

Selective vulnerability: validation of atypical neurodegenerative disease variants in histopathological reference cohorts

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Research Article

Keywords: motor neuron disease, frontotemporal dementia, multiple system atrophy, red flags, reverse matching, onto-phylogenetic coordinate system

Posted Date: October 16th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-11296547/v1>

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Additional Declarations:

The authors declare no competing interests.

Ethics Statement: This study is based entirely on secondary analyses of previously published, fully anonymized histopathological cohorts and retrospective clinical case descriptions. No new human subjects or tissue samples were recruited for this research. Therefore, prior institutional review or ethics committee approval was not required.

Patient Consent Statement: For the aggregated clinical case history, formal consent was not required as all source data were previously published and strictly anonymized. For the specific clinical artwork newly presented in the Supplementary Material, the patient provided written informed consent for publication.

Selective vulnerability: validation of atypical neurodegenerative disease variants in histopathological reference cohorts

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Email: felix.geser@gmail.com

Abstract word count: 250

Text word count: 11,329

Running title: Neurodegenerative Disease Variants

Keywords: Motor neuron disease; frontotemporal dementia; multiple system atrophy; red flags; reverse matching; onto-phylogenetic coordinate system

Abstract

Objective: Standard guidelines for neurodegenerative diseases rely on cohort-level criteria, frequently misclassifying isolated atypical phenotypes. This study tests whether atypical variants mirror topographically determined systemic central nervous system (CNS) conditions rooted in pre-existing vulnerability.

Methods: Using "reverse-matching", phenotypes from six atypical cases—representing motor neuron disease/frontotemporal dementia ($N = 3$) and multiple system atrophy, parkinsonian type ($N = 3$)—were mapped onto a protein-agnostic network matrix (onto-phylogenetic coordinate system, OPC; Geser 2026). Spatial network recruitment was quantified using Jaccard coefficients (J). Spearman rank correlations (ρ) evaluated systemic hierarchies against conventional reference matrices (Geser 2008 cohort, TDP-43, $N = 31$; Jellinger 2005 cohort, α -synuclein, $N = 42$). Model comparison was performed using Steiger's Z -test.

Results: Conventional, cohort-based staging exhibited profound topographical inversion, yielding negative correlations for TDP-43 ($\rho = -0.9113, p < 0.001$) and α -synuclein ($\rho = -0.8660, p = 0.003$) sub-cohorts. Conversely, the novel OPC system resolved this mismatch, reversing the correlation into a highly precise positive range (TDP-43: $\rho = 0.9113, p < 0.001, R^2 = 0.83$; α -synuclein: $\rho = 0.8660, p = 0.003, R^2 = 0.75$). In the combined pool ($N = 18$ data pairs), the OPC model achieved strong global validation ($\rho = 0.8825, p < 0.001, R^2 = 0.78$; Steiger $Z = -6.497, p < 0.0001$). Individual anchoring demonstrated absolute topological consistency ($J = 1.00$).

Interpretation: Atypical variants are not statistical outliers but topographically determined systemic states reflecting inherent CNS vulnerability. Clinical anomalies serve as highly sensitive, topographically anchored early indicators ("red flags") of underlying proteinopathies.

1 Introduction

The clinical architecture of neurodegenerative diseases presents an apparent paradox for modern neuropsychiatric diagnostics. On one hand, clinical guidelines and therapeutic trials rely heavily on statistical cohort criteria—specifically on chronological cross-sectional “core symptoms” that define a nosological entity at the group level.^{1–5} On the other hand, clinicians routinely encounter isolated, atypical phenotypes in the early stages of disease, which heavily influence individual clinical decision-making.^{6–11} Historically, these early or “aberrant” manifestations have often been dismissed as statistical outliers or stochastic “noise.” This discrepancy arises from a fundamental methodological limitation: conventional staging schemes and data-driven alignment models (such as linear pseudotemporal trajectories) frequently conflate statistical cohort prevalences with directional causality. Consequently, they often draw arbitrary, unconstrained directional “disease vectors” across anatomically uncoupled systems where no primary structural infrastructure supports direct axonal spread. Crucially, when individual clinical trajectories deviate deeply from—or directly oppose—these statistical cohort averages, conventional cross-sectional models collapse. Because the latter cannot reconcile individual phenotypic inversions with group-level trends, such divergent cases often face methodological skepticism, including concerns about the statistical analysis; this highlights the urgent need for an analytical approach that evaluates individual spatial trajectory dynamics without forcing conformity to cohort-wide assumptions about the direction of progression.

Resolving the dichotomy between the individual phenotypic uniqueness and cohort-level statistics is critical for an accurate and early diagnosis. From a translational perspective, the practicing clinician requires a predictive framework that treats the individual patient not as a noisy statistical fraction, but rather as an autonomous, self-contained deterministic system ($N = 1$).

Growing evidence indicates that neurodegeneration does not progress randomly. Rather, it affects stereotyped, preformed neuroanatomical networks within the central nervous system (CNS).^{12,13} The concept of selective vulnerability suggests that rare individual phenotypes and core group-level symptoms are governed by the same underlying biological principles of intrinsic tissue vulnerability.¹⁴ This mechanistically shared causal origin is grounded in structural neurology, unifying the concept of local tissue susceptibility, i.e., pathoclinis¹⁵ and elective vulnerability.¹⁶ The classic patterns of macroscopic tissue loss and multisystemic neuronal destruction had been described previously in landmark clinicopathological cohort studies at the group level.^{17–21} Rather than operating with inflexible, absolute chronological disease stages, a susceptibility map can be conceptualized in terms of large-scale spatiotemporal gradients.

To resolve the underlying biophysical ambiguities of these gradients, a universal thermodynamic field framework was recently formalized: the onto-phylogenetic coordinate (OPC) system,²² including cross-disease validation using large-scale, data-driven pseudotemporal trajectories generated by the "Subtype and Stage Inference" (SuStaIn) algorithm.²³ The OPC framework demonstrated that typical disease trajectories follow pre-existing biophysical gradients, showing that relative tissue susceptibility (V) constitutes a scale-invariant relational continuum determined by macro-phylogenetic volumetric expansion ($\log_{10} x$) and the time budgets of linear ontogenetic differentiation (y). Within this continuous field, regional tissue susceptibility is strictly determined by the local tangential point tension (κ) of individual neuroanatomical nodes ($V = 1/\kappa$). Under localized pathogenetic stress operationalized via a pathogenetic operator (γ)—acting as a bioenergetic drain—macroscopic structural progression does not follow arbitrary chronological lines; instead, it manifests as a sequential cascade of localized, nested fractal collapses occurring strictly within pre-existing regional field curvatures. Since γ functions as a localized trigger rather than a uniform monolith

encompassing the entire brain, the phenotypic divergence of different disorders is preserved, while the structural hierarchy of the breakdown is entirely determined by the invariant geometric field.

Based on the formal definition of this continuous field, a trajectory model within the OPC framework must strictly distinguish between these localized, point-specific, discrete field parameters and long-range structural vectors. Legitimate trajectory lines—or macro-secants—cannot be arbitrarily plotted based solely on statistical frequencies. Instead, they are strictly restricted to established neuroanatomical pathways that possess verifiable clinical-functional relevance and direct pathological significance for the disease spectrum. Within this geometric architecture, the structural impedance and pathodynamics of these macro-secants are mathematically governed by the interregional trajectory tension (σ), where the manifest pathway vulnerability scales as its reciprocal ($V_{\text{path}} = 1/\sigma$). Outside these structurally and functionally anchored corridors, the forced directional linkage of distant, uncoupled networks results in methodological artifacts that are incompatible with the individual clinical reality.

Crucially, since the OPC landscape describes an intrinsic geometric law of the underlying CNS architecture, its mathematical validity must transcend protein-specific boundaries. This includes the “two-axes model” of 43 kDa transactive response sequence DNA binding protein (TDP-43)-linked degeneration.²⁴ Further, it extends directly to other system proteinopathies, such as the dichotomic concept of motor dysfunction in multiple system atrophy (MSA), which comprises striatonigral degeneration (SND) and olivopontocerebellar atrophy (OPCA) unified by oligodendroglial cytoplasmic inclusion pathology (GCI).^{25–27} Hence, the identical structural law must apply. Both of these architectural concepts define macroscopic trajectories of system-wide involvement and accommodate non-linear patterns of degeneration at the subregional level.^{24,26,28} Consequently, individual clinical anomalies can be

mapped onto these pathways dynamically using topographic lesion frequency or ordinal grading of pathology.

To bridge the gap between individual variance and group statistics, translational research approaches must shift from purely descriptive categorization to mechanistic, topological spatiotemporal mapping. While conventional cohort studies extrapolate downstream population averages, evaluating targeted spatial configurations within discrete regional topologies of a single organism preserves statistical validity at the individual level without relying on population-wide assumptions. If an unusual, isolated clinical phenomenon represents the localized manifestation of a broader onto-phylogenetic field curvature, it should be possible to map this individual clinical dysfunction topographically back onto established neuroanatomical circuits, pinpointing the structural collapse to a network-defined, putative epicenter.^{29,30} This approach, termed “reverse matching” herein, can then be validated against large, highly standardized histopathological datasets.

