMS emerge early in PD, vary across individuals (including sex-related differences), and shape quality of life, caregiver burden, and social participation.	Liu et al., 2015; Limongi, 2017; Minibajeva et al., 2023; Javidnia et al., 2020; Carolan, 2024; Kalampokini et al., 2022
Physiopathologic Frameworks	Brainstem noradrenergic degeneration (LC) and non-dopaminergic neurotransmitter involvement (e.g., serotonergic changes) explain NMS beyond classic nigrostriatal pathology.	Madelung et al., 2022; Xia et al., 2018; Carroll, Deutschmann, & Andrews, 2020
Biomarker Development	Candidate biomarkers for NMS: LC neuromelanin MRI, retinal OCT, EEG/ERP (cognitive/neuropsychiatric features), plasma biomarker panels combining biological and non-canonical clinical features.	Madelung et al., 2022; Chrysou, Jansonius, & van Laar, 2019; Gupta et al., 2025; Rocha et al., 2025; Peng et al., 2024
Therapeutic Approaches	Broad, symptom-domain approach: early pharmacotherapy, structured exercise for cognition/psychology, emerging pharmacological trials targeting NMS—with varying levels of evidence maturity.	Javidnia et al., 2020; Murray et al., 2014; Gobbi et al., 2021; Peball et al., 2020; Yakabi et al., 2017; Athauda et al., 2018; Mattos et al., 2024

Abbreviations: NMS = Non-motor symptoms; LC = Locus coeruleus; OCT = Optical coherence tomography; MRI = Magnetic resonance imaging; EEG/ERP = Electroencephalography/Event-related potentials; PD = Parkinson's disease.

Collectively, these studies support a modern clinical and research framing: understanding PD requires mapping brain-wide and system-wide degeneration to non-motor signs and integrating those signs into diagnosis, monitoring, and individualized care (Madelung et al., 2022; Peng et al., 2024; Liu et al., 2015; Javidnia et al., 2020).

5. HRV Modifications in Parkinson's Disease

5.1. The Link Between HRV Changes and Brain Dysfunction

HRV indexes beat-to-beat variability in cardiac intervals and is widely used as a noninvasive readout of autonomic (sympathetic–parasympathetic) modulation of the heart. In PD, autonomic dysfunction is a frequent non-motor feature and commonly includes cardiovascular dysautonomia (notably orthostatic hypotension and impaired reflex control), for which HRV abnormalities are often reported as an objective physiological correlate (Ke et al., 2017; Bódi et al., 2020). Empirically, PD cohorts show altered HRV metrics compared with controls in studies designed to detect autonomic involvement (e.g., Holter-derived HRV measures and related autonomic tests), supporting the view that "HRV modifications" in PD typically reflect disrupted neurocardiac autonomic regulation rather than a purely cardiac disorder (Bódi et al., 2020; Metzler et al., 2017). However, the HRV literature in early PD is not fully consistent across conventional time- and frequency-domain metrics, motivating newer analytical approaches and underscoring heterogeneity by disease stage, protocol, and possibly medication status (Bódi et al., 2020, Iniguez et al., 2022).

Regarding the brain implications, PD-related HRV abnormalities are not only markers of peripheral autonomic impairment; they are increasingly interpreted as signatures of dysfunction within brain networks that regulate autonomic outflow (often termed the central autonomic network, CAN) and/or of impaired coupling between brain activity and cardiac dynamics (Basri & Turki, 2025; Dadar et al., 2020). This framing is consistent with neuropathology reviews emphasising that autonomic dysfunction in synucleinopathies reflects variable involvement of both central and peripheral autonomic structures, rather than a single lesion site (Dadar et al., 2020; Coon, Cutsforth-Gregory, & Benarroch, 2018).

Neuropathological syntheses argue that PD pathology can involve autonomic-related structures at multiple levels of the neuraxis (brainstem and beyond) and that clinical autonomic manifestations depend on the distribution of α-synuclein pathology across central and peripheral autonomic networks (Dadar et al., 2020; Coon, Cutsforth-Gregory, & Benarroch, 2018). A complementary clinicopathological perspective proposes early involvement in lower brainstem regions (including vagal-related complexes) with subsequent ascending involvement toward more rostral structures, offering a mechanistic route by which HRV changes could reflect (and potentially track) central neurodegeneration affecting autonomic control circuits (Coon, Cutsforth-Gregory, & Benarroch, 2018). In parallel, clinical reviews emphasise that cardiovascular autonomic dysfunction is common in PD and can be clinically consequential, reinforcing that the brain systems controlling blood pressure and heart rate are often compromised in the disease course (Ke et al., 2017; Bódi et al., 2020).

There is also evidence for peripheral autonomic involvement in PD, which includes demonstrations of small-fibre nerve damage and parasympathetic function abnormalities in patient studies that combine structural or microscopic measures with autonomic physiological testing (Kass-Iliyya et al., 2015). More broadly, neuropathology reviews of synucleinopathies describe that autonomic dysfunction can arise from both central and peripheral lesions, implying that HRV changes may conflate impaired central autonomic regulation with impaired peripheral autonomic pathways that convey efferent output to the heart and afferent feedback to the brain (Dadar et al., 2020; Kass-Iliyya et al., 2015).

Adding nuance, experimental neuropathology has questioned whether peripheral α-synuclein aggregates from PD patients necessarily have pathogenic "seeding" potential for central

spread, suggesting that while peripheral autonomic pathology is well documented in PD, its causal role in driving central degeneration remains uncertain and may not be uniform across aggregate types or contexts (Oka et al., 2010). This uncertainty matters because it affects how strongly one can interpret HRV abnormalities as drivers of brain pathology versus correlates of distributed synucleinopathy (Dadar et al., 2020; Oka et al., 2010).

Therefore, there is direct evidence in PD that HRV abnormalities coincide with disrupted heart–brain synchronization. The most direct PD-specific evidence that HRV modifications affect (and reflect changes in) the brain comes from work measuring HRV concurrently with resting-state functional MRI. In a case–control study, PD patients showed a breakdown of synchronization between HRV and resting-state BOLD activity, interpreted as altered coupling between cardiac autonomic dynamics and CAN activity. Because this approach links HRV metrics to spatially resolved brain activity, it supports the claim that PD-related HRV changes are associated with altered brain-level autonomic network function rather than being purely peripheral phenomena. The same study also related these physiological measures to autonomic symptom burden and objective cardiovascular autonomic parameters, strengthening the inference that the observed heart–brain decoupling has clinical relevance to dysautonomia in PD (Basri & Turki, 2025).

