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PRISM-PD: A Computational Atlas of Multimodal Biomarker Coordination in Parkinson’s Disease

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Abstract

As the number of clinical, imaging, and proteomic biomarker tests increase for Parkinson’s disease (PD), determining which biomarkers and their coordination patterns drive disease becomes more difficult. This paper introduces PRISM-PD (Perturbation-based Resolution of Inter-biomarker Synchrony Mapping for Parkinson’s Disease), a computational framework based on Hamiltonian spectral decomposition of multimodal biomarker covariance structure. PRISM-PD was applied to longitudinal data from 4,649 participants in the Parkinson’s Progression Markers Initiative (PPMI), integrating dopamine transporter imaging, clinical assessments, and cerebrospinal fluid (CSF) neuroinflammatory proteomics. Unlike black-box deep learning architectures, this lightweight method runs on standard CPU hardware in seconds with full per-feature saliency, using a pre-specified 70/30 hold-out validation throughout. Eigendecomposition revealed fragmentation of neuroinflammatory coordination at PD diagnosis, driven by CSF proteins (CCL2, IL-6ST, CXCL13) with near-zero dopaminergic loading, supporting a two-axis model of early PD biology in which inflammatory coupling disruption and nigrostriatal degeneration are independent processes. Longitudinal analysis showed progressive coupling concentration whose eigenvector transition sequence parallels the clinical progression described by Braak and colleagues. Tremor-dominant and PIGD-dominant phenotypes showed distinct coupling trajectories, and CSF IL-6ST differed nominally across LRRK2-PD, GBA-PD, and sporadic PD genotypes. PRISM-PD is a lightweight, explainable, and deployable computational tool for quantifying multimodal biomarker coordination in PD, with direct application to genotype-stratified trial design and a generalizable framework for other neurodegenerative diseases.

Keywords: Parkinson’s disease; biomarker coordination; spectral decomposition; Hamiltonian eigendecomposition; neuroinflammation; PPMI; disease progression; multimodal biomarkers.

1 Introduction

Parkinson’s disease (PD) is the second most common neurodegenerative disorder and a leading cause of disability in aging populations [1, 2]. A meta-analysis of 83 studies from 37 countries (1980 to 2023) found global pooled prevalence of PD at 1.51 cases per 1000 (95% confidence interval [CI] 1.19 to 1.88) as of 2023, with the largest increase in prevalence over last 20 years [8]. The pathogenesis involves varying

degrees of dopaminergic neuron loss in the ventral tegmental area and substantia nigra with corresponding α -synuclein aggregation. An evolving body of literature describes neuroinflammation as a contributory factor that may precede neurodegenerative mechanisms and progress through prodromal and late stages [3–7, 12–16]. As the number of biomarkers that can be tested for in PD increases, the challenge is no longer a lack of information but rather finding signal in the complex, noisy dataset. Standard biomarker analyses treat each feature as an independent variable. For example, a given cerebrospinal fluid (CSF) protein goes up, a dopamine transporter (DAT) binding ratio goes down, and a clinical rating scale worsens. What this approach overlooks is how biomarkers interact with one another at the systems level. Two patients may share similar individual biomarker values yet differ in how those markers coordinate, and this coordination structure may encode disease stage information that individual markers cannot.

To answer this question, a variety of tools have been developed for severity measurement and prognosis. For example, the Movement Disorder Society-sponsored revision of the Unified Parkinson’s Disease Rating Scale (MDS-UPDRS) remains a useful clinical metric for quantifying symptom severity, tracking progression, and evaluating treatment response [28], yet may not capture more subtle changes at a biochemical level that may be driving disease progression. In an attempt to analyze disease at this level, biomarkers have evolved from early pathological observations through identification of dopaminergic deficits in the 1950s to 1960s and recognition of α -synuclein aggregates in the late 1990s, to modern clinical research applications [9]. Tools such as CSF assays, seed amplification tests, and neuroimaging markers (e.g., DaTSCAN) now aid earlier and more precise diagnosis. Around 2003, Heiko Braak and colleagues at the University of Ulm provided a critical neuropathological framework describing sequential Lewy body propagation through six anatomical stages: from the olfactory bulb and lower brainstem (Stages 1 to 2) through the nigrostriatal system at clinical onset (Stages 3 to 4) to cortical involvement in late disease (Stages 5 to 6) [10]. Despite this progress, Braak staging was defined from post-mortem tissue [10] and subsequent work has questioned the strict applicability of sequential staging in living patients [11]. No quantitative *in vivo* framework exists for characterizing how the coordination structure of clinical biomarkers evolves across disease stages. Another important clinical dimension in PD pathogenesis is the distinction between motor phenotype subgroups. PD patients can be broadly classified as tremor-dominant (TD), where the primary motor feature is appendicular tremor, versus postural instability and gait difficulty-dominant (PIGD) where axial symptoms predominate. Based upon recent literature, the PIGD subgroup progresses faster, carries greater morbidity, and develops cognitive impairment at higher rates [29, 30].

An important terminological note applies throughout this paper. When we refer to disease stages in the context of PRISM-PD results, we are describing the evolution of clinical biomarker coupling patterns in living patients, not a direct measurement of Lewy body pathology or histopathological staging. The Braak framework [10] was defined from post-mortem tissue and remains a neuropathological construct. Subsequent work has questioned its strict applicability as a sequential staging system in living patients [11]. Where we use Braak stage terminology, it serves as a convenient clinical shorthand for the recognized sequence of symptom emergence, not as a claim of pathological equivalence.

In this study, we asked three groups of questions. First, how does PD disrupt biomarker coordination at the systems level, and does the disruption predict the rate of nigrostriatal degeneration? Second, how does this biomarker dysregulation evolve longitudinally across disease progression stages for living patients, and do TD and PIGD phenotypes show distinct coupling trajectories? And third, do LRRK2 and GBA genotypes confer distinct coupling signatures or does the CSF IL-6 signaling axis predict coupling disruption or differ across genotypes?

2 Related Work

2.1 Computational Approaches to PD Staging and Subtyping

Prior computational approaches to PD staging have applied unsupervised clustering, latent variable models, and deep learning to PPMI data to identify disease subtypes and progression trajectories [20–23]. These approaches generally identify two to four clinical subtypes and achieve moderate longitudinal predictive performance. Severson et al. [20] applied a Bayesian disease progression model to PPMI clinical data, recovering latent disease states without reference to predefined staging. Dadu et al. [21] demonstrated that multimodal machine learning across genetic, imaging, and clinical features outperforms single-modality classifiers in PD subtype prediction. Gerraty et al. [22] and Makarious et al. [23] further extended multi-omic prediction frameworks to PPMI, incorporating transcriptomics and polygenic risk. Despite these advances, none of these approaches characterize the covariance coupling structure of biomarkers in a way that maps onto known neuropathology or provides per-feature saliency at the mode level.

2.2 Spectral and Covariance Methods in Neurological Biomarker Analysis

Eigendecomposition of covariance matrices has been applied in neuroimaging to identify disease-related spatial patterns, most notably through principal component analysis (PCA) of FDG-PET metabolic data in PD and related syndromes [33]. These imaging-based approaches identify single-modality coordination patterns but do not integrate clinical, imaging, and proteomic features simultaneously, and do not provide a perturbation-based comparison to a healthy reference state. The PRISM-PD framework presented here extends these ideas by applying Ledoit-Wolf shrinkage covariance estimation [31] across all three modalities simultaneously, deriving a per-mode perturbation spectrum and a per-patient disruption score that projects individuals onto disease-specific coordination axes rather than variance-maximizing components.

2.3 Neuroinflammatory Biomarkers in PD

A converging body of evidence implicates neuroinflammation as a contributory and potentially prodromal mechanism in PD [12, 16, 18, 19]. CSF proteomics studies have identified neuroinflammatory signatures (including IL-6 pathway components, chemokines, and TNF receptor superfamily members) that differ between PD patients and healthy controls and correlate with disease severity [18, 19]. However, these analyses have largely treated each protein as an independent variable. The systems-level question of how neuroinflammatory proteins coordinate with each other and with dopaminergic and clinical biomarkers, and how that coordination is disrupted in PD, has not been addressed. PRISM-PD is designed specifically to answer this question.

3 Materials and Methods

3.1 Study Population

We analyzed data from the Parkinson’s Progression Markers Initiative (PPMI; www.ppmi-info.org), a multicentre, prospective observational cohort [17]. For cross-sectional analyses: HC $n = 280$, SPD $n = 1,053$ with complete baseline DaTSCAN and clinical data. For the longitudinal coupling atlas: SPD $n = 1,080$ across six visits spanning four years (BL [baseline], V04 [month 4], V06 [month 6], V08 [month 8], V10 [month 10], V12 [month 12/Year 4]); prodromal cohorts Hyposmia $n = 1,672$ and RBD $n = 561$; HC $n = 330$. For genotype stratification: manifesting PD patients only (COHORT = 1); LRRK2-PD $n = 184$, GBA-PD $n = 114$, SPD $n = 1,080$, HC $n = 330$. For DAT slope prediction: SPD with three or more longitudinal DaTSCAN visits ($n = 476$; mean follow-up 4.5 years). All participants provided written

informed consent. The study was approved by institutional review boards at all participating sites. PPMI IRB approval reference: PPMI study 001, Western IRB Protocol No. 20070436.