Rather than evaluating typical clinical presentations—which have already been reconciled at the cohort level via the aforementioned computational and biophysical frameworks—the critical structural test for any universal geometric law lies at its boundaries: it must be capable of successfully deciphering and predicting the seemingly chaotic, non-linear trajectories of rare, highly divergent individual phenotypes. Therefore, this study aims to validate the biological plausibility of rare, individual-case phenomena using established, methodologically consistent approaches to neuropathological mapping, anchored to the mathematical boundary conditions of the OPC geometry.

To this end, the divergent clinical phenotypes of six previously published, precisely characterized cases—representing atypical motor neuron disease (MND)/a frontotemporal dementia (FTD) variant ($N = 3$), and MSA-parkinsonian type (MSA-P) variants ($N = 3$)—were reverse-matched and projected onto a histopathological system matrix derived from two

previously published, large reference cohorts (Geser 2008, TDP-43, $N = 31$; Jellinger 2005, alpha-synuclein, $N = 42$). Specifically, this work tests the hypothesis that these rare clinical variants mirror topographically determined, deterministic system states of an inherent CNS vulnerability.

Taken together, an empirically grounded framework, characterized by methodological and investigatory consistency, is established, redefining individual clinical anomalies not as outliers but as highly sensitive, structurally predictable early indicators (“red flags”) of underlying systemic proteinopathies. This demonstrates that the clinical trajectory of an individual patient constitutes a mathematically robust, autonomous validation suite. Consequently, rigorous validation of the invariant OPC field law requires testing under extreme boundary conditions, where conventional cross-sectional models fail; this makes it possible to determine whether these atypical variants represent highly structured, predictable manifestations of the underlying geometric field.

2 Materials and Methods

2.1 Study design

This study introduces a retrospective, conceptually cross-validated network approach that links clinical phenotypes and ancillary paraclinical investigations such as qualitative *in vivo* imaging data to post-mortem microstructural neuropathology. Figure 1 visually summarizes the overarching analytical architecture and workflow for this systemic-anatomical mapping.

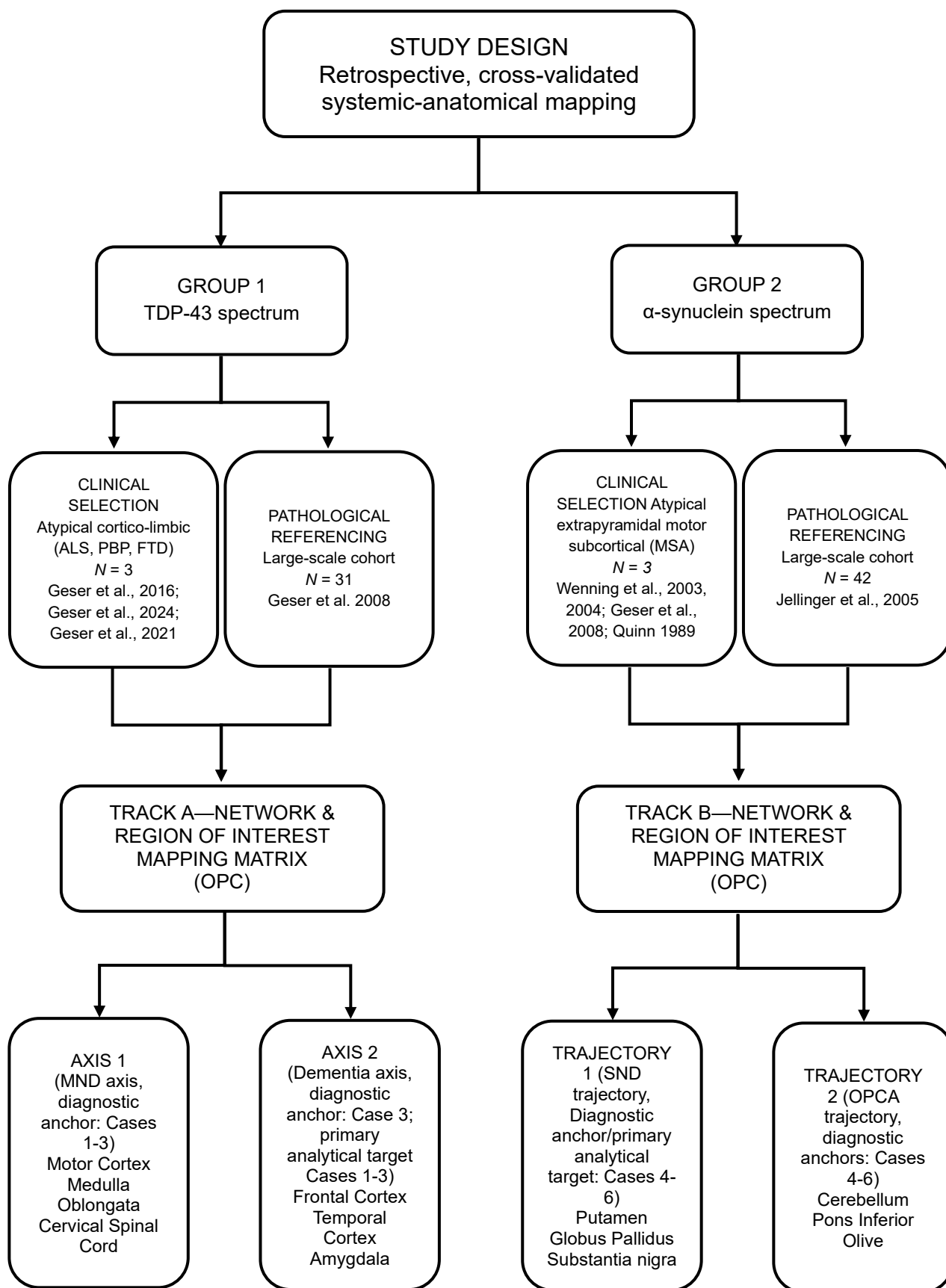


Figure 1. Flowchart of the retrospective, cross-validated systems-anatomical mapping.

This methodological workflow illustrates the parallel, dual-track architecture used to map individual phenotypic variants to large-scale, standardized post-mortem reference matrices by means of a two-track conceptual evaluation framework (Track A: Topographic Reference Baseline vs. Track B: Monolithic Grading Paradigm). Patients were classified *a priori* into two main groups of central nervous system proteinopathies: Group 1 (TDP-43 spectrum; left) and Group 2 (α -synuclein spectrum; right). The clinical *in vivo* case series cohorts ($N = 3$ per group)^{31–37} were linked to post-mortem histopathological datasets via a standardized "Network & Region of Interest Mapping Matrix" operating under the OPC system framework. For Group 1, the reference matrix is derived from the foundational cross-sectional baseline cohort ($N = 31$).³⁸ For Group 2, the referencing is anchored in a monolithic cross-sectional cohort ($N = 42$).²⁶ To rule out spatial arbitrariness and mathematical pseudoreplication, the individual multimodal severity rankings were anatomically counter-balanced via an "intra-spectrum" conceptually symmetric study design employing two distinct anatomical pathways for each spectrum: Axis 1 (MND axis) and Axis 2 (Dementia axis) for Group 1, utilizing 3 distinct gray matter nodes per axis; Trajectory 1 (SND trajectory) and Trajectory 2 (OPCA trajectory) for Group 2, also using 3 nodes per trajectory. Continuous ordinal modeling and the analysis of spatial network recruitment focused exclusively on the predominant target channels to account for the biological asymmetry of the manifestations; in this process, Jaccard similarity coefficients were strictly reserved for the primary atypical target networks, while the associated diagnostic anchor pathways provided a purely qualitative nosological framework. This dual-spectrum setup allows for a direct, "inter-spectrum" cross-validation of topographical network hierarchies through the mathematical use of symmetric OPC system nodes to contrast the constraints derived from historical cohorts against individual vulnerability vectors. Abbreviations: ALS, amyotrophic lateral sclerosis; FTD, frontotemporal dementia; MND, motor neuron disease; MSA, multiple system atrophy; OPCA, olivopontocerebellar atrophy; OPC, onto-phylogenetic

coordinate; PBP, progressive bulbar palsy; SND, striatonigral degeneration; TDP-43, transactive response DNA-binding protein 43.

To systematically rule out spatial arbitrariness and prevent mathematical pseudoreplication, the individual multimodal severity rankings were anatomically counterbalanced via a conceptually symmetric study design. This architecture implements two distinct, parallel anatomical pathways for each subject: Axis 1 (MND axis) and Axis 2 (dementia axis) for Group 1, and Trajectory 1 (the SND trajectory) and Trajectory 2 (the OPCA trajectory) for Group 2. By projecting individual, multi-node phenotypic vectors onto these independent paths within the same subject, systems-anatomical validity is preserved directly at the level of the individual (intra-subject), rendering the framework mathematically independent of population-wide sample expansions.^{39,40}

On an operational level, the analytical architecture distinguishes between three distinct tiers: First, “symmetrically designed reverse matching” serves as an overarching principle, defining the simultaneous clinical and spatial alignment of patient characteristics across two separate pathways to eliminate regional bias.