Taken together with reviews emphasising that autonomic dysfunction in PD reflects variable central/peripheral network involvement, the heart–brain synchronization findings suggest a systems-level mechanism: degeneration or dysfunction within CAN-related circuitry alters the temporal coordination between brain fluctuations and cardiac autonomic output, yielding measurable HRV abnormalities and reduced brain–heart coupling (Basri & Turki, 2025; Dadar et al., 2020; Coon, Cutsforth-Gregory, & Benarroch, 2018).

5.2. HRV, vascular brain injury and cognition in PD

A key link from cardiovascular autonomic dysfunction (of which HRV is a marker) to brain outcomes in PD is cerebrovascular injury. In a large de novo PD cohort, baseline measures of dysautonomia (including orthostatic hypotension and autonomic dysfunction) were linked to later cognitive decline, and importantly, this association was mediated by white matter hyperintensity (WMH) burden, an MRI marker commonly interpreted as cerebral small-vessel disease. This mediation result provides PD-specific evidence consistent with a causal chain in which autonomic dysregulation contributes to cerebral microvascular injury (WMH accumulation), which in turn contributes to cognitive decline (Recasens et al., 2018).

Clinical reviews and physiologic studies in PD emphasise that cardiovascular autonomic dysfunction (especially orthostatic hypotension) is prominent and clinically important, supporting the plausibility that chronic or recurrent hemodynamic instability could stress cerebral perfusion and thereby promote vascular brain injury (Ke et al., 2017; Bódi et al., 2020; Recasens et al., 2018).

The same PD cohort analysis explicitly connects more severe autonomic dysfunction with increased cognitive deficits and faster decline, again implicating WMH burden as a mediator. This way, to the extent that HRV modifications operationalize autonomic impairment in PD, they can be understood as part of a pathway that affects the brain by increasing vulnerability to vascular white matter injury and downstream cognitive impairment (Recasens et al., 2018). This interpretation aligns with broader PD autonomic literature suggesting the clinical impact of cardiovascular dysautonomia and the need to recognize autonomic dysfunction as a major non-motor contributor to morbidity (Ke et al., 2017; Bódi et al., 2020).

Although not a mechanistic brain-imaging study, a case report describing fatal autonomic failure in premanifesting PD underscores that autonomic breakdown can be profound and life-threatening in rare presentations, highlighting the potential magnitude of systemic dysregulation associated with PD-related autonomic network failure (Pfeiffer, 2020). While this does not prove brain injury causation, it supports the clinical reality that autonomic failure in PD can be severe enough to plausibly endanger cerebral perfusion and brain function, consistent with the vascular/cognitive pathway proposed above (Recasens et al., 2018; Pfeiffer, 2020).

5.3. Nuances and limitations in interpreting HRV as a brain marker in PD

There is also a bidirectionality aspect to be considered, as brain injury can also depress HRV (context for interpreting PD findings). Evidence from acute brain injury populations supports a bidirectional brain–heart relationship: decreased HRV is associated with brain injury patterns (e.g., MRI-characterized injury in neonatal hypoxic-ischemic encephalopathy) and is used as a physiologic indicator of neurologic injury severity (Madsen et al., 2025). Similarly, in intracerebral hemorrhage, reduced HRV on admission has been associated with subsequent fever development, consistent with disrupted central autonomic/thermoregulatory control after brain injury (Park, 2023). Stroke literature likewise emphasises that acute ischemic stroke can induce autonomic tone abnormalities measurable by HRV, and that lesion location (e.g., brainstem or insular involvement) has been implicated in post-stroke autonomic dysfunction (Bae, Cheon, & Kim, 2009). These non-PD findings reinforce interpretive caution: HRV modifications in PD may be both either consequences of neurodegeneration affecting central autonomic circuits and/or contributors to downstream brain injury through chronic hemodynamic instability (Basri & Turki, 2025; Recasens et al., 2018; Madsen et al., 2025; Bae, Cheon, & Kim, 2009).

Multiple PD studies and analyses indicate that autonomic dysfunction severity and HRV abnormalities also vary with disease stage and context. For example, cardiovascular autonomic dysfunction has been evaluated across mild-to-advanced PD and contrasted by dopaminergic treatment status, implying that both progression and therapy can modulate autonomic readouts (including HRV-related measures) and thus potentially modulate brain risks linked to dysautonomia (Bódi et al., 2020). Observational work combining HRV with other autonomic tests (e.g., sympathetic skin response) similarly supports measurable autonomic involvement in PD but does not imply a single uniform HRV signature across all patients (Metzler et al., 2017).

Recent work focusing on early-stage PD highlights that conventional HRV metrics can yield inconsistent findings and proposes information-theoretic approaches to better detect early parasympathetic dysfunction, again implying heterogeneity that could translate into heterogeneous brain consequences (e.g., variable cerebrovascular risk) (Iniguez et al., 2022). Clinical correlations between early non-motor manifestations (e.g., olfactory dysfunction) and cardiovascular dysautonomia/HRV in PD further suggest that HRV changes may track particular pathological subtypes or progression patterns, rather than reflecting a single pathway in all patients (Momiyama et al., 2002).

Table 2 synthetizes the main brain-HRV related certainties and nuances that continue to be debated on this topic.

Table 2. Synthesis: what the evidence supports and what remains uncertain

Supported by PD-specific evidence	**Nuances/uncertainties explicitly raised by the literature**
HRV modifications in PD reflect autonomic dysregulation linked to central autonomic network (CAN) dysfunction, with demonstrable disruption of heart–brain synchronization via concurrent HRV and resting-state fMRI (Basri & Turki, 2025; Dadar et al., 2020); Coon, Cutsforth-Gregory, & Benarroch, 2018.	Causality is difficult to prove from HRV alone. Heart–brain decoupling links HRV to brain function but does not establish if HRV changes cause CAN dysfunction or vice versa (Basri & Turki, 2025).
Neuropathology reviews support distributed central and peripheral autonomic involvement in synucleinopathies (Dadar et al., 2020; Coon, Cutsforth-Gregory, & Benarroch, 2018).	Mediation analyses (dysautonomia → WMH → cognition) strengthen causal interpretations but rely on observational cohort structures and modelling assumptions (Recasens et al., 2018).