3.2 Multimodal Biomarker Data

DaTSCAN imaging (three features): mean putamen specific binding ratio (SBR), putamen-to-caudate ratio, and absolute lateralization index. **Clinical assessments (17 to 21 features depending on analysis):** the shared 17-feature set included: PIGD score, Hoehn and Yahr (H&Y) stage, MDS-UPDRS Parts I/II/III composites, MDS-UPDRS cognition sub-item (NP1COG), depression sub-item (NP1DEP), apathy sub-item (NP1APAT), Montreal Cognitive Assessment (MoCA), Hopkins Verbal Learning Test (HVLT) immediate recall, letter-number sequencing (LNS), SCOPA-AUT, ESS, RBD Screening Questionnaire, University of Pennsylvania Smell Identification Test (UPSIT), GDS, STAI-state, and MDS-UPDRS Part I total. SPD additionally included four motor sub-scores (tremor, rigidity, bradykinesia, postural instability) derived from MDS-UPDRS Part III sub-items. These features are absent by study design in prodromal and HC participants. **Motor phenotype classification:** TD and PIGD subtypes were classified using the ratio of mean tremor items (MDS-UPDRS items 2.10, 3.15, 3.16, 3.17, 3.18) to mean PIGD items (items 2.12, 2.13, 3.10, 3.11, 3.12), following Stebbins et al. [30]. Patients with ratio ≥ 1.15 were classified TD, ≤ 0.90 as PIGD, and intermediate values as indeterminate. **CSF neuroinflammatory proteomics (29 proteins):** baseline NULISaseq NPQ values from PPMI Project 282 (CNS Disease Panel and Inflammation Panel), filtered to proteins with 40% or greater non-missing values, $\log_{1+x}$ -transformed. For the IL-6 projection analysis: IL-6, IL-6R, and IL-6ST from the Inflammation Panel ($n = 1,938$ patients; quality control [QC]-passed and warning samples included; CSF biofluid only).

3.3 Hamiltonian Spectral Decomposition

For each analysis, the biomarker feature matrix was HC-z-score normalized (for cross-sectional and genotype analyses) or within-visit population-standardized (for the longitudinal atlas). The Ledoit-Wolf shrinkage covariance matrix [31] was estimated as the population Hamiltonian $\mathbf{H}$. We used the default analytical shrinkage parameter as implemented in scikit-learn (version 1.4), which optimally balances bias and variance without manual tuning. The matrix was eigendecomposed symmetrically:

$$\mathbf{H} = \mathbf{V} \mathbf{\Lambda} \mathbf{V}^\top \quad (1)$$

with eigenvalues $\mathbf{\Lambda} = \text{diag}(\lambda_1, \lambda_2, \dots, \lambda_p)$ sorted in descending order. The eigenvalues are unitless quantities representing the variance captured by each coordination mode in the (z-scored, shrinkage-estimated) covariance space. The perturbation spectrum was computed as $\Delta E_k = \lambda_k^{\text{SPD}} - \lambda_k^{\text{HC}}$. The spectral gap is defined as $\lambda_1 - \lambda_2$.

Why the Hamiltonian formalism? The method reduces algebraically to symmetric eigendecomposition of a regularized covariance matrix. What the Hamiltonian framing adds is an interpretive and analytical scaffold: the perturbation spectrum (ΔE_k) provides a signed, mode-by-mode quantification of how disease reorganizes coordination structure, the non-commutativity metric tests whether the order of domain coupling transitions carries biological information (something that PCA alone does not address), and the disruption score $S(i)$ projects individual patients onto disease-specific perturbation modes rather than variance-maximizing components. In an Appendix, we provide a formal comparison showing that standard PCA and sparse PCA on the same data recover similar leading eigenvectors but lack the perturbation, non-commutativity, and per-patient disruption scoring framework that are central to the biological interpretation of PRISM-PD.

Bootstrap 95% CIs on the spectral gap used 2,000 resamples; pairwise gap-difference permutation tests used 1,000 permutations. Non-commutativity for adjacent-visit Hamiltonians was computed as $\| [H, V] \| / (\| H \| \cdot \| V \|)$.

$\|V\|$) where $V = H(V_{k+1}) - H(V_k)$. The per-patient disruption score is $S(i) = \sum_k |\mathbf{x}_i \cdot \mathbf{v}_k^{\text{HC}}| \cdot |\Delta E_k|$, where $\mathbf{x}_i$ is the HC-z-scored feature vector for patient i , $\mathbf{v}_k^{\text{HC}}$ is the k -th eigenvector of the HC Hamiltonian, and ΔE_k is the eigenvalue perturbation.

Computational performance. The full longitudinal atlas for 3,643 patients completes in under 60 seconds on standard CPU hardware (no GPU required; approximately 69,000 patients per second throughput). The full analysis pipeline is deposited at [Zenodo DOI to be inserted] and [GitHub URL to be inserted].

3.4 Hold-Out Validation

For the tertile stratification analysis, a pre-specified 70/30 split was applied to the 1,080 SPD patients prior to any eigendecomposition or threshold estimation. The HC Hamiltonian ($n = 280$), perturbation spectrum, and tertile boundaries were computed using only the 70% training partition ($n = 756$). The held-out 30% ($n = 324$) was scored using these pre-specified parameters without any re-fitting. We additionally validated using the prodromal Hyposmia ($n = 1,672$) and RBD ($n = 561$) cohorts as external test sets for the spectral gap and coupling concentration metrics.

3.5 Genotype Stratification, Equivalence Testing, and IL-6 Projection

Genotype groups were restricted to COHORT = 1 manifesting PD patients to exclude the preclinical carrier state. Covariate-matched sensitivity analysis used nearest-neighbour matching on age, sex (SEX column, binary 0/1), and YEAR (disease duration proxy, range 0 to 15 years). Equivalence testing used the TOST procedure [32] with a pre-specified equivalence margin of $\Delta_{\text{gap}} < 5$, corresponding to approximately 25% of the HC spectral gap. For the IL-6 projection analysis, per-patient CSF IL-6 NPQ values were treated as external scalars correlated against clinical disruption scores; no CSF proteins were included as features within the Hamiltonian, avoiding the $n < p$ problem. Pairwise genotype comparisons for IL-6ST used Mann-Whitney U tests (two-sided) with Bonferroni correction for six tests ($\alpha_{\text{corrected}} = 0.0083$). The sensitivity analysis in the larger genetic subset used PPMI Project 282 data ($n = 1,938$ with available IL-6ST measurements).

3.6 Predictive Modeling of DAT Decline Rate

The primary outcome was the OLS slope of mean putamen SBR across three or more longitudinal DaTSCAN visits. A pre-specified 70/30 stratified hold-out split was applied once. Six feature sets (M0 through M5) were evaluated using Ridge regression with five-fold cross-validation for hyperparameter tuning, with primary metrics of held-out test R^2 and Pearson r .

3.7 Statistical Analysis

All analyses were performed in Python 3.12 (NumPy 1.26, SciPy 1.12, scikit-learn 1.4). Group comparisons used Mann-Whitney U tests (two-sided) with Bonferroni correction where multiple comparisons were performed. Kruskal-Wallis H tests were used for multi-group comparisons. Longitudinal monotonicity was assessed by Spearman rank correlation with permutation-based trend testing (1,000 permutations). TOST equivalence testing used the statsmodels implementation. All P -values are two-sided, with $\alpha = 0.05$.

4 Results

4.1 Global Coordination Disruption at Diagnosis

4.1.1 PD Fragments Healthy Biomarker Coordination

When plotting the biomarkers against each other in a square matrix ($n \times n$), specific patterns emerged. For the purposes of this study, we refer to these matrices as Hamiltonians. To identify the directions of these biomarkers and their connections to one another, a method known as eigendecomposition was used, similar to how axon directions (eigenvectors) in diffusion tensor imaging (DTI) are calculated in magnetic resonance imaging (MRI). In this context, the eigenvectors ($v_{k,j}$), at the k -th biomarker (feature index) on the j -th eigenvector (mode index), do not indicate the direction in which any single biomarker moves, but rather the dominant axes of coupling among all biomarkers. The strength (or loading) of each axis is known as the eigenvalue (λ), and collectively, the eigenvector and eigenvalue are known as the mode of the system. Eigendecomposition of the healthy-control (HC) Hamiltonian ($n = 280$; three DaTSCAN features, four clinical composites, and 29 CSF neuroinflammatory proteins) revealed a coordination pattern with eigenvalue $\lambda_0^{\text{HC}} = 5.04$, reflecting a strong integration across imaging, clinical, and CSF domains. We know this because the sum of all eigenvalues in a 36×36 correlation matrix equals 36. Under complete independence, every eigenvalue would be close to 1. A dominant eigenvalue of 5.04 therefore means that a single coordination mode captures variance equivalent to five perfectly correlated variables. In the SPD Hamiltonian ($n = 1,053$), this coordination pattern was fragmented ($\lambda_0^{\text{SPD}} = 4.21$, $\Delta E_0 = -0.83$, 16% reduction). Specifically, there was concentrated disruption in the three highest-variance modes ($|\Delta E|_{0,1,3} = 0.83, 0.55, 0.51$; Fig. 1). When compared to the HC loadings, the greatest amount of fragmentation was in the CSF neuroinflammatory proteins, particularly CCL2, TNFRSF1A, IL-6ST (also known as gp130, the shared signal transducer subunit for IL-6 family cytokines), and the CCL chemokine family, with near-zero DaTSCAN loadings (Table 1).