Second, the “intra-spectrum” (or “intra-cohort”) analysis operates within each distinct disease category (Group 1: TDP-43 spectrum and Group 2: α -synuclein spectrum). To account for the inherent clinical and biological asymmetry of atypical manifestations—where core diagnostic networks and phenotype-modifying signaling pathways can dynamically overlap or diverge—all quantitative analyses were strictly anchored to the primary analytical target pathways as shown in Figure 1.

Depending on the specific nosological entity, the spatial and functional relationship between these pathways shifts systematically: In the atypical frontotemporal behavioral-like

variants of MND (Cases 1–2), the atypical cortico-limbic network (Axis 2) serves as the primary analytical target for a continuous gradation, whereas the motor network (Axis 1) functions as a qualitative diagnostic anchor point. In the FTD variant (Case 3), both the diagnostic anchor and the primary analytical target axes converge functionally within the cortico-limbic network, thereby defining the multisystemic phenotype. For the atypical subcortical manifestations concerning the extrapyramidal system of MSA (Cases 4–6), the striatonigral pathway (Trajectory 1) functions as both the primary diagnostic core and the primary analytical target for continuous clinical ranking, whereas the olivopontocerebellar network (Trajectory 2) serves as a parallel diagnostic anchor point for capturing secondary multisystem involvement or clinically silent co-tracks (such as submaximal cerebellar symptoms in individual MSA-P cases)

Crucially, full neuropathological or clinical expression within the corresponding diagnostic anchor tracts is neither strictly required nor uniformly present across the cohort. This anatomical and clinical flexibility directly accommodates variable validation profiles without compromising the topological validity of the primary analytical target. Consequently, this design choice prevents mathematical artifacts and variance inflation in pathways where subtle or clinically overshadowed signs (such as early motor features in FTD or minor cerebellar dysfunction in MSA-P)—while qualitatively documented—are not natively suited for linear gradation or discrete binary node sequencing. Instead, these “secondary” pathways serve as qualitative nosological frameworks for confirming assignment to a diagnostic entity, without contributing to the quantitative validation matrices.

Third, the "inter-spectrum" (or "inter-cohort") comparison cross-validates the overarching pathodynamic principles of the two distinct proteinopathies. It evaluates whether the respective network trajectories reflect universal biological laws governing CNS tissue vulnerability and proteinaceous deposition.

2.2 Histopathological reference datasets

Individual network circuits inferred from the clinical phenotype were systematically verified across large-scale, published, standardized, post-mortem datasets to validate systemic-anatomic hypotheses of topographically predicted disease susceptibility. To rigorously validate the clinical utility of the OPC system,²² the study design abandons population-wide averaging and instead establishes a symmetrical, dual-track mathematical analysis matrix as its conceptual framework. This architecture directly reflects the spatial arrangement shown in Figure 1.

Track A: The Topographic Prevalence (Group 1; TDP-43 spectrum). For the TDP-43 spectrum, individual phenotypic vectors were benchmarked against the foundational cross-sectional reference cohort established by Geser³⁸ ($N = 31$). This framework establishes a purely frequency-based cross-sectional baseline of lesion prevalence without temporal assumptions. This framework utilizes raw, cohort-wide lesion frequencies at defined anatomical nodes to establish an ordinal reference hierarchy, without imposing unconstrained chronological timeline assumptions. In strict accordance with the single-subject network validation framework, individual spatial network anchoring is quantified at the single-subject level using the non-parametric Jaccard similarity coefficient (J) as the primary endpoint at the subject level, whereas continuous Spearman rank correlation coefficients (ρ) are applied exclusively at the group and pooled global aggregate levels.

To maintain strict mathematical and anatomical consistency across all three strata of analysis, alternative staging systems from the literature were systematically excluded from quantitative reference matrix due to limitations regarding node assignment and mathematical ceiling effects. The four-stage categorical staging framework proposed by Brettschneider et al.⁴¹ ($N = 76$), which expanded the original single-center study to conceptualize raw frequencies as a sequential, four-stage progression hierarchy, was conceptually evaluated. Crucially, however, the operationalized scoring within the Brettschneider framework is optimized primarily for the

motor axis (Axis 1). It lacks independent, sequentially segregated ordinal metrics for the middle frontal cortex, the superior-middle temporal cortex, and the amygdala (Axis 2). Specifically, while the third stage aggregates prefrontal and temporal neocortical recruitment, it consolidates these distinct regions into an undifferentiated category. To prevent mathematical asymmetry, regional data masking, and the introduction of artifacts into the symmetrical multi-node vector matrix, this generation was excluded from the formal quantitative network mapping.

Similarly, data-driven machine learning sequences generated using the SuStaIn algorithm²³ ($N = 141$)—which utilizes a large probabilistic iteration of this single-center dataset—were excluded from the quantitative trajectory modeling. Although the SuStaIn framework theoretically aims to generate data-driven probabilistic sequences of pseudo-temporal progression, its sequence markers for the temporal cortex exhibit high statistical variance and fail to reach stable saturation stages before crossing the threshold of computational uncertainty. Consequently, a robust, mathematically balanced discrete rank calibration along the designated three-node atypical axis is impossible using these population-averaged probabilistic models. Due to this architectural limitation, the invariant OPC field law remains the only stable framework for cross-validation of these highly divergent individual phenotypic boundaries without the loss of cortical and limbic information.

Track B: The Monolithic Grading Paradigm (Group 2; α -synuclein spectrum). For the α -synuclein spectrum, individual disease courses are measured against the monolithic reference framework established by Jellinger²⁶ ($N = 42$). Crucial here is the recognition that Jellinger's paradigm pursues a fundamentally different epistemological approach than the serial system of Track A: Rather than constructing a purely linear timeline in which one stage must chronologically follow the next, Jellinger²⁶ intuitively combined metrics regarding raw frequency, topographical density, and clinical boundary zones into a multidimensional grading system across Grades I-III. By using this expert-based hybrid grading matrix as the definitive

reference for Track B, this study architecture evaluates whether a highly sophisticated, expert-based hybrid grading matrix remains susceptible to potential vulnerability masking when confronted with atypical, individual *in vivo* disease courses, parallel to the structural challenges hypothesized for the linear staging systems of Track A. loss. isolated, single-system metric of the earlier protocol was mandatory to preserve the rigorous anatomic symmetry of the dual-track approach applied in this study.

For Group 2, individual *in vivo* MSA phenotypes were systematically evaluated against this standardized neuropathological grading matrix (Track B).²⁶ This framework functions as a unified, comprehensive MSA grading scheme that expands the fundamental SND scoring grading matrix originally outlined by Wenning et al.⁴² to an extended cohort. To target the predominant extrapyramidal motor features, the quantitative rank evaluations were focused on the subcortical nodes of the SND system utilizing separate, uncoupled metrics for GCI density and neuronal loss. To contextualize this reference framework within the broader neuropathological literature, Track B was conceptually cross-linked to newer spatial distributional data including the cohorts of Brettschneider et al.⁴³ for SND, as well as to the multi-region mapping by Cykowski et al.⁴⁴; the latter relies on Jellinger's²⁶ metrics to assess canonical subregional severity; collectively, these studies describe and confirm the hierarchical and convergent tissue vulnerability associated with increasing pathological burden.

Crucially, since these comprehensive mapping approaches explicitly conceptualize their models as spatial and chronological hierarchies rather than operationalized numerical scales, Jellinger's²⁶ cohort remained mandatory to provide the actual reference topology. This monolithic matrix simultaneously integrates entry points, topographic distribution, and GCI density and neuronal loss within a single, quantifiable framework.

To evaluate the structural stability and marker robustness of the conventional staging MSA concepts compared to the novel OPC framework, a planned secondary sensitivity analysis

was integrated into Track B. While the primary validation matrix relies on frequency hierarchies of α -synuclein-positive GCIs at the cohort level,²⁶ an alternative, independent reference ranking was calibrated based strictly on the documented extent of neuronal loss based on the same cohort (hierarchy of neurodegenerative cell death). Rank variances between the frameworks—as well as shifts in monotonic directional trends—were quantified using comparative Spearman rank correlations (ρ) across two distinct metrics (GCI-based grading vs. hierarchy of neuronal cell loss) and clinical case profiles. To statistically determine whether the novel OPC framework's prediction accuracy—optimized compared to conventional models—represents a non-random, structurally significant transition rather than a mathematical artifact in the MSA group, direct dependent correlation comparisons sharing a common variable (the clinical case profile) were conducted. These analyses evaluated the statistical divergence of the correlation between clinical findings and OPC values relative to both the primary clinical-GCI correlation and the secondary clinical-neuronal loss correlation, employing Steiger's Z-test in accordance with the formal computational specifications established by Lee and Preacher.⁴⁵

Finally, the proposed unified resolution for atypical phenotypes: The OPC system serves as an invariant mathematical core across both Track A and Track B. The OPC framework is utilized to address the challenges associated with conventional assumptions of chronological linearity or cohort-based hybrid graduation. By projecting the individual, multi-node vectors of both groups onto an intrinsic, neuro-ontogenetically and phylogenetically derived matrix of tissue vulnerability ($V_{\text{node}} = 1/\kappa$), the OPC is tested to operate as a universal transfer function designed to model individual, highly atypical pathodynamics independently of cohort-specific structural constraints.