In de novo PD, autonomic dysfunction (dysautonomia), measured by HRV and related metrics, is associated with later cognitive decline; WMH (white matter hyperintensity) burden mediates this association, supporting a pathway from autonomic instability to small-vessel disease to cognitive impairment (Recasens et al., 2018; Ke et al., 2017; Bódi et al., 2020).	The hypothesis of peripheral-to-central pathogenic spread is debated. Peripheral autonomic α-synuclein pathology is widely recognized, but not all aggregates show pathogenic potential for central spread, complicating simple interpretations that peripheral lesions (and thus HRV abnormalities) directly drive brain degeneration (Dadar et al., 2020; Oka et al., 2010).
Clinical reviews highlight the prominence of cardiovascular dysautonomia in PD (Ke et al., 2017; Bódi et al., 2020).	Early PD HRV findings can be inconsistent across standard metrics, prompting newer analytic methods and implying that brain consequences of HRV-modified dysautonomia may be concentrated in particular subgroups (e.g., those with prominent orthostatic hypotension or demonstrable CAN decoupling) (Bódi et al., 2020; Iniguez et al., 2022; Basri & Turki, 2025).
Direct evidence from case–control studies shows breakdown of synchronization between HRV and resting-state brain activity in PD, interpreted as altered coupling between cardiac autonomic dynamics and CAN activity (Basri & Turki, 2025).	HRV modifications may be both a consequence of neurodegeneration and/or a contributor to brain injury; directionality and significance vary by patient subgroup and context (Basri & Turki, 2025; Recasens et al., 2018; Madsen et al., 2025; Bae, Cheon, & Kim, 2009).
HRV is a marker for central autonomic dysfunction and is associated with important brain outcomes (cognition, small-vessel disease) (Recasens et al., 2018; Ke et al., 2017; Bódi et al., 2020).	Substantial heterogeneity in HRV findings depending on disease stage, analytic method, patient characteristics, and context complicates interpretation of HRV as a biomarker and its clinical application (Bódi et al., 2020; Iniguez et al., 2022; Momiyama et al., 2002).

6. NMS and the Distinctive Pharmacological Problems in PD

6.1. HRV abnormalities and the implication for treatment

The broad array of NMS in PD substantially affects daily functioning and quality of life, as well as complicate management, since multiple organ systems and specialties are implicated (Chiang & Lin, 2025; Gibbons et al., 2017). This multisystem nature makes it difficult to optimise pharmacotherapy across competing targets (e.g., improving one domain while worsening another), particularly when inter-individual variability in symptom burden and progression is high and treatment needs must be individualised (Gibbons et al., 2017).

PD pharmacotherapy is also widely understood as predominantly symptomatic (rather than clearly disease-modifying), which intensifies the challenge of balancing short-term benefit, long-term adverse effects, and underlying disease progression over time (Holford & Nutt, 2008).

Autonomic dysfunction is a central non-motor domain in PD and is clinically important because it can be present early (including prodromally) and may progress, yet it is not straightforward to measure or treat pharmacologically in a targeted way (Oka et al., 2010; Gibbons et al., 2017). Within autonomic dysfunction, *cardiovascular dysautonomia* (often operationalised using HRV metrics) creates particular pharmacological challenges because HRV is influenced both by PD pathophysiology and by medications commonly used to treat PD and PD-associated neuropsychiatric symptoms (Ruonala et al., 2015; Ricciardi et al., 2026; Gibbons et al., 2017).

6.2. Methodological considerations and confounding factors in HRV assessment

Well-established methodological considerations affect interpretability of HRV (recording duration, analytic domain, and context such as posture or provocation (Billman et al., 2015). Lower

HRV is used as a cardiovascular risk-related marker (including associations with adverse outcomes in other conditions), and even as a safety signal, especially since medications may affect autonomic balance (Brunoni et al., 2013; Billman et al., 2015). For PD specifically, cardiovascular autonomic dysfunction is frequently discussed as an early feature, and reduced HRV is repeatedly investigated as a candidate early marker; however, the literature includes heterogeneity and inconsistencies across HRV measures, protocols, and patient subgroups, which complicates the use of HRV as a stable pharmacodynamic endpoint or a clinically actionable monitoring tool (Krohová et al., 2025; Ruonala et al., 2015; Gibbons et al., 2017). This methodological and biological variability becomes a pharmacological challenge: if HRV is both *disease-sensitive* and *drug-sensitive*, then medication changes may confound attempts to infer disease state or progression from HRV, and conversely underlying disease-related dysautonomia may alter drug tolerability and cardiovascular risk (Ruonala et al., 2015; Gibbons et al., 2017; Billman et al., 2015).

Multiple PD studies emphasise that cardiovascular dysautonomia can be detectable early and may relate to other early non-motor manifestations. For example, Oka et al. (2010) examined relationships among olfactory dysfunction, cardiac sympathetic denervation (via reduced cardiac ^123I-MIBG uptake), and HRV in PD, reflecting the concept that autonomic impairment can accompany early non-motor features and may be measurable using HRV and cardiac imaging approaches. Consistent with early involvement, Gibbons et al. (2017) report that many publications suggest diminished HRV occurs early, potentially even prior to cardinal motor signs, and they evaluated HRV (derived from short ECG recordings) in a large longitudinal early PD cohort to test associations with PD severity/progression and ECG parameters such as the QT interval. Additional contemporary discussion similarly frames autonomic dysfunction (including neurogenic orthostatic hypotension and related cardiovascular autonomic abnormalities) as a recognized non-motor symptom across PD stages and potentially among early/prodromal features, supporting its relevance to early clinical evaluation and monitoring (Gibbons et al., 2017).

HRV changes observed after starting or adjusting therapy may not be easily attributable to medication alone because baseline dysautonomia is already evolving, as in Figure 2 (Gibbons et al., 2017; Holford & Nutt, 2008). This creates uncertainty within attempts to titrate symptomatic therapies over time, an issue that aligns with broader concerns in PD therapeutics about separating symptomatic drug effects, longer-term adverse effects, and disease progression, particularly when time-varying responses are expected (Holford & Nutt, 2008; Gibbons et al., 2017).