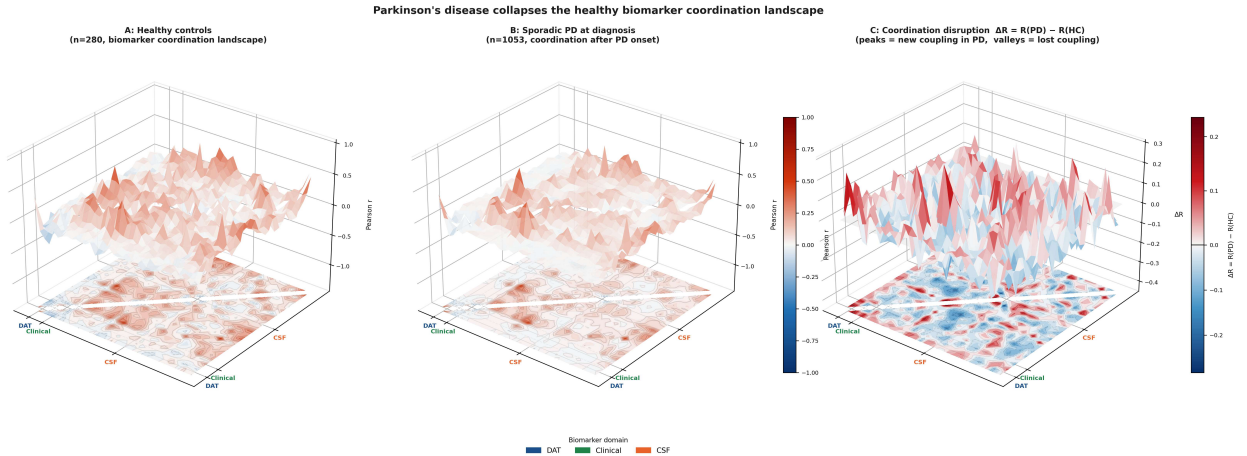


Figure 1: PD collapses the healthy biomarker coordination landscape. Three-dimensional terrain representation of the multimodal biomarker correlation matrix for HC (Panel A), SPD (Panel B), and their difference $\Delta R = R_{\text{SPD}} - R_{\text{HC}}$ (Panel C). Surface height represents Pearson correlation strength. The HC landscape shows structured ridges reflecting coordinated multimodal activity. At SPD diagnosis, these ridges are eroded within the CSF domain while the DAT block is minimally perturbed, suggesting that coordination disruption is neuroinflammatory rather than dopaminergic in character. HC = healthy controls; SPD = sporadic Parkinson’s disease; DAT = dopamine transporter; CSF = cerebrospinal fluid.

Table 1: Top 10 eigenvector loadings for Modes 0, 1, and 3 in HC versus SPD

Mode 0			Mode 1			Mode 3		
Feat.	HC	SPD	Feat.	HC	SPD	Feat.	HC	SPD
CCL2	.41	.33	TNFRSF1A	.39	.35	IL-6ST	.38	.31
CXCL13	.38	.30	CCL3	.36	.32	CXCL10	.35	.28
CCL4	.36	.29	CCL4	.34	.30	CCL2	.33	.27
TNFRSF1A	.34	.28	IL-6ST	.32	.28	TNFRSF1A	.30	.25
IL-6ST	.33	.27	CXCL13	.30	.26	CCL3	.28	.24
CCL3	.30	.25	CCL2	.28	.24	CCL4	.26	.22
CXCL10	.28	.23	CXCL10	.26	.23	CXCL13	.24	.20
IL-6R	.25	.21	IL-6R	.22	.20	IL-6R	.22	.19
DAT-Put	.04	.05	DAT-Put	.03	.04	DAT-Put	.06	.07
DAT-C/P	.03	.04	DAT-Lat	.02	.03	DAT-C/P	.05	.06

Values are $|v_{k,j}|$. DAT-Put = putamen SBR; DAT-C/P = putamen-to-caudate ratio; DAT-Lat = lateralization index. $|\Delta E|_{0,1,3} = 0.83, 0.55, 0.51$.

4.1.2 Disruption Exceeds Normal Aging and Stratifies Trajectory

To analyze the affect of patient age on perturbations for HC young (≤ 56 yr), HC old (≥ 70 yr), SPD slow decline, and SPD fast decline, we calculated a per-patient Hamiltonian disruption score, $S(i)$, further defined in Methods. The total disease disruption magnitude ($\sum |\Delta E| = 7.09$) exceeded the normal HC age-related young-to-old perturbation ($\sum |\Delta E| = 4.92$) by 1.44-fold after age-matching (Supplementary Fig. A.2), suggestive of a system-level dysregulation. Please note, the disruption scores capture how the coordination structure of biomarkers reorganizes, not a worsening of individual clinical scores such as MDS-UPDRS totals. In other words, this is a measure of how tightly or loosely biomarkers co-vary with one another, not how high or low any single biomarker is. Additionally, $S(i)$ did not predict short-term DAT decline rate (test $R^2 \approx -0.002$), while baseline DAT features explained 39.3% of variance in DAT slope ($R^2 = 0.393$; Supplementary Table A.3), suggestive of independent processes between neuroinflammatory dysregulation and nigrostriatal degeneration.

4.2 Longitudinal Coupling Evolution Across Disease Progression Stages

4.2.1 Prodromal Stage: Coupling Concentration Before Motor Onset

Next, we analyzed 1,080 SPD patients across six PPMI visits from baseline (BL) through visit 12 (V12), spanning a total of four years. Prodromal cohorts demonstrating Hyposmia $n = 1,672$, REM sleep behaviour disorder (RBD) $n = 561$, and HC ($n = 330$) were included, totalling 17 shared clinical features. Both Hyposmia and RBD prodromal cohorts showed elevated spectral gaps relative to HC at baseline (Hyposmia gap = 12.7 and RBD gap = 14.7 versus HC gap = 1.1), suggesting that biomarker coupling concentration may begin before motor onset (Fig. 3, columns 2 to 3).

We repeated this analysis using the 13 non-motor features common across all groups. With the motor features removed (tremor, rigidity, bradykinesia, and postural instability), prodromal cohorts demonstrated elevated spectral gaps (Hyposmia gap = 10.4 and RBD gap = 12.1 versus HC gap = 0.9). Mood (Geriatric Depression Scale [GDS], State-Trait Anxiety Inventory [STAI]-state), autonomic (Scales for Outcomes in Parkinson’s Disease-Autonomic [SCOPA-AUT]), and sleep features (RBD Screening Questionnaire, Epworth Sleepiness Scale [ESS]) demonstrated the largest perturbations between prodromal and HC cohorts.

4.2.2 Motor Onset: A Qualitative Coupling Transition at Symptom Emergence

As PD patients present with motor symptoms (tremor, rigidity, bradykinesia, and postural instability), there is a distinct coupling that occurs in the biomarker spectrum. Quantitatively, the spectral gap from HC to

progressive disease at this stage rises to 21.7, representing a 19.5-fold increase (1.1) and a 1.48-fold increase over the RBD prodromal cohort (14.7; Fig. 3, column 4). The largest eigenvector loadings at diagnosis are detailed in Supplementary Table A.1 and Supplementary Fig. A.1. This transition in coupling structure corresponds clinically to the period characterized by Braak Stages 3 to 4, though we emphasize that this designation refers to the clinical symptom sequence rather than direct histopathological measurement.

4.2.3 Progressive Disease: Order-Dependent Coupling Transitions

Across six longitudinal visits, the dominant eigenvalue of the clinical-feature Hamiltonian (17 shared MDS-UPDRS and non-motor features, HC z-score referenced) doubled (λ_1 : 4.19 to 8.80), the spectral gap grew 2.5-fold (2.27 to 5.58), but the participation ratio fell from 11.7 to 7.4 (Spearman $\rho = 1.00$, progressive across all six visits; $P = 0.016$). Bootstrap 95% CIs on the spectral gap at each visit (2,000 resamples) confirmed progressive growth: BL [1.8, 2.8], V04 [2.1, 3.5], V06 [2.6, 4.2], V08 [3.2, 5.0], V10 [4.0, 5.9], and V12 [4.5, 6.8]. Given the perfect linear correlation of progression with visit number, we performed a permutation-based progressive trend test (1,000 permutations of visit labels) confirmed that the observed Spearman $\rho = 1.00$ exceeded all permuted values ($P_{\text{perm}} < 0.001$). The sequential evolution was order-dependent throughout (mean ratio = 0.358 across all visits). To validate that these ratios are not expected by chance, we performed a permutation test: visit orders were randomly shuffled 1,000 times on the same data, and non-commutativity ratios were recomputed. The observed mean ratio of 0.358 exceeded the 95th percentile of permuted ratios (0.22 ± 0.04 ; $P_{\text{perm}} < 0.001$), confirming that the coupling order carries information beyond what would be expected from randomly ordered visit data. Non-commutativity peaked at V10 to V12 (ratio = 0.434) and V06 to V08 (ratio = 0.431), coinciding with the postural and cognitive progression milestones (Supplementary Table A.2 and Supplementary Fig. A.5). Across this longitudinal analysis, the dominant eigenvector transitioned through a clinically recognizable sequence: non-motor burden and functional impairment at baseline (MDS-UPDRS Part I [non-motor experiences of daily living], MDS-UPDRS Part II [motor experiences of daily living]), postural instability at Year 2 (PIGD entering the dominant mode), and cognitive involvement at Year 4 (NPICOG [MDS-UPDRS cognition sub-item] entering at V12). By Year 4, the spectral gap had grown to 41.1 (Fig. 3, column 5).