Taken together, histopathological reference matrices and clinical categorization criteria were derived from established, standardized protocols. Consequently, tissue processing and ordinal grading criteria remained consistent across all analyzed strata, as outlined in previously

published datasets and multicenter collaborative studies (see Sections 2.3–2.7 for the respective references). Furthermore, established consensus diagnostic guidelines were used to re-evaluate the atypical manifestations. A shared investigator lineage minimized inter-investigator bias, ensuring that both clinical-phenotypic characterization and neuropathological grading were anchored in the same operationalized framework.

For the structural and functional definitions of neuronal networks, established neuroanatomical literature and consensus connectivity models were used. The network approach was grounded in classical neuroanatomical studies of topical diagnosis, network connectivity, and cyto-, myelo-, and dendroarchitectonics.^{46–52} These works provide the historical and structural basis for understanding the topographically determined, tissue-selective vulnerability and pathoclinosis examined in these proteinopathies.

2.3 Patient selection

A total of six well-characterized neuropsychiatric cases ($N = 3$ per disease spectrum) with salient, atypical clinical phenotypes were selected for system-anatomical mapping. To avoid population-wide averaging and preserve the idiosyncratic network topology, patients were derived from established international and regional neurodegenerative disease registries—specifically the ALS Registry Swabia Study Group⁵³ and the European MSA Study Group (EMSA-SG) registry^{54,55}—complemented by landmark historical case reports.

The following stringent inclusion criteria were applied: (1) A confirmed clinical diagnosis of a primary neurodegenerative proteinopathy in accordance with established (consensus) criteria.^{1,4,56,57} (2) The presence of a thoroughly documented, atypical phenomenological neuropsychiatric, cognitive, or motor manifestation challenging standard monolithic diagnostic tracks. (3) The availability of structural *in vivo* neuroimaging or granular clinical evidence sufficient to map network-level dysfunction onto the reference matrices. Cases

presenting with concomitant, severe CNS lesions of non-neurodegenerative etiology (e.g., severe traumatic brain injury) were excluded. Case 2 gave written informed consent for the publication of personal illustrative artwork (see Supplementary Material, Fig. S1).

To establish a symmetrical, intra-subject anatomically counterbalanced study design, the cohort was stratified into two distinct system-functional groups (Figure 1): First, the “Cortico-Limbic”/“Cognitive-Behavioral” spectrum (TDP-43 Spectrum, evaluated via Track A) comprised three individual cases, including two variants of MND and one patient with FTD. These patients demonstrated early or profound, non-motor phenomenological shifts: A patient with ALS (Case 1) demonstrated a peculiar neuropsychiatric phenotype including structural changes in emotion processing and music perception;³² Case 2 diagnosed with progressive bulbar palsy showed eccentric behavior traits and a profoundly canalized expression of his inner world through creativity;³⁴ and an FTD case (Case 3) showed a distinct stylistic shift in creativity, bursting prior to full cognitive decline³³.

Second, the "Subcortical"/"Brainstem-Striatal-Cerebellar" spectrum (α -synuclein spectrum, evaluated via Track B) comprised 3 individuals with MSA. All of these patients exhibited pronounced craniocervical and axial motor features. These manifestations represent early clinical warning signs or “red flags”, which were originally conceptualized to distinguish MSA from idiopathic Parkinson’s disease,⁵⁷ and for which formalized operational criteria were developed later.⁷ Specifically, the clinical features of these cases comprised focal and spontaneous craniocervical dystonia. Case 4 and Case 5 exhibited a prominent “risus sardonicus” due to distinctive orofacial and platysma muscle dystonia.^{31,36,37} Case 6 showed a highly “disproportionate”, isolated antecollis, presenting as severe, involuntary forward flexion of the head and neck, out of proportion to trunk flexion.³⁵

From a systems-anatomical perspective, these atypical clinical features form the phenotypic basis for classification within the OPC framework model. Depending on the

individual case, these atypical features project either onto complementary, non-diagnostic axes (such as behavioral changes in MND) or manifest as hyperfocal accelerations within canonical diagnostic pathways (such as isolated craniocervical and axial dystonias corresponding to the nigro-striato-pallidal circuitry in MSA).

Standardized clinical evaluation ensured consistency in results. To ensure maximum methodological accuracy and eliminate inter-rater variability, the phenomenological features of the antecollis case were characterized using the operationalized diagnostic criteria proposed by Quinn,^{35,57} thereby aligning with and reinforcing the shared investigator lineage. *In vivo* structural neuroimaging data (computed tomography/magnetic resonance imaging) were available for four of the six patients (one ALS, one FTD, and two MSA cases) for anchoring the systemic anatomical network architecture onto the reference matrices. These datasets were utilized to confirm and map region-specific macroscopic atrophy patterns directly onto the corresponding OPC nodes, thereby ensuring that the individual *in vivo* phenotypes were cleanly operationalized before being projected onto the post-mortem reference matrices.

2.4 Region of interest selection

Based on the established neuroanatomical framework of the dual-axis model,²⁴ pathological TDP-43-linked degeneration (Group 1) progresses along structurally segregable and stereotyped trajectories (Supplementary Material, Section S1.1): “Axis 1” (the MND axis) represents the pyramidal motor network, characterizing the stereotypic involvement of the lower motor neurons (spinal cord and brainstem) and the upper motor neurons in the primary motor cortex. “Axis 2” (the dementia axis) charts an extra-motor trajectory, featuring vulnerability to pathological TDP-43 lesions in the medial temporal structures (including allocortex/corticoid areas) and wider frontotemporal neocortical regions. Mapping the *in vivo* features of Cases 1–3 onto these two defined pathways eliminates anatomical arbitrariness, enabling a systematic investigation of the structural degeneration patterns of these clinical

variants within a standardized pathophysiological grid.^{24,32–34} To maintain a balanced study design across both axes and trajectories, resp., ensuring intra-spectrum consistency and to safeguard the statistical architecture against spatial pseudoreplication, exactly three independent anatomical core nodes of equal weight were selected for each axis based on post-mortem reference indices.^{23,38} Restricting trajectory tracking to three primary network nodes spanning the continuum from pathodynamic initiation to downstream propagation ensures that data points within a single subject remain biologically independent and resistant to localized signal distortions, regardless of whether individual nodes exhibit synchronous recruitment or sequential chronological shifts. Extending the selection of regions of interest beyond these dedicated nodes would incorporate highly interdependent, downstream anatomical variables from the same subject; this would violate the assumption of independent measurements and artificially inflate statistical significance. Specifically, the designated regions of interest for mapping the MND trajectory (Axis 1) comprise the primary motor cortex, the medulla oblongata, and the cervical spinal cord. The pathway tracing the extra-motor dementia trajectory (Axis 2) encompasses the medial frontal cortex, the temporal neocortex, and the amygdala complex.

An analogous methodological framework was deployed for the α -synuclein-linked MSA cohort (Group 2, Cases 4-6) to ensure inter-spectrum symmetry (Supplementary Material, Section S1.2). To preserve full mathematical equivalence with the dual-axis TDP-43 paradigm, six corresponding subcortical and brainstem anatomical nodes were selected to model the distinct pathodynamic of MSA. These nodes were systematically stratified into two distinct anatomical trajectories reflecting the classic motor phenotypic dualism of the disease: Trajectory 1 (the SND trajectory) comprising the dorsal putamen, the globus pallidus, and the substantia nigra, and Trajectory 2 (the OPCA trajectory), encompassing the inferior olivary nucleus, basis pontis, and the cerebellar cortex.

To account for the complex, multi-marker nature of the α -synucleinopathy, regional disease burden along the pathways was operationalized by means of two separate literature-derived reference ranks (R_X scaled 1 to 3) derived from GCI density. This standardized histopathological reference matrix leverages the chronological, non-linear progression patterns established in a large-scale post-mortem reference cohort ($N = 42$).^{25,26} Rather than relying on aggregate statistics or cross-sectional group means, these reference ranks mathematically capture the nested fractality and hierarchical topographical recruitment within the respective core pathways. Crucially, to protect the statistical architecture against metric-specific bias and to address the pathophysiological transition from the primary oligodendroglial inclusion handling to structural neuronal death, these reference hierarchies were calibrated independently for both the density of GCIs and the severity of histographic neuronal depletion. This provided the computational matrices for subsequent sensitivity tests, allowing for direct statistical comparisons between these two competing, overlapping predictor profiles against the shared clinical case criteria, using Steiger's Z -test for dependent correlations.⁴⁵

By establishing these two independent subcortical pathways, the framework provides a highly symmetrical, mathematically closed architecture intra-subject spatial network anchoring and for parallel cross-cohort comparisons.

2.5 *In vivo* regional severity grading

To evaluate the regional disease burden and capture individual variations across Cases 1–6,^{31–37} a standardized ordinal grading scale—ranging from 0 (absent/unremarkable), 1 (mild), 2 (moderate), to 3 (severe/profound)—was applied to the twelve independent core anatomical nodes in accordance with the dual-axis TDP-43 model²⁴ and the dual-trajectory MSA concept.²⁵ These rank-order values were systematically extracted from the *in vivo* clinical, electrophysiological, and structural neuroimaging measures, or a combination thereof, documented in the original case reports.