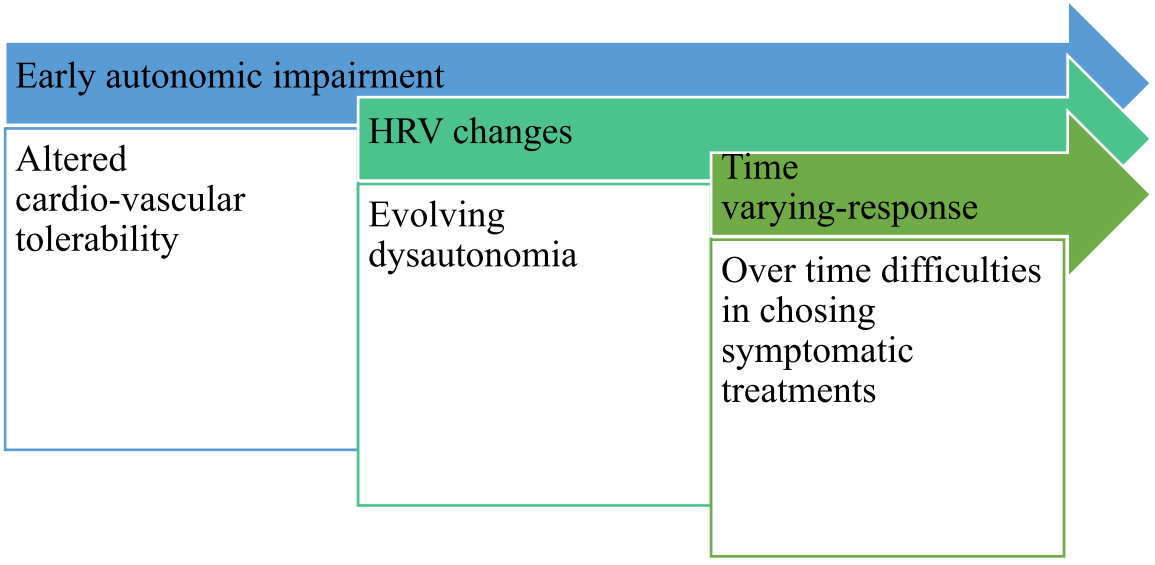

Figure 2. Pharmacological implications of HRV treatment in PD

A core challenge further arises, as HRV findings in PD are heterogeneous, and "parasympathetic dysfunction" is not captured uniformly across methods. Even though parasympathetic dysfunction is frequently evaluated in PD with conventional time- and frequency-domain HRV metrics, Krohová et al. (2025) emphasise that findings across studies have been inconsistent, motivating the use of additional analytic approaches (including information-theoretic measures) across standardized phases (rest, tilt, recovery) in early PD. This explicitly highlights a key obstacle for pharmacological research: if different HRV methods or contexts yield different inferences about parasympathetic function, then HRV may be an unstable endpoint for assessing medication effects or stratifying patients (Krohová et al., 2025; Billman et al., 2015). Ruonala et al. (2015) and Krohová et al. (2025) similarly note that evidence about levodopa's effect on HRV is "not coherent between studies," underscoring inconsistency even when focusing on a single, central PD drug class and a defined autonomic metric family.

These inconsistent HRV readouts can lead to ambiguous conclusions about whether a medication is improving dysautonomia, worsening it, or simply shifting HRV metrics in a context-dependent way (e.g., posture, timing, or analytic method) (Krohová et al., 2025; Ruonala et al., 2015; Billman et al., 2015). Consequently, HRV-guided medication adjustment is not straightforward, and clinical trials using HRV as an outcome may face reproducibility and interpretability problems unless protocols and analyses are carefully standardized (as urged in general HRV methodology guidance) (Billman et al., 2015; Krohová et al., 2025).

6.3. Dopaminergic therapy, patient heterogeneity and pharmacological management

Levodopa remains a mainstay of symptomatic PD treatment, but understanding its autonomic effects is difficult. Ruonala et al. (2015) directly examined autonomic response to a levodopa challenge in advanced PD using HRV at baseline and at 30 and 60 minutes post-dose, explicitly because levodopa's autonomic effects remain unclear and prior results are inconsistent. This fits a broader pharmacologic framing: PD drug effects unfold on multiple time scales (minutes-to-hours within a dosing interval vs. longer-term changes across disease progression), and failing to incorporate time explicitly can confound interpretation of drug action versus disease evolution (Holford & Nutt, 2008).

Thus, even when HRV changes occur after dosing, attributing them to levodopa's direct autonomic pharmacodynamics versus indirect effects (e.g., via changes in motor state, stress, or baroreflex engagement) is methodologically challenging in principle and is recognized as empirically unresolved in the levodopa–HRV literature (Ruonala et al., 2015; Holford & Nutt, 2008; Billman et al., 2015).

6.4. Pharmacological complexity: drug effects, patient variability and HRV interpretation

Dopaminergic medications may also modify relationships between HRV and non-motor symptoms. Ricciardi et al. (2026) and Ruonala et al. (2015) examined anxiety, cardiovascular function/HRV, and neural structural correlates in PD, and they also investigated the effect of dopaminergic medications on the anxiety–autonomic relationship, reinforcing that dopaminergic therapy can interact with non-motor symptom networks that include HRV as a physiological component.

All of this matters, because neuropsychiatric symptoms are common and often treated pharmacologically in PD, but these treatments may themselves affect autonomic function, producing layered confounding in HRV interpretation (Koychev & Okai, 2017; Ricciardi et al., 2026). The same medication regimen may influence HRV directly and also indirectly by altering anxiety, motor fluctuations, or other states, and these effects may be time-dependent (acute vs. chronic), making HRV a complex composite signal rather than a single-purpose biomarker of "autonomic improvement" (Ricciardi et al., 2026; Holford & Nutt, 2008; Billman et al., 2015).

On the other hand, not all PD subtypes show the same HRV signature. Naranjo et al. (2019) report that while cardiac autonomic dysfunction often manifests as reduced HRV in idiopathic PD, PD associated with the LRRK2 mutation may not show the same significant reduction, and they investigated standard and novel HRV features in LRRK2-associated PD and related groups. This indicates that autonomic phenotypes (and thus HRV baselines and trajectories) may differ by etiology/genotype, which can affect both (i) the baseline cardiovascular risk profile and (ii) the detectability of medication-related autonomic effects using HRV (Naranjo et al., 2019; Krohová et al., 2025; Billman et al., 2015). If HRV impairments are not uniform across PD subtypes, then a drug's apparent "autonomic effect" measured by HRV may differ simply because the underlying dysautonomia differs, complicating trial design, stratification, and individualized monitoring (Naranjo et al., 2019; Krohová et al., 2025). This heterogeneity aligns with the broader clinical problem that PD manifestations vary substantially across individuals, making tailored treatment difficult (Gibbons et al., 2017).