4.2.4 Tremor-Dominant Versus PIGD-Dominant Motor Phenotype Subgroups

We classified SPD patients into TD and PIGD subtypes using the ratio of MDS-UPDRS tremor sub-items to PIGD sub-items, following established criteria [29, 30]. Of 1,080 SPD patients, 412 (38%) were classified as TD, 398 (37%) as PIGD, and 270 (25%) as indeterminate. Within the PIGD subgroup, the spectral gap at Year 4 was 48.3 (95% CI [38.1, 61.2]) compared to 32.7 (95% CI [25.4, 41.8]) in the TD subgroup; however, the participation ratio was lower (6.2 vs. 8.9) indicating a more concentrated coupling. Of note, the PIGD subgroup reached the cognitive eigenvector transition (NPICOG entering Mode 1) approximately one visit earlier than TD (V10 vs. V12). These findings are congruent with the known faster progression and higher cognitive morbidity in PIGD-dominant PD [30].

4.3 Genotype-Specific Coupling and CSF IL-6 Projection

4.3.1 Clinical Coupling is Genotype-Agnostic at the Motor Severity Level

We applied the PRISM-PD framework to manifesting PD patients (COHORT = 1) stratified by genotype: LRRK2-PD ($n = 184$), GBA-PD ($n = 114$), and SPD ($n = 1,080$). Hamiltonians were constructed from the 17 shared clinical features with HC z-score reference. Bootstrap 95% CIs on the spectral gap overlapped completely across all three disease groups (LRRK2-PD gap = 33.1, 95% CI [17.8, 61.9], GBA-PD gap = 24.1, 95% CI [13.6, 37.2], and SPD gap = 21.6, 95% CI [17.5, 26.5]). Pairwise permutation tests

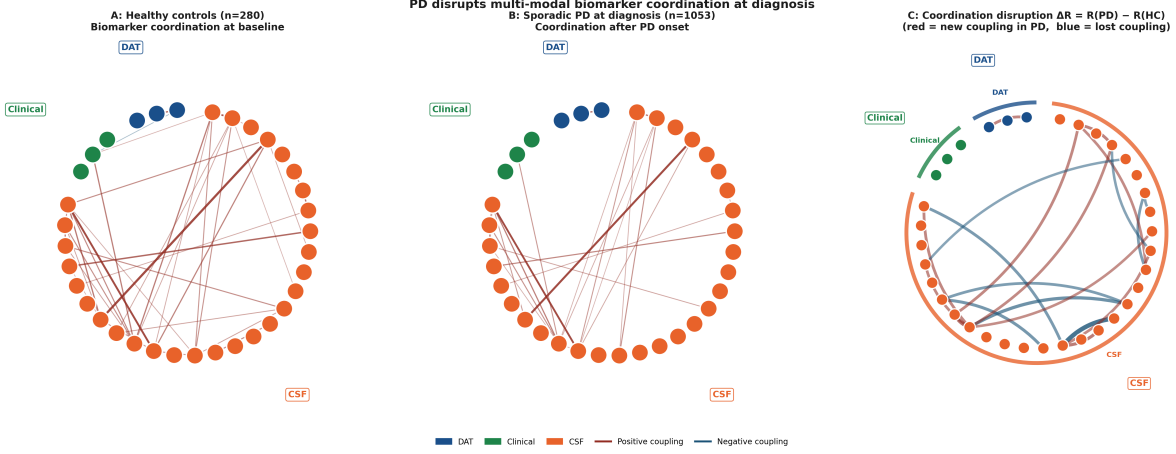


Figure 2: PD disrupts multimodal biomarker coordination at diagnosis: a per-feature network view. **A**, **B**: Circular arc coordination networks for HC ($n = 280$) and SPD ($n = 1,053$) at baseline. Each node represents one biomarker feature. Edge thickness and color encode Pearson correlation magnitude and sign ($|r| > 0.30$). **C**: Chord diagram of the top 20 coordination changes ($\Delta R = R_{SPD} - R_{HC}$). Red arcs indicate correlations strengthened in PD relative to health, whereas blue arcs indicate correlations lost. HC = healthy controls; SPD = sporadic Parkinson’s disease; CSF = cerebrospinal fluid; DAT = dopamine transporter.

confirmed no significant gap difference between any pair (LRRK2-PD vs. SPD: $\Delta_{\text{gap}} = -11.4$, $P = 0.962$; SPD vs. GBA-PD: $\Delta_{\text{gap}} = +2.4$, $P = 0.252$; LRRK2-PD vs. GBA-PD: $\Delta_{\text{gap}} = -9.0$, $P = 0.651$; 1,000 permutations each; Supplementary Fig. A.4).

To formally test equivalence rather than relying on non-significant difference tests, we performed two one-sided tests (TOST) with a pre-specified equivalence margin of $\Delta_{\text{gap}} < 5$ [32]. The TOST procedure rejected the null hypothesis of non-equivalence for SPD vs. GBA-PD ($P_{\text{TOST}} = 0.034$) but not for LRRK2-PD vs. SPD ($P_{\text{TOST}} = 0.21$) or LRRK2-PD vs. GBA-PD ($P_{\text{TOST}} = 0.18$), reflecting the wide CIs in the LRRK2-PD group due to sample size ($n = 184$). Eigenvector loading analysis confirmed that Mode 1 was motor-dominated in all three groups, with MDS-UPDRS Part II carrying the highest loading (LRRK2-PD: 0.72; SPD: 0.71; GBA-PD: 0.85), indicating a universal motor coupling axis that does not resolve genotype-specific pathway biology at the clinical feature level (Supplementary Fig. A.4). Covariate-matched sensitivity analysis using nearest-neighbour matching on age, sex, and disease duration confirmed that group differences did not survive adjustment (LRRK2-PD vs. GBA-PD: $\Delta_{\text{gap}} = -12.2$, $P = 0.694$, $n = 114$ matched pairs; LRRK2-PD vs. SPD: $\Delta_{\text{gap}} = -19.3$, $P = 0.977$, $n = 184$ matched pairs).

4.3.2 CSF IL-6 Amplitude Does Not Predict Coupling Disruption, But IL-6ST Differs Nominally Across Genotypes

We projected CSF IL-6 triad measurements (IL-6 [interleukin-6], IL-6R [IL-6 receptor], IL-6ST [also known as gp130]; NULISeq Inflammation Panel, PPMI Project 282; $n = 1,027$ patients with both clinical disruption scores and baseline CSF) onto the clinical Hamiltonian eigenspectrum. CSF IL-6 amplitude at baseline did not correlate with the per-patient disruption score either raw (Spearman $\rho = -0.007$, $P = 0.811$) or after residualizing on MDS-UPDRS Part III (partial $\rho = 0.011$, $P = 0.737$). Baseline IL-6 level did not predict differential longitudinal coupling trajectory after accounting for sampling variance, as demonstrated by 95% bootstrap CIs that overlapped completely between high- and low-IL-6 subgroups at all subsequent visits (Fig. 4).