This multimodal mapping approach incorporates clinical, paraclinical, and subclinical network features rather than relying on structural neuroimaging (computed tomography/magnetic resonance imaging) alone. Volumetric radiological data frequently reflect continuous tissue loss and fail to provide discrete thresholds for differentiating between intermediate and terminal disease stages. By integrating clinical and electrophysiological measures, the grading framework achieves a higher topographic sensitivity. This ensures that early, focal pathological changes can be mapped onto the corresponding network nodes even when macroscopic atrophy remains below the detection threshold of *in vivo* imaging. This alignment is crucial for establishing a direct architectural equivalence with the high-resolution structural tissue alterations defined in the post-mortem reference matrices. A detailed, case-by-case pathophysiological rationale for each regional severity score is provided in the Supplementary Material, Section S2.

2.6 Pathophysiological operationalization and reference bridging

A probabilistic bridge for MND was established based on the premise that TDP-43 proteinopathy constitutes the invariable neuropathological hallmark in approximately 95% to 97% of all cases of sporadic ALS or its variants.^{58,59} This high prevalence justifies using the post-mortem TDP-43 reference cohort³⁸ as a robust, generalizable structural basis for *in vivo* phenotypic calculations.^{32–34} Critically, this cohort-mapping strategy assumes that the intrinsic, topographically determined, non-linear tissue vulnerability within a specific CNS network remains structurally stable. Under this premise, clinical dysfunction and phenotypic variants can be mapped back onto—and mathematically reconciled with—a shared, broader structural spectrum or network grid of vulnerability. Consequently, this framework examines whether TDP-43 proteinopathies presenting with phenotypes distinct from classic ALS can be mathematically reconciled with a structural matrix derived from ALS data, and whether,

analogously, cases clinically classified as MSA-P can be aligned with a matrix derived from the α -synuclein reference pathology of the Jellinger cohort.²⁶

Clinical frontotemporal syndromes are molecularly heterogeneous, with pathological TDP-43-linked degeneration occurring in approximately 50% of cases, tau in 40% to 45%, and fused in sarcoma or rarer proteins in the remaining cases.^{60–62} However, from a network-anatomical perspective, the macro-anatomical boundaries of tissue penetration along cortico-limbic trajectories remain largely congruent across these proteinopathies, thereby satisfying the premises for a binary recruitment logic based on the Jaccard similarity concept^{12,30,63,64}. Tauopathies, such as progressive supranuclear palsy or corticobasal degeneration, extend this pathological recruitment to involve subcortical networks, including the basal ganglia⁶⁵. Importantly, the mathematical analysis of these atypical phenotypes remained strictly focused on the cortico-limbic pathway (Track A/Axis 2), thereby excluding subcortical confounding factors. Furthermore, the use of a primary FTD cohort was deliberately avoided to prevent statistical saturation effects in cortico-limbic regions, which would otherwise mask spatial gradients. Notably, the current neuropathological literature lacks a standardized, multiregional histopathological grading matrix for sporadic ALS (outside Guam) based on tau pathology alone. The biological plausibility of this cross-pathology network overlap is further supported by rare clinicopathological entities, such as tau-associated MND with FTD⁶⁶ and mixed TDP-43 and tau pathologies, as observed in the amyotrophic lateral sclerosis and parkinsonism-dementia complex of Guam.⁶⁷

This method correlates the ordinal, frequency-derived, or grading-derived baseline scores with the patients' clinico-radiological severity ratings. It circumvents the non-linear relationship between microscopic aggregate burden and macroscopic tissue loss. Instead, it evaluates the kinetic alignment—the spatiotemporal congruence between network vulnerability and individual clinical manifestations—without requiring case-specific autopsy data.

2.7 Mathematical network quantification and correlation analysis

In strict adherence to the single-subject network validation framework, the recruitment of spatial networks was mathematically quantified using the binary Jaccard similarity coefficient (J).⁶⁸ To delineate the macroanatomical boundaries of systemic disease penetration, a mathematical metric for network overlap was applied. This measure is conceptually based on Jaccard's original coefficient of community and represents an established metric for assessing the spatial network intersection of disease phenotypes and structural features in neurodegenerative reference frameworks.^{69,70} It was operationalized in its algebraic, binary contingency form as shown in equation 1:

$$J = \frac{M_{11}}{M_{11} + M_{01} + M_{10}} \quad (1)$$

where M_{11} denotes matching positive regions, M_{01} signifies structures that are positive in the cohort only, and M_{10} represents unique outliers occurring only in the patient. For individual cases, this metric successfully dichotomized the clinical phenotype by mapping a multimodal severity score ≥ 1 as positive network involvement (phenotype = 1), thereby validating that an atypical phenotype remains structurally anchored within the overarching diagnostic cohort radius (cohort = 1).

The axis-specific and trajectory-specific structural hierarchy of the reference cohorts (R_X) was derived directly from spatial prevalence ranks and hierarchical severity tiers. For the reference datasets, any region with a post-mortem lesion frequency greater than 0% or a grade ≥ 1 was considered pathologically recruited (cohort = 1). Indeed, for Track A, ranks (1 to 3) were assigned in ascending order based on regional lesion frequency³⁸ with the highest lesion frequency receiving the highest rank. For Track B, the hierarchical reference ranks were operationalized using the non-linear, semi-quantitatively and topographically assessed GCI density and, additionally, neuronal loss, across the three grading tiers²⁶ with the highest rank

denoting the highest GCI load or most pronounced neuronal depletion. To prevent statistical artifacts caused by non-linear tissue reorganization—specifically the temporal decoupling of GCI clearance and terminal neuronal loss—these parameters were evaluated as separate, uncoupled validation vectors. By prioritizing the framework of ordinal rank dynamics over cumulative scales, this setup effectively protects comparative Spearman rank correlations from these regional kinetic inversions and structural saturation artifacts. The neuroanatomical node-matching matrices, including the selected structural proxies for both reference cohorts, are provided in the Supplementary Material, Section 1.

To comprehensively evaluate structural consolidation across multiple systems, binary analyses of spatial network overlap were conducted for the pathodynamic target tracks—thereby mathematically objectifying the degree of system-specific network penetration. To account for blocks of equal severity occurring within the individual clinical profile owing to synchronous symptoms, the standard mathematical method of averaging tied ranks was applied to both datasets. Consequently, the primary pathodynamic entry hub within each pathway was assigned the maximum rank of 3.0, while synchronous downstream network components were operationalized as tied nodes with an averaged rank of 1.5. In instances of two synchronous maximum or two synchronous intermediate scores, they were averaged as 2.5, and the lowest score was assigned a rank of 1.0. This procedure successfully isolates the dynamics of focal target regions and prevents mathematical ties from distorting the analyses.

These cohort-derived hierarchy ranks (R_X) were systematically calculated and directly correlated with the patient-specific *in vivo* severity ranks (R_Y) using Spearman's rank correlation coefficient (ρ) across the analytical target pathways to assess rank dynamics. Intra-group and pooled, total study-wide correlations were calculated. In accordance with the dual-track rationale (Section 2.1), the correlation analysis was executed for the pathodynamic target pathways (Track A/Axis 2 for Group 1; Track B/Trajectory 1 for Group 2). Statistical analyses

were performed using JASP (Version 0.98.1), an open-source framework powered by the R statistical computing environment) and Microsoft Excel (v16.0, Microsoft Corp., Redmond, WA, USA).

2.8 Data availability

The author confirms that the data supporting the findings of this study are available within the article and its supplementary material.

3 Results

3.1 Topological mapping architecture and cohort stratification

The mapping architecture successfully aligned individual clinical manifestations of atypical phenotypes with the specified neuroanatomical pathways across both analytical tracks (Table 1; Supplementary Tables 1-6). Using the structural dimensions defined in the study protocol, regional lesion patterns from the TDP-43 spectrum (Group 1; Cases 1–3) and the α -synuclein spectrum (Group 2; Cases 4–6) were cataloged against conventional reference frameworks and the OPC system. This formal anatomical assignment established the structural baseline for the subsequent within-cohort rank correlations (Track A and Track B, respectively), ensuring that the individual clinical severity ranks could be systematically cross-referenced with the histopathological profiles.

Table 1. Quantitative network mapping in individual neurodegenerative disease variants

Analytical Pool/Cohort stratum	Conventional models Spearman's coefficient	OPC system (ref. 22) Spearman's coefficient, ρ	Coefficient of determination, R^2	Steiger's Z-Test (p)	Jaccard index, J
Track A: TDP-43 spectrum (ref. 38), $n = 9$ pairs; Cases 1-3 (ref. 32–34)	-0.9113 ($p < 0.001$)	0.9113 ($p < 0.001$)	0.83	$r_{kh} = -1.000^a$	1.00
Track B: α -synuclein spectrum (ref. 26), $n = 9$ pairs; Cases 4-6 (ref. 31,35–37)	-0.8660 ($p = 0.003$)	0.8660 ($p = 0.003$)	0.75	-3.725 ($p < 0.001$)	1.00
Combined aggregate pool ($N = 18$ pairs, cases 1-6)	-0.8825 ($p < 0.001$)	0.8825 ($p < 0.001$)	0.78	-6.497 ($p < 0.001$)	1.00

Quantitative network mapping validation and comparative statistical modeling across individual variants and aggregated cohort strata. The data pairs (N) represent the active, non-zero neuroanatomical pathways evaluated under single-subject validation rules.