Psychosis in PD is also clinically significant and difficult to manage pharmacologically, in part because medication side effects and trial design limitations have impeded advances; clozapine is described as the most effective antipsychotic without motor worsening but carries serious safety burdens (e.g., agranulocytosis risk), and there remains a need for safer and more effective treatments (Goldman, Vaughan, & Goetz, 2011). This therapeutic gap is relevant to HRV because antipsychotic drugs can have cardiac effects due to pharmacologic actions, and HRV has been proposed as a potential index of cardiotoxicity. Within this context, Silke, Campbell, and King (2002) studied acute HRV changes following antipsychotic agents starting from concerns about cardiotoxicity and the limits of QT-only monitoring. Complementarily, Linder et al. (2014) and Silke, Campbell, and King (2002) found associations between antipsychotic exposure and lower HRV (and altered blood pressure variability) in another clinical population, reinforcing that antipsychotics can reduce HRV and thus may plausibly worsen an already vulnerable autonomic profile in PD. PD patients may already exhibit reduced HRV/dysautonomia early, and adding antipsychotics with HRV-lowering potential creates a layered risk: distinguishing disease-related HRV reduction from drug-related HRV reduction may be difficult, while the combined effect could theoretically heighten cardiovascular vulnerability (Gibbons et al., 2017; Silke, Campbell, & King, 2002; Linder et al., 2014). This is particularly notable because clinical monitoring often emphasises QT effects, yet HRV is discussed as an additional or alternative marker of cardiac/autonomic impact, suggesting that a QT-focused safety strategy may be incomplete in contexts where autonomic impairment is central (Silke, Campbell, & King, 2002; Gibbons et al., 2017).

Neuropsychiatric symptoms are quite common in PD and disproportionately affect quality of life. Pharmacological treatment is commonly used but is limited by variable efficacy and drug interaction risks, motivating interest in non-pharmacological approaches such as cognitive–behavioural therapy (CBT) for depression/anxiety, impulse-control disorders, and insomnia (Koychev & Okai, 2017). This intersects with HRV, as reduced HRV is widely treated as a cardiovascular risk-related signal, and the field debates whether HRV reductions in depression reflect disorder traits or medication effects. Brunoni et al. (2013) address this question in major depressive disorder via a randomized comparison including sertraline, explicitly framing reduced HRV as a cardiovascular predictor of mortality and examining whether treatment changes HRV.

Ricciardi et al. (2026) and Koychev and Okai (2017) further link anxiety and HRV in PD and evaluate dopaminergic medication effects on this relationship, emphasising that both psychiatric state and PD medications can modulate HRV-related physiology.

In PD, treating depression/anxiety pharmacologically may affect HRV, while the psychiatric condition itself may be associated with HRV alterations; therefore, HRV-based assessment of autonomic dysfunction in PD can be confounded by both psychiatric comorbidity and its treatment, strengthening the rationale for considering non-pharmacologic therapies (e.g., CBT) when

appropriate to reduce polypharmacy and interaction burden (Koychev & Okai, 2017; Brunoni et al., 2013; Ricciardi et al., 2026).

GI dysfunction is another common problem in PD, since it affects multiple levels of the digestive tract, and can lead to malnutrition/weight loss and impaired medication absorption. Chiang and Lin (2025) emphasise that GI problems can impair medication absorption and thereby exacerbate both motor and non-motor symptoms.

From a pharmacological standpoint, impaired absorption introduces variability in drug exposure over time, complicating the already time-sensitive interpretation of drug action versus disease progression described by Holford and Nutt (2008) and Chiang and Lin (2025).

Because autonomic state (reflected in HRV) can vary with physiological stressors and systemic instability, absorption-driven fluctuations in symptomatic control may indirectly modulate HRV, confounding attempts to attribute HRV changes to primary autonomic neurodegeneration versus secondary effects of fluctuating clinical state (a concern consistent with HRV's sensitivity to context and measurement conditions) (Billman et al., 2015; Holford & Nutt, 2008; Chiang & Lin, 2025).

Overall, HRV related pharmacological challenges in PD NMS up to this point, can be categorized as in Table 3.

Table 3. HRV challenges in PD

Key Points	References
Baseline dysautonomia makes PD patients pharmacologically "cardiovascularly fragile," and HRV may be reduced early; this raises the stakes for any medication with autonomic/cardiac effects.	Oka et al., 2010; Gibbons et al., 2017; Ruonala et al., 2015; Silke, Campbell, & King, 2002; Goldman, Vaughan, & Goetz, 2011
HRV is appealing but imperfect as a pharmacodynamic endpoint; results vary by method, context, and subgroup, and genetic subtype differences further challenge interpretation.	Billman et al., 2015; Krohová et al., 2025; Ruonala et al., 2015; Naranjo et al., 2019
Medication effects on HRV are hard to disentangle from disease progression and time-varying state; Levodopa's autonomic/HRV effects remain unclear and inconsistently reported.	Holford & Nutt, 2008; Ruonala et al., 2015; Ricciardi et al., 2026
Treatments for non-motor neuropsychiatric symptoms (e.g., antipsychotics, antidepressants) can themselves reduce HRV or add cardiac risk signals, complicating management.	Goldman, Vaughan, & Goetz, 2011; Silke, Campbell, & King, 2002; Linder et al., 2014; Gibbons et al., 2017; Koychev & Okai, 2017; Brunoni et al., 2013; Ricciardi et al., 2026
System-level complexity (polypharmacy, absorption variability, multispecialty needs) intensifies HRV-related uncertainty; GI dysfunction can destabilize medication exposure and symptom control.	Chiang & Lin, 2025; Holford & Nutt, 2008; Billman et al., 2015

Among this discussion about NMS, addressing GI dysfunction remains pharmacologically consequential. Because impaired absorption can destabilize medication exposure and symptom control, it should be considered part of the therapeutic strategy, potentially reducing downstream variability in physiological state that could influence HRV (Chiang & Lin, 2025; Holford & Nutt, 2008; Billman et al., 2015).

Other research and clinical implications can be expressed as in Table 4.

Table 4. Classification of clinical implications of HRV in PD's NMS

Research and Clinical Implications	Key Recommendation or Implication	References
Standardization	Standardized and richer protocols are likely required if HRV is used to evaluate therapy effects in PD; recommend multi-phase autonomic testing.	Billman et al., 2015; Krohová et al., 2025
Stratification	Stratification (including by genotype/etiology) may be necessary for HRV-guided inference in research and clinical trials.	Naranjo et al., 2019; Krohová et al., 2025
Monitoring	Medication safety monitoring in PD should consider autonomic markers (like HRV) in addition to traditional ECG intervals where appropriate (e.g., antipsychotic cardiotoxicity).	Silke, Campbell, & King, 2002; Gibbons et al., 2017
Non-pharmacologic options	Reducing confounding from psychiatric comorbidity and its treatment may require integrated, non-pharmacologic options (e.g., cognitive–behavioural therapy) to reduce polypharmacy and HRV confounding.	Koychev & Okai, 2017; Brunoni et al., 2013

7. Autonomic dysfunction and physiotherapy challenges in PD

Autonomic dysfunction is clinically relevant because it can influence everyday function and interact with motor performance (e.g., gait) (Sergi et al., 2025). In PD, autonomic dysfunction is also framed as a contributor to blood pressure and circulation abnormalities that can be highly disruptive to quality of life (Bane et al., 2024). Because physiotherapy is typically organized around repeated bouts of physical activity (often with postural transitions, balance challenges, and progressive intensity), the presence of dysautonomia in PD creates practical constraints on exercise prescription, monitoring, and safety management (Sergi et al., 2025; Bane et al., 2024).