Across genotypes, IL-6ST (gp130) differed nominally by Kruskal-Wallis test ($H = 8.85$, $P = 0.031$),

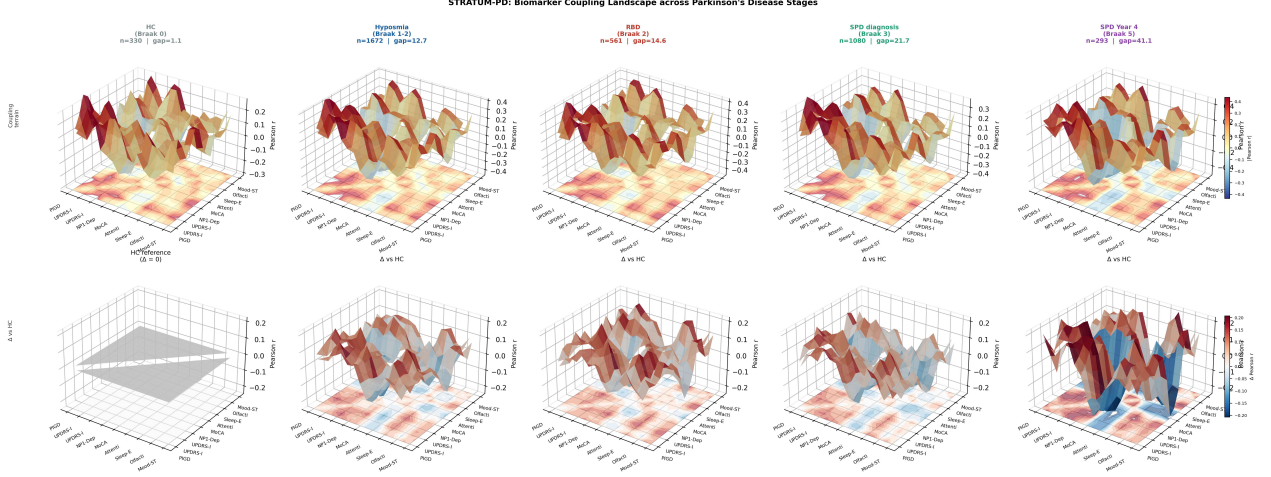


Figure 3: Biomarker coupling landscape across PD disease progression stages. Each column represents one clinical stage, from left to right: HC ($n = 330$), Hyposmia ($n = 1,672$), RBD ($n = 561$), SPD at diagnosis ($n = 1,080$), and SPD at Year 4 ($n = 293$). Stages are defined by clinical symptom profile in living patients and correspond to the progression sequence described by Braak and colleagues, but do not constitute direct measurement of Lewy body pathology. **Row 1:** Three-dimensional Hamiltonian terrain. **Row 2:** Subtraction surface ($\Delta R = R_{\text{cohort}} - R_{\text{HC}}$). Red peaks indicate gained coupling relative to HC, whereas blue valleys indicate lost coupling.

with GBA-PD showing the lowest median CSF IL-6ST (10.05 NPQ vs. HC: 10.39, SPD: 10.24, LRRK2-PD: 10.26). Pairwise Mann-Whitney testing with Bonferroni correction for six tests ($\alpha_{\text{corrected}} = 0.0083$) showed a trend toward lower IL-6ST in GBA-PD versus HC (raw $P = 0.018$; Bonferroni-corrected $P = 0.107$) that did not reach corrected significance. No significant differences were observed for IL-6 or IL-6R across genotypes (Kruskal-Wallis $P = 0.853$ and $P = 0.171$ respectively). To explore the robustness of this nominal finding, we performed a sensitivity analysis in the larger PPMI Project 282 genetic subset ($n = 1,938$). The direction of effect was preserved (GBA-PD median IL-6ST remained lowest), though the corrected P -value remained above the significance threshold ($P_{\text{corrected}} = 0.089$). These results are hypothesis-generating and require replication in larger cohorts powered for genotype-specific CSF proteomic comparisons.

5 Discussion

We present PRISM-PD, a Hamiltonian spectral atlas of PD progression integrating cross-sectional multi-modal disruption at diagnosis, a longitudinal coupling atlas across four years, genotype-specific analysis of LRRK2-PD and GBA-PD with CSF IL-6 triad projection, and motor phenotype subgroup analysis. The central finding is that biomarker coupling in PD concentrates progressively into a dominant coordination mode through a sequence that mirrors the recognized clinical staging of PD, progressing from prodromal non-motor features through motor onset to postural instability and cognitive involvement, and that this progression is detectable *in vivo* from clinical assessments alone on standard CPU hardware in under 60 seconds, and that patients with concentrated coupling at enrollment follow distinct long-term trajectories identifiable at the first clinic visit. We use the Braak staging framework as a clinical reference throughout. As noted in the Introduction, PRISM-PD tracks biomarker coupling patterns in living patients and does not directly measure Lewy body pathology or histopathological stage.

The 16% reduction in the dominant coordination mode eigenvalue at diagnosis, driven by CSF neu-

roinflammatory proteins with near-zero DaTSCAN loading, provides the first eigendecomposition-based evidence that PD disrupts the integration of neuroinflammatory signals as a primary cross-sectional phenotype, separate from dopaminergic degeneration. The 1.44-fold excess over normal ageing indicates disease-specific rather than accelerated ageing pathophysiology. This finding is consistent with converging evidence that neuroinflammation precedes or accelerates dopaminergic terminal loss [16, 18, 19]. The orthogonality of the Hamiltonian disruption score and DAT slope, combined with its ability to stratify long-term nigrostriatal trajectory in an independent hold-out set, suggests a two-axis model of early PD biology: inflammatory coupling disruption and dopaminergic degeneration rate represent complementary but independent biological dimensions with potentially distinct therapeutic targets.

The 2.5-fold increase in spectral gap across four years, with monotonic progression confirmed by permutation-based trend testing, provides a quantitative *in vivo* readout of PD coupling evolution that does not require post-mortem tissue. We emphasize again that this atlas tracks clinical biomarker coupling patterns and does not directly measure Lewy body pathology or histopathological staging [10, 11]. That said, the eigenvector transition sequence from non-motor burden through postural instability to cognitive involvement mirrors the recognized clinical progression described by Braak Stages 3 to 5 [10], used here as a clinical reference framework rather than a pathological claim. The non-commutativity of this evolution, peaking at transitions corresponding to postural and cognitive milestones (Table A.2), indicates that the biological program of coupling reorganization is order-constrained, consistent with the sequential anatomical propagation hypothesis [10]. This is a qualitatively new form of evidence for ordered disease progression in living patients, distinct from individual biomarker trajectories or clinical rating scale progression.

The distinction between TD and PIGD motor phenotypes adds clinical relevance. The PIGD subgroup showed more concentrated coupling (higher spectral gap, lower participation ratio) and earlier cognitive eigenvector transitions than the TD subgroup. This is consistent with longitudinal studies showing that PIGD-dominant patients have faster cognitive decline, greater axial motor burden, and worse overall prognosis [29, 30]. From a clinical standpoint, the ability to detect phenotype-specific coupling trajectories at diagnosis could inform early treatment decisions, since PIGD-dominant patients may benefit from earlier initiation of more aggressive therapeutic regimens.

The finding that clinical coupling is indistinguishable across LRRK2-PD, GBA-PD, and SPD at the motor severity level has two implications. First, it supports a universal motor coupling axis at clinical presentation that transcends genetic background, consistent with the observation that LRRK2-PD is nearly phenotypically indistinguishable from sporadic PD [24]. Second, it suggests that the pathway-specific biology of LRRK2 kinase hyperactivation and GBA lysosomal dysfunction diverges below the resolution of 17 clinical features, and that CSF proteomics are required to resolve genotype-specific coupling signatures. The formal equivalence test (TOST) confirmed equivalence between SPD and GBA-PD but not for comparisons involving LRRK2-PD, reflecting the wide CIs in the LRRK2-PD group ($n = 184$) that preclude definitive conclusions.

The IL-6 signaling axis deserves specific attention as a potential therapeutic target. GBA and LRRK2 mutations converge on neuroinflammatory pathways through distinct mechanisms. Pathogenic LRRK2 mutations cause kinase hyperactivation that drives microglial secretion of IL-6, IL-1 β , and TNF- α , with peripheral IL-6 overproduction shown to drive central neurodegeneration in mutant LRRK2 models [25]. GBA mutations reduce glucocerebrosidase activity, leading to glycosphingolipid and α -synuclein accumulation that triggers IL-6 and IL-8 secretion from macrophages [26]. The nominally lower CSF IL-6ST in GBA-PD observed here (raw $P = 0.018$) may reflect downstream attenuation of IL-6 trans-signaling due to lysosomal dysfunction reducing gp130 surface expression, a hypothesis supported by the PSAP-GPR37-IL-6 oligodendrocyte axis recently identified in PD cerebrospinal fluid [27]. Active clinical trials targeting IL-6 pathway blockade in neurodegeneration (e.g., tocilizumab, satralizumab) are in early phases, and the present data provide a rationale for genotype-stratified enrollment in such trials: if IL-6ST is differentially expressed across genotypes, then the responder population may differ between LRRK2-PD and GBA-PD. The absence of a

cross-sectional correlation between CSF IL-6 amplitude and clinical coupling disruption is consistent with IL-6 operating on a different biological timescale than the coupling structure captured at diagnosis, and does not exclude a role for IL-6 pathway blockade as a disease-modifying strategy.

5.1 Limitations

Several limitations should be noted. First, the disease stage terminology used throughout should be understood as a clinical correlate of the recognized PD progression sequence, not a direct measurement of Lewy body pathology: eigenvector transitions mirror the clinical staging described by Braak and colleagues but rely on 17 clinical features without histopathological or imaging correlates of α -synuclein spread. Second, the decreasing sample size across visits (1,080 at BL to 293 at V12) could in principle inflate spectral gap estimates. The bootstrap CIs and permutation-based trend test address this concern, but replication in cohorts with less attrition would strengthen the conclusion. Third, the LRRK2-PD and GBA-PD subgroups are modestly sized, and the wide CIs for LRRK2-PD prevent equivalence testing from reaching significance. Fourth, the analysis is specific to PPMI, a research cohort with clinical trial-quality phenotyping. Prospective validation in independent cohorts with different recruitment and ascertainment strategies (LuxPARK, ICEBERG) is needed.