^aNote: Due to the perfect deterministic inversion ($r_{kh} = -1.000$), the asymptotic covariance calculation reaches its analytical boundary condition (division-by-zero); this demonstrates absolute model optimization and renders an asymptotic p -value mathematically superfluous. Abbreviations: R^2 , coefficient of determination; J , Jaccard similarity coefficient; ρ , Spearman rank correlation coefficient; p , asymptotic significance value; r_{kh} , Steiger's relational model correlation coefficient; Z , Steiger's Z test statistic; OPC, onto-phylogenetic coordinate system.

3.2 Individual topological precision and network recruitment

Spatial network involvement was mathematically assessed at the single-subject level using the binary Jaccard similarity coefficient (J). This metric quantified the precise topographic overlap between individual lesion distributions and the model's anatomical target pathways. At this individual level, spatial network anchoring demonstrated absolute topological consistency ($J = 1.00$) across all six index cases (Supplementary Tables S1–S6).

For the TDP-43 spectrum (Group 1, Cases 1–3), the analytical target trajectory reflected complete coverage of Axis 2 (limbic cortical axis) (Group 1, Cases 1–3; mean $J = 1.00$), thereby providing a standardized topographic baseline for all individual trajectories examined prior to cross-cohort pooling (Table 1). This characterization was qualitatively anchored by the concurrent presence of lesion profiles characteristic of the classic motor network (Axis 1), thereby confirming the baseline diagnostic classification within the ALS/FTLD spectrum (Table 1).

The absolute spatial coverage of the analytical target axis was identically mirrored in the α -synuclein spectrum (Group 2, Cases 4–6) with complete system-level involvement (mean $J = 1.00$), i.e., total spatial coverage of the target Trajectory 1 (SND). Qualitatively, this presentation was contextually anchored by concomitant pathognomonic involvement along the pathway of OPCA (Trajectory 2) confirming that, despite their atypical subcortical manifestation, all subjects in Group 2 remained fundamentally linked to the systemic α -synuclein spectrum. Importantly, in accordance with consensus diagnostic standards, a fully developed cerebellar or extrapyramidal syndrome is not a prerequisite for systemic anchoring; rather, the qualitative presence of isolated nosological features suffices to confirm the systemic classification.

3.3 Quantitative metrics of the TDP-43 spectrum (Track A)

Analysis of the primary analytical path in the TDP-43 sub-cohort (Track A, $n = 9$ data pairs, cases 1–3) revealed a highly significant, negative Spearman rank correlation coefficient ($\rho = -0.9113$, $p < 0.001$; Table 1) when evaluated using conventional frequency-based metrics. In contrast, application of the OPC system yielded a strong positive correlation coefficient of identical magnitude ($\rho = 0.9113$, $p < 0.001$), explaining an identical proportion of rank variance ($R^2 = 0.83$; Table 1). Direct statistical model comparison verified a perfect deterministic model inversion ($r_{kh} = -1.000$, $p < 0.001$) relative to the conventional reference matrix. Detailed case data revealed clinical evidence of dense tissue pathology localized to the amygdala in cases 1 and 2, and mediotemporal lobe structure including the amygdala in Case 3 (Supplementary Tables S1–S3).

3.4 Quantitative metrics and sensitivity analysis of the α -synuclein spectrum (Track B)

Projecting the subcortical variants onto the conventional α -synuclein reference matrix (Track B, $n = 9$ data pairs, cases 4–6) yielded a significant negative Spearman rank correlation ($\rho = -0.8660$, $p = 0.003$; Table 1) when applying the baseline cohort-level criteria based on GCIs. The OPC system completely reversed this correlation coefficient into the significant positive range ($\rho = 0.8660$, $p = 0.003$), thereby accounting for a substantial proportion of rank variance of $R^2 = 0.75$ (Table 1). The Steiger's Z-test for dependent correlations verified that this direct model comparison (i.e., the OPC's model optimization over the conventional GCI reference matrix) was highly significant ($Z = -3.725$, $p < 0.001$).

To rigorously test the diagnostic robustness of the framework, an additional quantitative sensitivity analysis was conducted at the cohort level; this involved cross-testing the clinical severity rankings with the alternative histopathological dimension of classical neuronal cell loss derived from the Jellinger reference cohort. This conventional reference matrix failed entirely

to capture the patho-clinical progression of the atypical variants in any way, resulting in a completely decoupled, non-significant rank correlation of ($\rho = 0.000$, $p = 1.000$). A direct model comparison using Steiger's Z-test confirmed that the positive correlation observed with the OPC system ($\rho = 0.8660$) represents a statistically superior basis for capturing progression compared to the conventional neuronal cell loss matrix ($Z = -3.226$, two-tailed $p = 0.001$).

To maintain methodological symmetry with the TDP-43 spectrum (Track A)—where pathology is predominantly characterized by neuronal inclusions—the individual rank correlation matrices for Cases 4–6 strictly operate on primary oligodendroglial inclusion profiles (Supplementary Tables S4–S6). As defined by morphological criteria for the SND trajectory in the supplementary data (Section S1.2.1), the advanced structural tissue disintegration captured by the model corresponds closely to the alternative vulnerability pathway of localized neuronal cell death in the pallidum; in the variants mentioned, this region acts as a hyperacute, individual epicenter and manifests clinically through severe craniocervical and axial motor symptoms, notably risus sardonicus (Cases 4 and 5) and marked antecollis (Case 6).

3.5 Global protein-agnostic validation (combined aggregate pool)

To test the overarching hypothesis that atypical manifestations across different proteinopathies are governed by shared, systemic topological rules, data pairs from both sub-cohorts were combined into a single, protein-agnostic validation pool ($N = 18$ independent data pairs, Cases 1–6). Analysis across this aggregated cohort level revealed a strong global, paradoxical negative correlation of $\rho = -0.8825$ ($p < 0.001$) for conventional pathological reference systems. In sharp contrast, the protein-agnostic OPC model achieved strong global positive validation, with a correlation of $\rho = 0.8825$ ($p < 0.001$), and explained a substantial proportion of the total rank variance ($R^2 = 0.78$; Table 1). A global statistical model comparison using Steiger's Z-test confirmed that this direction-based correction represents a highly

significant improvement in explaining topographical variance compared to conventional standards ($Z = -6.497$, $p < 0.001$; Table 1).

4 Discussion

4.1 Key findings

The clinical classification of neurodegenerative diseases has historically been constrained by a diagnostic dichotomy, relying predominantly on cohort-derived group-level statistics^{1,4} which frequently fail at the single subject level. Routine clinical practice, especially in the early stages of disease, routinely encounters idiosyncratic, atypical phenotypes^{6–8} that are often misclassified as statistical noise or random anomalies.

To resolve this gap, a novel, mathematically formalized, and “reverse-matching” framework is presented here to map individual clinical ranks onto histologic disease matrices, including conventional pathology distributional schemes and the novel OPC system, which established a protein-agnostic vulnerability-network framework. The critical finding of this study is that atypical neurodegenerative variants do not represent stochastic deviations; rather, they reflect highly organized, topographically determined network states governed by the structural principles of intrinsic tissue vulnerability (pathoclisis).^{15,16} By integrating multi-dimensional network recruitment with directional rank correlations, this approach decouples spatial localization from the kinetics of directional progression, thereby successfully aligning the single-subject phenotypic heterogeneity with established post-mortem reference standards.

4.2. Spatial network anchoring and qualitative nosological verification

To balance this strict quantitative topology without introducing over-mechanistic assumptions, the framework applied here employs symmetrical, qualitative nosological anchors for both tracks. Indeed, a key component of this approach is the objective operationalization of

the anatomical boundaries of the disease distribution within the CNS, mathematically indicated by the binary Jaccard similarity coefficient (J), which showed complete, flawless consistency of the primary analytical target pathways across all six index cases.

Consequently, even the most clinically or behaviorally atypical individuals remain bound to their respective systemic proteinopathy patterns. For the TDP-43 spectrum (Group 1, Cases 1–3), absolute spatial anchoring to the limbic cortical axis (Axis 2) was verified (mean $J = 1.00$) and qualitatively balanced by the concurrent presence of classic, lower and upper motor neuron network pathology (Axis 1). Likewise, total spatial penetration along the SND trajectory (Trajectory 1) was observed in the α -synucleinopathy group (Group 2, Cases 4–6) across all three patients (mean $J = 1.00$), contextually anchored by qualitative pathway involvement along the OPCA tract (Trajectory 2). Importantly, in accordance with consensus diagnostic standards—a fully developed cerebellar or extrapyramidal syndrome is not a mathematical prerequisite for systemic anchoring;^{1,5} rather, the qualitative presence of isolated nosological features is sufficient to confirm the systemic alignment.