HRV is repeatedly positioned in this literature as a central, non-invasive marker of cardiac autonomic (sympathovagal) modulation and thus a convenient "window" into cardiovascular autonomic (CVA) dysfunction that may co-occur in parkinsonism/PD (Berkebile, Inan, & Beach, 2025; Siepmann et al., 2022). PD-focused studies suggest that HRV abnormalities in PD reflect altered autonomic balance and can serve as a modifiable biomarker within rehabilitation programs (Basri & Turki, 2025; Siepmann et al., 2022). These points together imply a dual role for HRV in physiotherapy: risk stratification/monitoring (autonomic vulnerability during exercise and daily life), and target for interventions intended to improve non-motor autonomic regulation alongside motor function (Basri & Turki, 2025; Bane et al., 2024; Diotaiuti et al., 2025).

7.1. HRV as an appealing biomarker, but not a straightforward one

Across the cited PD and broader autonomic literature, HRV is treated as the most common method for assessing CVA function and as a general measure of neurocardiac function reflecting autonomic nervous system activity (Berkebile, Inan, & Beach, 2025; Siepmann et al., 2022; Basri & Turki, 2025). In PD rehabilitation research specifically, HRV impairments are described as indicating altered autonomic balance, and structured exercise is explored as a way to modify that balance (Basri & Turki, 2025). This creates a rationale for the rehabilitation context to include HRV in assessment batteries to better characterize non-motor autonomic constraints that could affect training tolerance, recovery, and symptom fluctuations (Basri & Turki, 2025; Sergi et al., 2025).

However, HRV interpretation is sensitive to context, and this becomes a core challenge when moving from laboratory to real-world physiotherapy settings. Even outside PD, HRV varies with circadian timing and chronotype, and the time-of-day effect can complicate comparisons across sessions if not controlled or modeled (Vitale et al., 2019). Likewise, "acute state effects" of different movement modalities (e.g., yoga postures vs cycling) have been examined specifically because autonomic modulation can shift rapidly with activity type and state (Metkari & Phadke, 2021). Thus, in PD physiotherapy, HRV is simultaneously attractive (non-invasive, scalable, mechanistically linked to dysautonomia) and difficult (highly state-dependent, requiring standardized acquisition conditions) (Metkari & Phadke, 2021; Vitale et al., 2019; Basri & Turki, 2025).

7.2. Challenges in interpreting HRV during physiotherapy

Exercise modality and intensity can change HRV in ways that complicate PD training programming. A persistent challenge is that autonomic responses differ by exercise modality even when heart rate is matched. In healthy participants, dynamic vs static (isometric) lower-limb exercise at similar heart rate levels yields different blood pressure responses and different HRV patterns, indicating distinct autonomic control strategies under ostensibly comparable "intensity" (Weippert et al., 2013). Complementary work using nonlinear metrics (e.g., sample entropy) likewise shows that traditional and entropy-based measures can reflect different modes of cardiovascular control during low-intensity dynamic vs isometric exercise (Weippert et al., 2014). Because PD physiotherapy commonly includes mixed-mode tasks (e.g., resistance exercises, isometrics for postural control, cycling/treadmill training), HRV readouts may shift because of task type rather than improved or worsened dysautonomia per se. This makes it harder to use HRV to titrate intensity or to compare responses across heterogeneous physiotherapy sessions without careful protocol design and analytic choices (Weippert et al., 2013; Weippert et al., 2014).

In athletic and non-PD clinical contexts, interval exercise and recovery structure also change linear and nonlinear HRV indices during and after sessions, and resistance exercise can produce acute HRV changes in cardiopathic patients depending on load (e.g., percentage of 1RM) (Gronwald, Hoos, & Hottenrott, 2019). While these studies are not in PD domain, they strengthen the methodological point that physiotherapy-relevant variables (interval structure, recovery, resistance load) can acutely perturb HRV and therefore must be treated as confounders (or intentional stimuli) when HRV is used as an autonomic outcome in PD rehabilitation (Gronwald, Hoos, & Hottenrott, 2019; Weippert et al., 2013; Weippert et al., 2014).

7.3. HRV, gait, medication effects and practical implications for rehabilitation

Autonomic dysfunction can interact with gait and cognition, linking non-motor physiology to "core" physiotherapy targets. Recent PD work using chest-worn sensing reports that autonomic dysfunction is a key non-motor feature and investigates links between resting HRV time-domain measures and spatiotemporal gait parameters. This further frames HRV as related to gait phenomena such as freezing of gait, while acknowledging uncertainty regarding broader gait relationships. This is also directly relevant to physiotherapy because it suggests that autonomic status (as indexed by HRV) may correlate with functional ambulation performance, implying that gait training outcomes may be partly constrained by non-motor autonomic burden (Sergi et al., 2025). In parallel, PD-focused wearable research emphasises that CVA dysfunction may co-occur in parkinsonism and that HRV is commonly used to assess it, motivating multimodal sensing approaches to better capture the holistic nature of autonomic effects beyond symptom reporting (Berkebile, Inan, & Beach, 2025). Collectively, these studies motivate a "systems" view: physiotherapy targeting gait and balance may need to account for autonomic status both as a moderator of performance and as a co-target of therapy (Berkebile, Inan, & Beach, 2025; Sergi et al., 2025).

Medication effects can also confound HRV, autonomic symptoms, and therapy response. Levodopa has potential to exacerbate cardiovascular autonomic dysfunction that may co-occur in patients (Berkebile, Inan, & Beach, 2025). This is a specific and clinically important physiotherapy challenge: session-to-session autonomic physiology (and therefore HRV) may vary with medication state, potentially altering exercise tolerance and HRV-derived conclusions about rehabilitation efficacy (Berkebile, Inan, & Beach, 2025; Basri & Turki, 2025). Berkebile, Inan, and Beach (2025) further argue that typical monitoring of CVA function and levodopa effects is often limited to clinical settings and symptom reporting, which may fail to capture the holistic nature of autonomic fluctuations, precisely the fluctuations that physiotherapists encounter across home and clinic contexts. Therefore, physiotherapy research and practice that use HRV must consider medication timing and its potential autonomic effects as a primary design variable rather than background noise (Berkebile, Inan, & Beach, 2025; Basri & Turki, 2025).