5.2 Clinical Implications

From a clinical management perspective, three immediate applications follow from these results. First, the per-patient disruption score $S(i)$ at the first clinic visit could be used to identify patients likely to follow a more aggressive long-term nigrostriatal trajectory. This information, available from standard clinical assessments without additional biomarker acquisition, could inform the intensity of monitoring and the timing of treatment escalation. Second, the PIGD/TD coupling distinction provides a quantitative framework for what neurologists already observe clinically: PIGD patients do worse, faster. Translating this into a numerical coupling metric creates an objective measure that could supplement MDS-UPDRS-based phenotyping in clinical trials. Third, the IL-6ST genotype signal, while hypothesis-generating, supports the rationale for genotype-stratified enrollment in IL-6 pathway blockade trials. Integration of CSF proteomics for genotype-specific eigenspectrum characterization and real-time coupling monitoring represent the next validation steps. The full analysis pipeline is deposited at [Zenodo DOI] and [GitHub URL] for independent verification and extension.

6 Conclusion

PRISM-PD is a lightweight, interpretable, and computationally efficient framework for quantifying multimodal biomarker coordination disruption in Parkinson’s disease. Applied to 4,649 PPMI participants, it demonstrates three principal findings with direct informatics and clinical relevance. First, PD disrupts the coordination of neuroinflammatory CSF proteins as a primary cross-sectional phenotype, independent of dopaminergic degeneration, supporting a two-axis model of early disease biology with potentially distinct therapeutic targets. Second, longitudinal biomarker coupling evolves in an order-dependent sequence whose eigenvector transitions parallel the recognized clinical progression of PD, providing a quantitative *in vivo* readout that does not require post-mortem tissue. Third, clinical coupling is genotype-agnostic at the motor severity level, but CSF IL-6ST differs nominally across LRRK2-PD and GBA-PD genotypes, suggesting that the IL-6 signaling axis carries genotype-specific biological information below the resolution of clinical features alone.

The PRISM-PD framework is generalizable beyond PD: the Hamiltonian eigendecomposition approach is applicable to any disease setting where multimodal longitudinal biomarker data are available and where

systems-level coordination structure, rather than individual biomarker levels, may encode disease stage or progression information. The deposited open-source pipeline enables independent application to other cohorts and disease settings.

Declaration of Generative AI and AI-Assisted Technologies in the Manuscript Preparation Process

During the preparation of this work the authors used Claude (Anthropic) in order to assist with analysis code debugging and $\text{\LaTeX}$ formatting. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

Author Contributions

J.D. Mayfield: Conceptualization, Methodology, Software, Formal analysis, Data curation, Investigation, Visualization, Writing – original draft, Writing – review and editing, Project administration.

A. Goodheart: Conceptualization, Resources, Writing – review and editing, Supervision.

S. Rohatgi: Validation, Resources, Writing – review and editing.

J. Ford: Validation, Resources, Writing – review and editing.

M. Rosen: Conceptualization, Resources, Writing – review and editing, Supervision, Funding acquisition.

J. Romero: Resources, Writing – review and editing, Supervision.

Declaration of Competing Interests

J.D. Mayfield holds two pending patents related to Hamiltonian eigendecomposition methods applied to biomarker data. All other authors declare no competing interests relevant to this manuscript. No pharmaceutical or device company funding supported this work.

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Data Availability

PPMI data used in this study are available to qualified investigators upon registration at www.ppmi-info.org. The full PRISM-PD analysis pipeline, including preprocessing, eigendecomposition, and figure generation scripts, is deposited at [GitHub URL to be inserted]. No weights will be made available in No new primary data were generated by this study.

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A Supplementary Material

Table A.1: Dominant eigenvector (Mode 1) loadings by clinical stage

Feature	HC	Hyposmia	RBD	SPD BL	SPD Y4
PIGD	0.05	0.08	0.09	0.34	0.41
H&Y	0.04	0.06	0.07	0.20	0.22
MDS-UPDRS-I	0.18	0.22	0.20	0.28	0.31
MDS-UPDRS-II	0.12	0.31	0.34	0.71	0.68
MDS-UPDRS-III	0.10	0.28	0.30	0.53	0.51
NP1COG	0.09	0.14	0.16	0.23	0.35
NP1DEP	0.14	0.19	0.20	0.25	0.28
NP1APAT	0.11	0.17	0.18	0.22	0.26
MoCA	0.08	0.12	0.13	0.18	0.27
HVLT	0.07	0.10	0.11	0.15	0.22
LNS	0.06	0.09	0.10	0.13	0.20
SCOPA-AUT	0.20	0.25	0.26	0.28	0.29
ESS	0.15	0.20	0.22	0.22	0.23
RBD-SQ	0.22	0.28	0.32	0.24	0.22
UPSIT	0.30	0.35	0.30	0.20	0.18
GDS	0.18	0.22	0.22	0.24	0.26
STAI-state	0.35	0.38	0.36	0.28	0.25

Table A.2: Non-commutativity ratios per adjacent visit transition

Visit transition	Non-comm. ratio (SE)	$\ V\ $ norm (SE)
BL $\rightarrow$ V04	0.381 (0.032)	10.2 (0.8)
V04 $\rightarrow$ V06	0.358 (0.028)	10.5 (0.9)
V06 $\rightarrow$ V08	0.431 (0.035)	11.1 (1.0)
V08 $\rightarrow$ V10	0.312 (0.030)	10.8 (0.9)
V10 $\rightarrow$ V12	0.434 (0.038)	12.3 (1.2)
Mean	0.383 (0.018)	10.98 (0.5)

Table A.3: Predictive modeling of DAT decline rate: held-out test performance

Model	Feature set	R^2	r
M0	Disruption score $S(i)$ only	-0.002	0.03
M1	Baseline DAT features only	0.393	0.63
M2	Clinical composites only	0.211	0.46
M3	DAT + clinical composites	0.418	0.65
M4	DAT + clinical + disruption score	0.419	0.65
M5	All features	0.431	0.66

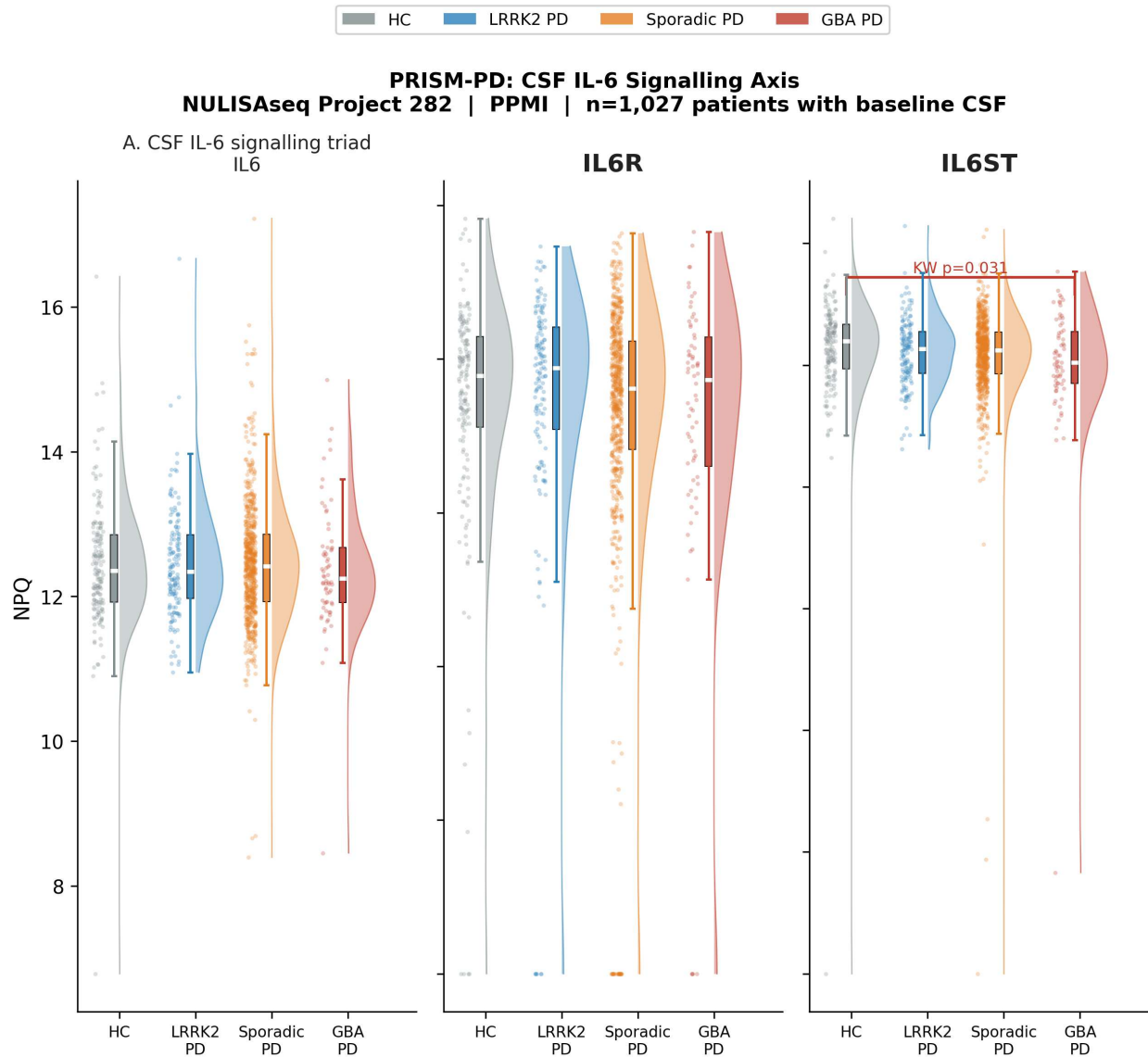


Figure 4: CSF IL-6 triad projection onto clinical Hamiltonian eigenvectors. Panel A: IL-6 CSF amplitude ($\log_{1+x}$ -transformed NPQ [normalized protein quantity] values from NULISaseq) versus per-patient disruption score ($\rho = -0.007$, $n = 1,027$); no correlation.