4.3 Directional pathodynamics

The operationalization of the reverse-matching approach is the central conceptual outcome of this work, built directly upon the already pre-established OPC framework. Translational neurobiology often faces the challenge of reconciling *in vivo* clinical deficits with post-mortem histopathological measures of progression, the topographic distribution of pathological protein aggregates at the histological level. These difficulties arise from non-linear degradation kinetics and intensity biases that hamper clinico-pathological correlation studies. The reverse-matching approach circumvents these limitations by converting fixed, population-wide histopathological standards (frequency distributions or density grades) into ordered hierarchical ranks (R_X) and correlating them directly with mathematically normalized patient-specific ranks of clinical severity (R_Y). Thus, in addition to spatial anchoring, which determines

where the disease manifests, the framework presented here decouples this parameter from directional kinetics and, hereby, shows *how* the pathology propagates across interconnected nodes. A crucial finding of this study is that purely mathematical results must be clearly distinguished from actual biological reality. There can be only a single biologically plausible vector for given nodes that is uniquely represented by a robust positive correlation ($\rho \gg 0$) within the baseline OPC matrix.

Conversely, negative correlations ($\rho \ll 0$) and network dissociations ($\rho \approx 0$) reflect neither alternative biological pathways nor actual tissue mechanics. Instead—despite representing mathematically precise and error-free statistical analyses of the dataset—they reveal the profound biological blindness of conventional pathology metric-systems. When conventional frameworks encounter an atypical phenotype, they force an artificial, mathematically inverted pseudo-vector ($\rho \ll 0$) or a complete signal loss ($\rho \approx 0$). The “reverse-matching” approach, analyzed with the vulnerability scores of the OPC, resolves this paradox by demonstrating that these negative measurements are not distinct biological phenomena but rather predictable methodological artifacts arising when individual phenotypic variants are forced into static, unoptimized frequency- or distribution-based pathology scales.

4.3.1 Track A progression dynamics (TDP-43 spectrum)

In Track A (Group 1, Cases 1–3), conventional staging methods yield a paradoxical, highly significant negative correlation. This occurs because these static frameworks collapse when encountering a highly organized, alternative anatomical variant, forcing clinicians and researchers to misinterpret the presentation as a reversed pathological flow or random statistical noise. Crucially, this discrepancy regarding direction neither implies that the raw conventional histopathological data were recorded incorrectly nor points to a hidden, reverse-progression macro-vector degradation pathway.

Instead, the "reverse-matching" method maps clinical severity ranks onto the fixed OPC reference matrix to resolve this paradox at the fractal and compartmental level. Biologically, a single, invariant macro-vector remains, propagating from limbic to neocortical structures. The apparent structural reversal captured by conventional scales is a methodological artifact; it arises because static pathology assessment models reduce localized biological differences to a one-dimensional score. This conventional view rests on an epistemological fallacy stemming from survival and frequency biases in cross-sectional data from cohort studies:³⁸ the low prevalence of severe amygdala lesions in classic cohorts of patients with rapidly progressive ALS reflects the fact that terminal neuromuscular decline—driven by the primary motor loop (Axis 1)—typically limits patient survival long before extra-motor pathology can successively cross neocortical boundaries and saturate downstream limbic target structures.

Consequently, when an atypical ALS case exhibits greater amygdala or limbic involvement relative to neocortical pathology, this does not represent a reversed cortex- to-core kinetic cascade. Rather, it reflects specific regional vulnerabilities operating within local tissue fractals—such as the hyper-susceptibility of specific nuclear subdivisions within the amygdala. At a biological level, the model establishes the principle that network spread is driven by a thermodynamic vector of least resistance; this originates in relatively phylogenetically older, highly vulnerable core structures and proceeds outward toward more recently formed, phylogenetically younger regions. Moreover, this approach of mapping an atypical, FTD or FTD-like case against the limbic-cortical areas of an unsaturated ALS cohort, successfully circumvents the structural ceiling effects and barriers due to early tissue saturation that inherently limit conventional FTD staging systems;^{63,71} in these systems, the near-maximal prevalence of pathology across both limbic and neocortical zones eliminates statistical variance, rendering a mathematical analysis of sequential tissue affliction impossible. To circumvent this saturation barrier, the framework utilized here is based on the two-axis concept of TDP-43-

linked degeneration.²⁴ Conceptualizing "Axis 2" not as an inflexible, categorical staging system but as a continuous spatiotemporal gradient—and comparing the disease variants against the non-saturated distribution of the ALS reference cohort³⁸—enabled the isolation of the localized, non-linear kinetic shifts characteristic of these atypical variants.

Biologically, the illusion of a linear sequential vector is corrected by clustering interconnected regional nodes into distinct anatomical compartments. By evaluating the tissue architecture, the amygdalar and temporal cortex domains tightly cluster to form a unified mesiotemporal compartment, which stands in sharp structural contrast to the evolutionarily newer neocortical compartment (middle frontal cortex). The apparent directional mismatch forced by conventional scales simply reflects the differential, intrinsic vulnerability of these large-scale compartments. Driven by the phylogenetic law of relative age equaling vulnerability ("old before new"), the phylogenetically older mesiotemporal compartment exhibits a profoundly higher baseline pathoclitic susceptibility than the neocortical gray matter when hit by a system-extrinsic pathogenetic operator.

When the framework correctly aligns the tracking axis with the true, biologically plausible macro-vector extending from the initial mesiotemporal compartment to the neocortical gray matter, the directional discrepancy is eliminated. The severe pathology in the limbic core region reflects not a reversed cascade, but rather the primary thermodynamic epicenter of tissue pathoclitosis, whereas the subsequent involvement of the neocortex follows pre-existing network pathways in accordance with the phylogenetic law. This limbic affinity for TDP-43 pathology implies that the phenotypic expression of these atypical variants represents the acute exploitation of a latent, generalized tissue vulnerability within the limbic system—a vulnerability that consistently operates consistently in both age-related neurodegeneration and secondary proteinopathies.^{72–74} Conversely, within the neocortical compartment itself of a typical patient, the hierarchy does not denote an inverted macro-vector,

but rather unmasks the highly localized, fractal susceptibility of cortical lamina V versus lamina II within the frontal cortex matrix.

This structural flip—mathematically unmasked by Steiger’s r_{kh} transformation—demonstrates that the atypical presentation does not violate the biological baseline. By analyzing individual tissue profiles within the OPC system, the framework demonstrates that the underlying proteinopathy remains strictly bound to the specific, biologically plausible macro-vector, proving that propagation follows a predictable topological sequence along the pre-existing network while simultaneously accounting for the independent, fractal vulnerabilities of interconnected regional nodes.

At the same time, this multi-compartmental architecture provides a precise mathematical explanation for the striking, non-linear clinical heterogeneity observed in these atypical variants; it firmly demonstrates that severe neuropsychiatric phenotypes represent neither unpredictable anomalies nor statistical noise. In Case 1, the hyper-vulnerability of specific amygdala subdivisions directly explains the premature onset of a catastrophic neuropsychiatric phenotype—clinically characterized by extreme anxiety (at the 95th percentile) and marked pseudobulbar affect—as the system-extrinsic pathogenetic operator unmasked this region, which is central to emotion regulation, long before the usual neocortical consolidation could occur.³² Case 2 strikingly illustrates the structural independence of these tissue fractals.³⁴ Despite advanced bulbar and motor collapse (Axis 1), the patient successfully utilized artworks—reminiscent of surrealist or abstract styles—as a complex medium of communication, presenting his physician with a highly symbolic multimedia collage (see Supplementary Figure S1). This deliberate, deeply conceptual act provides direct *in vivo* evidence that the neocortical compartment remains structurally and functionally viable as a cognitive and emotional reservoir capable of sustaining a profound psychotherapeutic engagement despite progressive motor deterioration. Ultimately, the preservation of these

specific cortical networks enables complex psychological coping mechanisms and profound neuropsychiatric processing, even in the terminal stages of motor decline; this confirms that the reverse matching approach successfully elucidates direct clinico-pathological correlations that remain entirely obscured by cohort-level averages.