Going back to basics, in PD, autonomic dysfunction is described as producing blood pressure and circulation abnormalities that are highly disruptive to quality of life (Bane et al., 2024). Although the cited PD exercise studies focus on HRV and endothelial/autonomic outcomes, the implication for physiotherapy is concrete: postural changes, resistance training, and aerobic training may need enhanced monitoring and progression rules in individuals with prominent autonomic dysfunction, because cardiovascular responses may be unstable or atypical (Bane et al., 2024; Weippert et al., 2013). Given that different exercise modes can produce different blood pressure responses even at matched heart rate, physiotherapists cannot assume that a heart-rate–based prescription alone ensures comparable hemodynamic stress across modalities, especially in a population with known autonomic/circulatory abnormalities (Weippert et al., 2013; Bane et al., 2024).

7.4. From physiotherapy-relevant interventions targeting HRV, to biofeedback

A PD rehabilitation study explicitly suggests HRV as a key biomarker of autonomic function and neurocardiac regulation, notes that reduced HRV has been associated with autonomic dysfunction in PD, and investigates aerobic exercise–induced HRV changes across a supervised three-month program. This supports the notion that physiotherapy-relevant aerobic training may modulate HRV in PD, and that HRV can be used to characterize heterogeneous autonomic adaptations to rehabilitation (Basri & Turki, 2025). At the same time, the broader exercise-HRV literature in other clinical groups shows that longer-term walking-based programs can change HRV (e.g., Nordic walking in cancer patients), and that structured training post–myocardial infarction can improve HRV-related indices of autonomic regulation (Niederer et al., 2013; Fujimoto et al., 1999). These non-PD findings strengthen biological plausibility that systematic exercise can shift HRV, but they do not resolve PD-specific questions about optimal modality, dose, or the degree to which HRV changes translate into meaningful non-motor symptom improvement in PD (Niederer et al., 2013; Fujimoto et al., 1999; Basri & Turki, 2025).

All of these admit that PD exercise programs may improve HRV in some patients, but HRV responsiveness likely varies across individuals and is influenced by modality, intensity, medication state, and measurement timing; thus HRV-based personalization requires careful standardization and interpretation frameworks (Berkebile, Inan, & Beach, 2025; Vitale et al., 2019; Basri & Turki, 2025; Weippert et al., 2013).

Bane et al. (2024) emphasise that while exercise interventions help motor symptoms in PD, improvements in associated non-motor symptoms remain limited; they specifically test low-intensity resistance training with blood flow restriction (LIRT-BFR) and compare it to high-intensity resistance training (HIRT) for effects on autonomic and endothelial function in PD. This directly illustrates another physiotherapy challenge: conventional PD exercise prescriptions often prioritize motor outcomes, yet autonomic outcomes may require different programming (e.g., lower intensity with BFR vs high-intensity strength work) and may not automatically improve

alongside motor gains (Bane et al., 2024). Because resistance exercise can acutely alter HRV in cardiopathic populations depending on intensity and because mode-specific autonomic control differs for dynamic vs static tasks, resistance-based interventions in PD should treat HRV/autonomic effects as potentially dose- and modality-dependent rather than guaranteed benefits (Weippert et al., 2013; Bane et al., 2024).

A scoping review/meta-analysis on AMPS in PD frames AMPS as emerging and explicitly includes autonomic regulation among outcomes of interest, alongside gait and balance. The inclusion of autonomic regulation in AMPS evidence synthesis suggests that some non-traditional physiotherapy adjuncts are being explored not only for motor outcomes but also for non-motor autonomic modulation (Tedeschi, Donati, & Giorgi, 2024). Nevertheless, as a scoping review, this also signals that evidence may be heterogeneous and still developing, which is itself a challenge for clinical translation: the physiotherapist may encounter promising autonomic-related outcomes without a mature consensus on protocols, responder profiles, or the durability of HRV/autonomic changes (Tedeschi, Donati, & Giorgi, 2024; Basri & Turki, 2025).

7.5. Emerging technologies and methodological considerations for HRV assessment

A comprehensive review of biofeedback/neurofeedback in PD rehabilitation explicitly includes HRV biofeedback among non-invasive interventions intended to modulate motor and non-motor symptoms through self-regulation of physiological signals, as it evaluates impacts on motor control, autonomic function, and cognitive performance. This supports the plausibility of directly targeting autonomic regulation using HRV as both feedback signal and outcome (Diotaiuti et al., 2025). Nonetheless, integrating HRV biofeedback into routine physiotherapy raises practical challenges highlighted across the HRV measurement literature: HRV is sensitive to state (activity type, recovery), time-of-day influences, and measurement conditions, all factors that can complicate feedback interpretation unless protocols are standardized (Metkari & Phadke, 2021; Vitale et al., 2019; Gronwald, Hoos, & Hottenrott, 2019; Diotaiuti et al., 2025).

Berkebile, Inan, and Beach (2025) directly address a key implementation gap: although HRV is commonly used for CVA function, broader monitoring of levodopa effects and autonomic function is typically limited to clinical settings and symptom reporting; they evaluate feasibility of a multimodal wearable chest patch to monitor CVA changes during clinical and 24-hour ambulatory conditions. This is central to physiotherapy because much PD rehabilitation occurs across clinic-to-home continuums; if HRV is to guide personalization or track non-motor outcomes, it must be measurable reliably outside tightly controlled environments (Berkebile, Inan, & Beach, 2025; Basri & Turki, 2025). Similarly, Sergi et al. (2025) use a chest-worn sensor approach to connect autonomic measures ("sympathetic burden"/HRV time-domain indices) with gait performance and cognition in PD, illustrating the direction toward ecologically valid, wearable-based autonomic assessment aligned with functional testing. These findings suggest that there is a methodological and operational burden to select sensors, defining recording contexts (resting vs ambulatory), and interpreting HRV signals in the presence of medication cycles and daily activity patterns, yet this burden is necessary if HRV is to become clinically actionable rather than a research-only metric (Berkebile, Inan, & Beach, 2025; Sergi et al., 2025; Diotaiuti et al., 2025).

HRV's circadian fluctuation and sensitivity to time-of-day and chronotype are specifically discussed in sports HRV literature, with the conclusion that results are "sparse and controversial," highlighting uncertainty even in otherwise healthy populations (Vitale et al., 2019). Environmental context can also affect HRV. For example, night-time HRV changes after a lunchtime walk in nature were studied to minimize confounding influences, underscoring the need for careful control of activity and mental state when interpreting HRV (Gladwell et al., 2016). Experimental work comparing yoga postures and cycling in yoga-naive volunteers is motivated by the concept of "acute state effects" on autonomic modulation, implying that simply changing the movement context can acutely shift HRV-derived autonomic markers (Metkari & Phadke, 2021). For PD physiotherapy, these findings collectively imply that HRV outcomes can be driven by timing and

contextual variables unless acquisition is standardized (e.g., consistent time-of-day; consistent posture; controlled breathing/activity) and unless analyses explicitly model these covariates (Metkari & Phadke, 2021; Gladwell et al., 2016; Vitale et al., 2019; Basri & Turki, 2025).