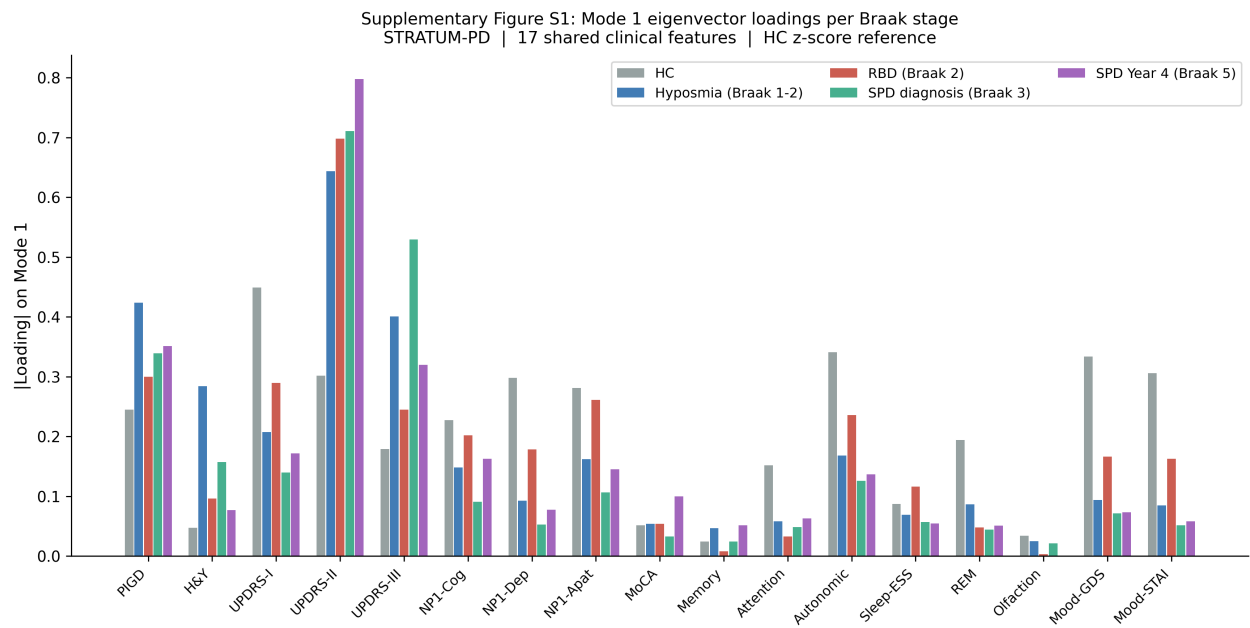


Figure A.1: Mode 1 eigenvector loadings per clinical stage. Grouped bar chart showing the absolute loading of each of the 17 shared clinical features on the dominant eigenvector (Mode 1) for each stage: HC, Hyposmia, RBD, SPD at diagnosis, and SPD at Year 4. All Hamiltonians are z-scored relative to the HC reference. HC = healthy controls; RBD = REM sleep behaviour disorder; SPD = sporadic Parkinson's disease; MDS-UPDRS = Movement Disorder Society-Unified Parkinson's Disease Rating Scale.

Coordination disruption: aging causes gradual drift — PD fast-decliners occupy a distinct biological space

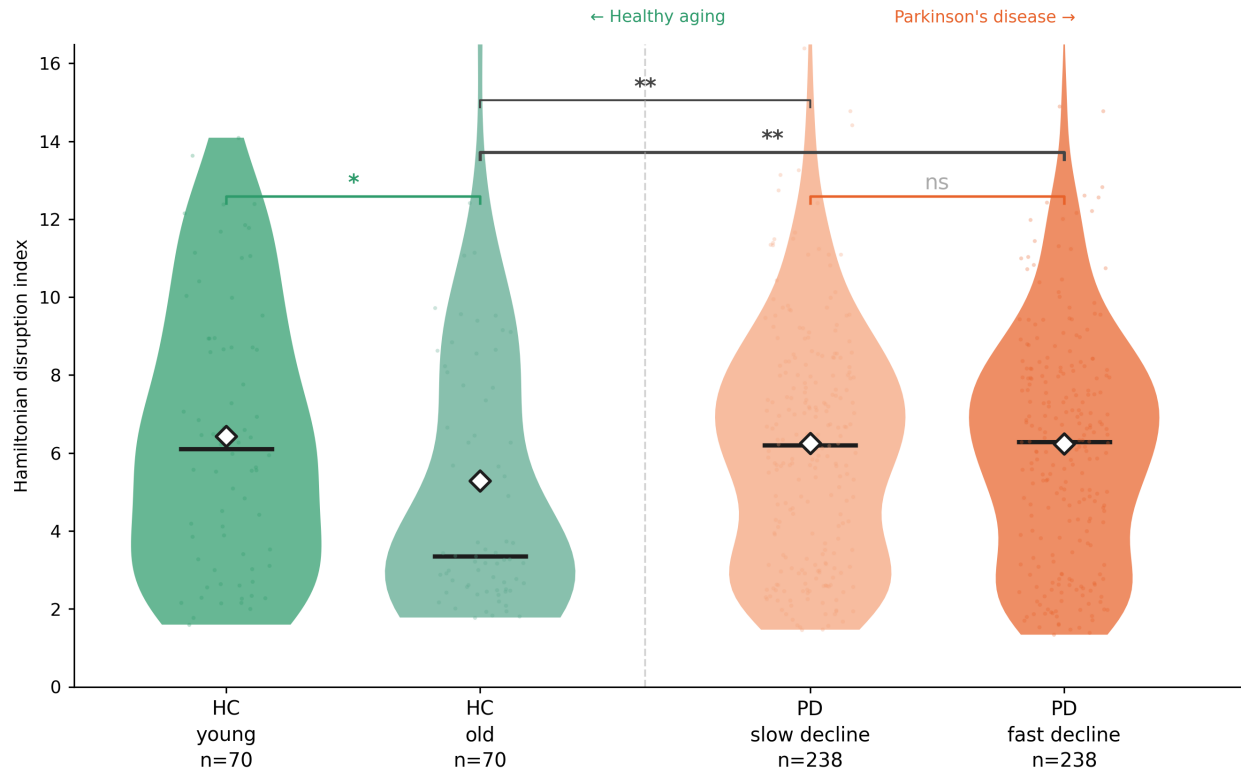


Figure A.2: Coordination disruption in PD exceeds normal ageing and is elevated in fast decliners. Violin plots of the per-patient Hamiltonian disruption index $S(i)$ for HC young (≤ 56 yr), HC old (≥ 70 yr), SPD slow decline, and SPD fast decline. HC = healthy controls; SPD = sporadic Parkinson's disease; DAT = dopamine transporter; SBR = specific binding ratio.

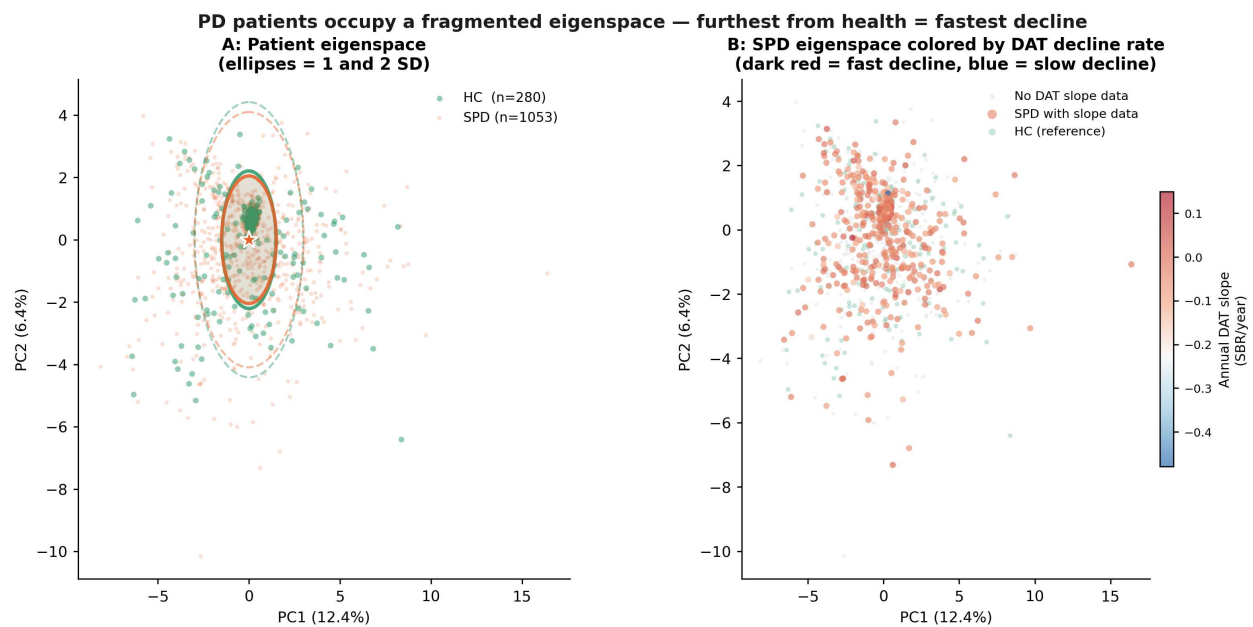


Figure A.3: Per-patient eigenspace projection and DAT decline rate. **Panel A:** PCA projection of all patients in the HC eigenvector basis. **Panel B:** SPD patients colored by annual DAT slope (putamen SBR change per year). HC = healthy controls; SPD = sporadic Parkinson's disease; DAT = dopamine transporter; PCA = principal component analysis.

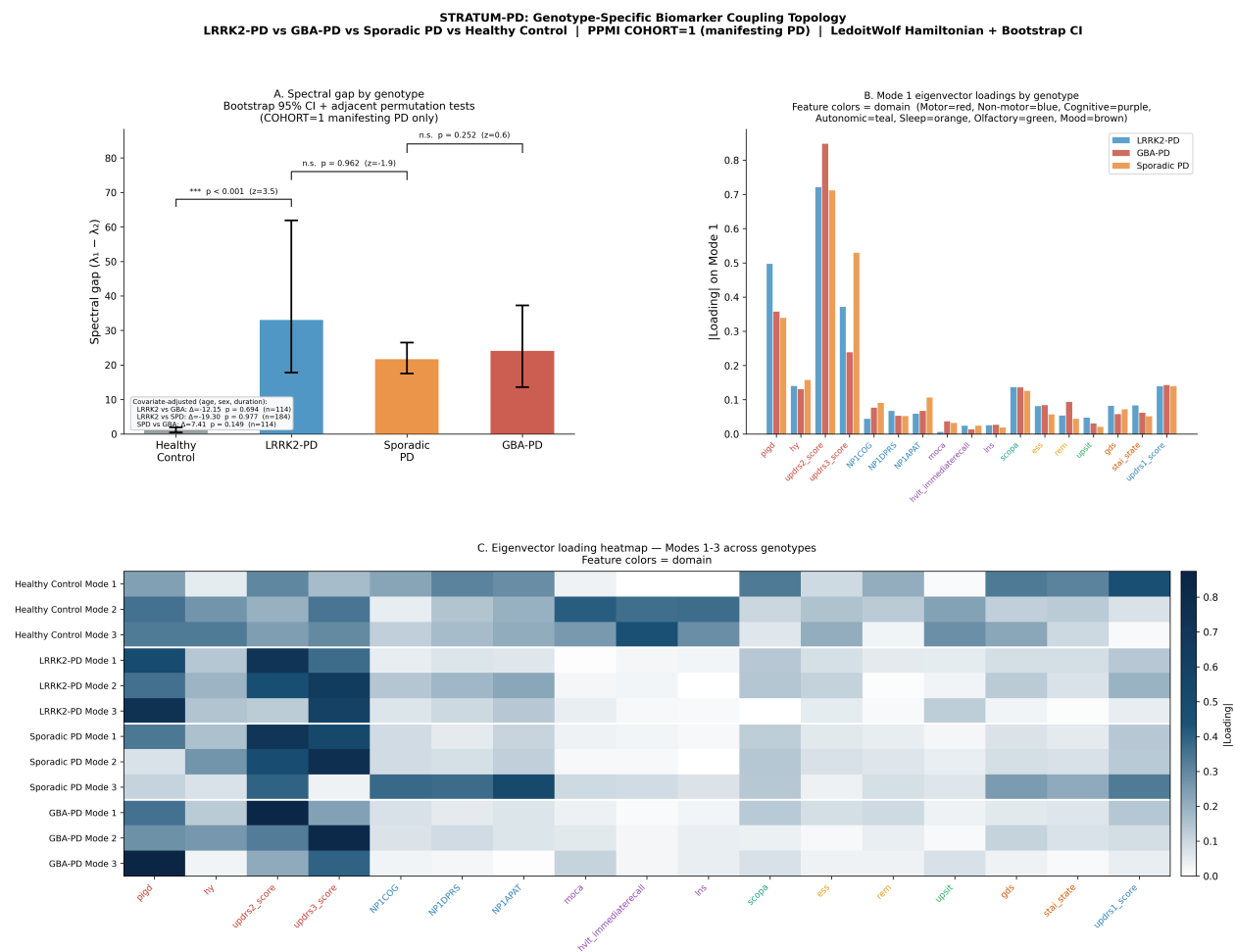


Figure A.4: Full genotype stratification results including eigenvector loading heatmap. **Panel A:** Bootstrap 95% CI spectral gaps for HC, LRRK2-PD, SPD, and GBA-PD. **Panel B:** Mode 1 absolute eigenvector loadings by genotype. **Panel C:** Full heatmap of Modes 1 to 3 loadings across genotypes. HC = healthy controls; CI = confidence interval; TOST = two one-sided tests.

Braak Stages 3-5: Coupling evolution during clinical care in Parkinson's disease
 SPD n=1080→837→293 at BL/V06/V12 | 21-feature set | HC z-score reference | Mean non-commutativity=0.399

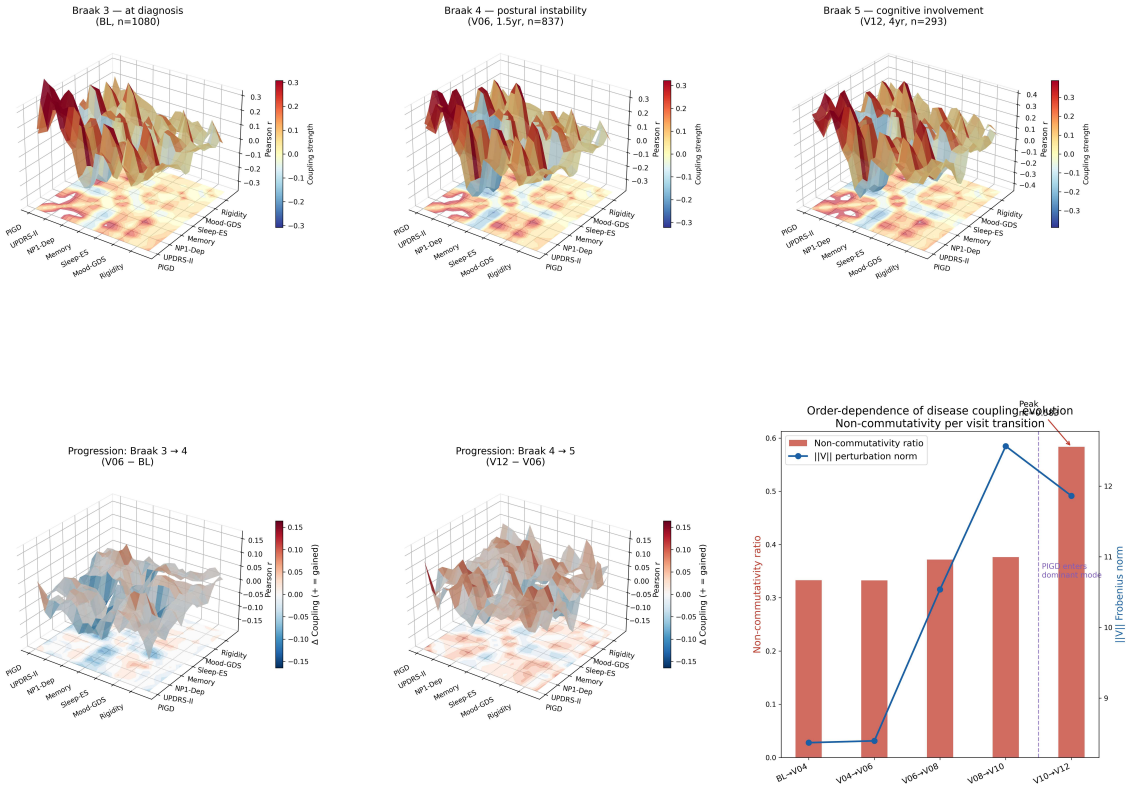


Figure A.5: Longitudinal Hamiltonian terrain evolution and non-commutativity (SPD, six visits). **Panels A to C:** Sequential three-dimensional Hamiltonian terrains at BL ($n = 1,080$), V06 ($n = 837$), and V12 ($n = 293$). **Panels D to E:** Subtraction surfaces for the BL-to-V06 and V06-to-V12 transitions. **Panel F:** Non-commutativity ratio per visit transition and perturbation norm $\|V\|$. SPD = sporadic Parkinson's disease; PIGD = postural instability and gait difficulty.