Nonlinear HRV measures are often proposed to provide complementary information, but their physiological interpretation may differ from traditional indices. For example, sample entropy and traditional HRV metrics can reveal different modes of cardiovascular control during low-intensity exercise, and nonlinear dynamics (e.g., fractal properties via DFA) change with exercise intensity and recovery in cyclists (Gronwald, Hoos, & Hottenrott, 2019; Weippert et al., 2014). In PD wearable gait/autonomic studies, time-domain indices are commonly used at rest and related to functional outcomes (Sergi et al., 2025). This creates a translational challenge: physiotherapy teams must decide whether they are tracking resting status (often time-domain measures) versus dynamic responsiveness (potentially nonlinear metrics), and whether metric changes reflect clinically meaningful autonomic improvements or merely altered task conditions and recovery dynamics (Gronwald, Hoos, & Hottenrott, 2019; Sergi et al., 2025; Weippert et al., 2014; Diotaiuti et al., 2025).

Non-motor autonomic dysfunction will remain a clinically relevant constraint on physiotherapy in PD, especially throughout potential interactions with gait performance (Sergi et al., 2025; Bane et al., 2024). HRV remains an important but context-sensitive biomarker for PD rehabilitation, positioned as a disease marker in PD-related autonomic disorders and investigated as a modifiable rehabilitation biomarker, strongly influenced by measurement context, time-of-day, and exercise modality (Siepmann et al., 2022; Vitale et al., 2019; Basri & Turki, 2025). Limitations, however, should be further considered, as expressed in Table 5.

Table 5. Key research gaps of HRV in PD regarding physiotherapy

Research Gap	Description	References
Clinically actionable HRV protocols in PD physiotherapy remain under-specified	HRV monitoring is motivated and shows associations with functional outcomes in PD, but broader HRV literature highlights strong dependence on timing, environment, and exercise modality. Protocol standardization is essential for comparability and clinical decision-making.	(Metkari & Phadke, 2021; Gladwell et al., 2016; Vitale et al., 2019; Sergi et al., 2025)
Dose–response and responder profiling needed for autonomic outcomes	PD rehabilitation work suggests HRV can change with aerobic training and that resistance/BFR approaches may target autonomic/endothelial function, but clearer guidance is needed on which patients respond and which training components drive benefit.	(Basri & Turki, 2025; Bane et al., 2024)
Medication–exercise interaction effects on HRV should be explicitly modeled	Given levodopa's potential to exacerbate CVA dysfunction and limitations of clinic-only monitoring, future physiotherapy research must integrate ambulatory monitoring to separate training effects from pharmacologic autonomic effects.	(Berkebile, Inan, & Beach, 2025; Basri & Turki, 2025)
Integration of HRV biofeedback and other adjuncts requires mechanistic and pragmatic trials	HRV biofeedback and AMPS are highlighted as non-invasive approaches with autonomic relevance, but robust implementation pathways (frequency, dose, exercise pairing, long-term adherence) are not yet established.	(Tedeschi, Donati, & Giorgi, 2024; Diotaiuti et al., 2025)

Medication state is a major confounder and safety consideration, because levodopa can potentially exacerbate CVA dysfunction and typical monitoring may miss real-world fluctuations, conditions under which physiotherapy is delivered (Berkebile, Inan, & Beach, 2025).

Intervention effects on autonomic outcomes are not guaranteed and may still require targeted programming, consistent with evidence that non-motor improvements are limited in general, that resistance training variants (including BFR) are being tested for autonomic/endothelial outcomes, and that aerobic training can produce measurable HRV adaptations in PD rehabilitation cohorts (Basri & Turki, 2025; Bane et al., 2024).

In this context, wearables and multimodal sensing are promising enablers but introduce new implementation demands, as feasibility for ambulatory CVA monitoring is being studied and sensor-derived autonomic measures are being linked to gait/cognition, but standardized protocols and clinically meaningful thresholds remain under development (Berkebile, Inan, & Beach, 2025; Sergi et al., 2025).

HRV remains mostly a research tool, but it does have practical utility in select subgroups, such as early PD patients with autonomic symptoms, those with suspected atypical parkinsonism, or patients in specialized programs monitoring autonomic function. Its use in these contexts should be further guided by standardized protocols and multidisciplinary interpretation.

8. Conclusions

PD is a multisystem disorder in which NMS, particularly autonomic dysfunction, emerge early and substantially contributes to disease burden and management complexity. HRV has potential as a non-invasive biomarker for autonomic dysfunction but is limited by heterogeneity in methodology, patient populations, and contextual factors such as medication and exercise.

Future research should focus on some prioritized directions. First of all, to standardize HRV assessment protocols, by developing and validating uniform HRV measurements for clinical and research use in PD, accounting for variables such as timing, physical activity, and medication state. This will enable more reliable comparisons across studies and patient groups. It is also necessary to define patient subgroups and stratification criteria. It will be more and more useful to identify and characterize clinically meaningful PD subtypes (e.g., by genotype, phenotype, early vs. advanced disease) to enable targeted application of HRV as a biomarker and to personalize treatment strategies.

Integration of real-world monitoring technologies will require the implementation and evaluation of wearable and ambulatory monitoring tools that can track HRV and related autonomic markers in everyday settings, backed-up by ecological validity.

It is also necessary to have pragmatic clinical trials to test HRV-guided interventions, such as biofeedback, exercise modalities, and adjunctive therapies, with the goal of identifying which approaches best improve autonomic and non-motor outcomes in specific PD populations. It is also mandatory to clarify dose–response relationships and to identify responders (patient profiles most likely to benefit). Also, addressing the impact of polypharmacy, neuropsychiatric comorbidities, and gastrointestinal dysfunction on HRV and autonomic outcomes, as well as developing strategies to minimize confounding in both research and clinical practice is a desired objective.

Addressing these challenges will enhance individualized care, improve patient outcomes, and advance the translation of biomarker-driven strategies into routine clinical practice. This way, HRV assessment should be considered in routine neurological care when there is clinical suspicion of autonomic dysfunction, for monitoring therapeutic interventions that may affect autonomic tone, or as part of a comprehensive evaluation of complex, multisystem neurological disorders.

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