This compartmental and fractal resolution is further validated by the syndromic complexity of Case 3—a phenotype showcasing a challenging convergence of a semantic FTD variant with progressive supranuclear gaze palsy-like vertical gaze deficits.⁶⁵ The latter complicates a definitive molecular classification within the TDP-43 spectrum cohort (frontotemporal lobar degeneration-TDP). Such clinical features frequently overlap with alternative neuropathologies such as tauopathies, particularly progressive supranuclear palsy. Although it is traditionally classified as an atypical parkinsonian syndrome due to its pronounced motor symptoms, it fundamentally belongs to the broader neuropathological spectrum of frontotemporal lobar degeneration.⁶⁰ Crucially, the phenotype of Case 3 could reflect a highly focal, temporally predominant FTD variant, in which the advanced tissue destruction is localized within the ancient mesiotemporal structures before progressing to global frontotemporal lobar degeneration.^{65,75} Topographically, this pronounced damage affects the amygdala and the anterior temporal regions as a cohesive unit—with both individually corresponding to the maximum clinical severity grade—whereas the frontal neocortex is less severely affected. Neuropsychologically, the case exhibited characteristic features of a semantic variant, with marked deficits in semantic word fluency and impaired naming performance, in contrast to relatively preserved phonemic word fluency. However, it does not represent a classic case of semantic dementia owing to the presence of executive dysfunction in planning and coordination, which initially raised clinical suspicion of a behavioral variant of FTD. Rather than resulting in a mathematical breakdown or distortion of the cohort's statistical signal, the pooled analysis of the $n = 9$ data pairs seamlessly absorbs this etiological and topographical

ambiguity. The framework reveals a highly significant latent structure, demonstrating that even when an extrinsic pathogenetic operator simultaneously affects widely divergent anatomical fractals, the underlying pathoclitic architecture remains predictable. The longitudinal evolution of the patient's artistic style provides a direct, non-invasive window into these architectural changes. The progressive loss of three-dimensional depth and fine geometric detail represents a manifestation of severe, selective degradation within the temporo-neocortical networks responsible for visuospatial construction and semantic object architecture. Conversely, the simultaneous expansion of the color spectrum and the intensification of contrast reflect the mechanism of paradoxical functional facilitation.^{76,77} In FTD it is known that early on in the disease, the themes and objects depicted are often concrete and realistic, but can become more abstract or symbolic at later stages.⁷⁸ In Case 3 presented here, the degeneration of anterior mesiotemporal structures may have removed their physiological inhibition of posterior visual pathways, thereby disinhibiting the dorsomedial occipital cortex and unleashing a drive for vivid visual expression.³³ This eruptive creativity over two decades required a functional anchor: the preservation of frontocortical executive control circuits, a fact psychometrically evidenced by her above-average phonemic verbal fluency (Z -score > 0). It was precisely this asymmetrical topographical configuration—in which terminal semantic-temporal failure unleashed the visual drive, while moderately preserved frontal networks maintained the cognitive-motor framework essential for artistic production—that enabled the flourishing of her creativity prior to the eventual, global consolidation of the systemic network. By incorporating these complex variations into a robust matrix across multiple subjects, the model captures spatiotemporal gradients that conventional linear statistical methods would inevitably miss.

4.3.2 Progression dynamics and sensitivity in Track B (α -synuclein spectrum)

For Track B (Group 2, Cases 4–6), the comparative sensitivity testing against the conventional Jellinger reference scheme reveals an identical methodological failure. When

atypical subcortical manifestations occur, conventional pathological measurement systems force an artificial, mathematically inverted mismatch along the GCI dimension and exhibit complete blindness to the actual course of neuronal loss. Crucially—as established for Track A—these negative or zero metrics do not indicate alternative biological propagation routes or a breakdown of tissue order. Rather, they reveal the inherent structural limitations of static assessment systems that reduce multidimensional network anatomy to a flat, linear scale.

Applying the "reverse-matching" method to project individual clinical severity levels onto the fixed OPC reference matrix resolves this subcortical paradox at the relational, fractal level by showing that progression is determined by compartmentalized vulnerability thresholds rather than a continuous, fluid cascade between adjacent nodes. Biologically, the cohort's quantitative tissue profiles strictly follow a single, invariant macro-vector that aligns with a clear thermodynamic gradient extending from the phylogenetically ancient substantia nigra, through the paleostriatal internal core of the basal ganglia (globus pallidus), to the phylogenetically more recent neostriatal compartment (dorsal putamen). This directed vector-cascade does not simply follow the traditional loops of classical nigrostriatal circuitry; rather, it structurally maps onto the direct nigropallidal dopaminergic projection pathway. By anchoring to the progression along this primordial axis, the clinical rating (substantia nigra = 3 → globus pallidus = 3 → striatum = 2) reflects a step-by-step unmasking of phylogenetic tiers—following the principle of "old before new"—rather than a linear, spatial diffusion across a homogeneous basal ganglia block.

The extreme lesion load observed in the substantia nigra and the internal segment of the globus pallidus represents neither a late endpoint nor a chaotic disruption of the system; rather, it reflects the primary thermodynamic starting point where the system-extrinsic pathogenetic operator first unmasks the lowest threshold of metabolic and structural resilience within the ancestral core coordinates of the subcortical network. The conventional explanatory model

imposes an artificial negative correlation because its linear metrics are blind to these independent, compartmentalized vulnerability thresholds—thresholds that are selectively unmasked by a system-extrinsic pathogenetic operator, while the underlying coordinates of the systemic network remain spatially fixed.

At the same time, this architecture—with its distinct compartments—provides a precise mathematical explanation for the striking clinical heterogeneity observed in subcortical presentations, rendering these focal phenotypes highly sensitive early indicators of regional vulnerability. Rather than pointing to chaotic dysfunction, the pooled analysis of the $n = 9$ data pairs seamlessly reconciles these divergent motor features by resolving them at the microstructural, somatotopic level within the basal ganglia compartment.

In the standard progression of SND, the medial globus pallidus serves as a peripheral, passive node with a low GCI lesion load across all disease grades.²⁶ In contrast, the model introduced here shows that severely debilitating craniocervical and axial motor symptoms—such as risus sardonicus (Cases 4 and 5) and disproportionate antecollis (Case 6)—are driven by a segmentally organized, pallidal dysregulation. The internal segment of the globus pallidus is not a homogeneous nuclear mass but is highly subdivided into distinct anatomical subregions that control specific muscle groups. The precise phenomenological manifestation depends on focal, segment-specific tissue vulnerability. In these atypical variants (“red flags”), the terminal, downstream output network of the basal ganglia undergoes advanced structural and functional disintegration, similar to the substantia nigra. In Cases 4 and 5, the system-extrinsic pathogenetic operator targets the cranial and orofacial subregions of the internal globus pallidus segment, thereby triggering a severe, segmentally organized dystonic facial deformity that manifests clinically as a spontaneous or L-Dopa-induced risus sardonicus. In contrast, the localized cellular disruption in Case 6 affects the cervical and axial subsegments of the pallidal circuit, resulting in severe involuntary forward neck flexion with minor flexion elsewhere—the

highly debilitating disproportionate antecollis. This somatotopic differentiation demonstrates that the reverse-matching approach successfully captures how focal entry points within a network's microenvironment determine clinical phenomenology without violating the overarching thermodynamic gradient.

Furthermore, this compartmentalized framework successfully contextualizes the development of diagnostic taxonomies in the field of speech pathology within a historical context, utilizing specific reference systems that ensure consistent methodology and examiner consistency across decades of literature. Established consensus criteria recognized the dysarthria associated with MSA as a complex, mixed phenomenon, manifesting as a "mainly hypokinetic" deficit in the parkinsonian realm and a "mainly ataxic" presentation in the cerebellar domain.^{1,79} In fact, speech disorders in MSA are grouped as nonspecific, hypokinetic motor deficits or classified purely within the context of cerebellar ataxia.¹ To ensure applicability to large multicenter cohorts, subsequent operationalized systems pragmatically consolidated these phenotypic variants. While severe craniocervical dystonias and postural deformities were successfully incorporated into recent consensus matrices as highly specific supportive motor features,⁵ bulbar symptoms and speech disorders were increasingly subsumed into highly reproducible yet broadly defined index categories—with the focus for clinical screening placed either binarily on "severe dysarthria" or with speech disorders strictly situated within the cerebellar core motor domain.^{5,80} Crucially, large-scale cohort studies have fundamentally altered the nosological status of these early indicators: the demonstration of an unexpectedly high epidemiological prevalence—such as severe dysarthria presenting in close to half of patients with MSA-P, orofacial dystonia in a quarter of patients, and the disproportionate antecollis situated about in between⁸⁰—effectively transformed these non-cardinal features into quasi-cardinal features. This clinical prevalence led to a lingering

taxonomic dilemma regarding whether to treat them as distinct clinical anomalies or to integrate them directly as core criteria.

The fundamental value of the current analysis lies in resolving the profound methodological and conceptual second dilemma inherent in this taxonomic compression. While aggregating clinical signs into a broad, screening category like “severe dysarthria/dysphonia”^{5,57}—captures a statistically typical cohort profile, it inevitably obscures highly specific, less frequent, yet pathognomonically distinct acoustic variations. In Case 4³⁷, the pronounced “quivering, strangled high-pitched dysarthria” dysarthria represents precisely the multifaceted phenotype defined by multiple parameters that was operationally defined by⁷, explicitly classifying the acoustic presentation as an “atypical quivering, irregular, severely hypophonic or slurring high-pitched dysarthria”. Rather than treating these nuanced features merely as descriptive anomalies or statistical noise hidden within a coarse screening category, the relational OPC system, together with the reverse-matching approach, expands the existing paradigm by integrating them as a qualitative topographical anchor into a mathematically formalized structural matrix. Without requiring additional quantitative dimensions for the primary axial tracking, the OPC reference matrix successfully incorporates this mixed acoustic phenotype, thereby confirming early, simultaneous involvement of the pontine projection loops. Since these pontine circuits control phonatory coordination in real-time and integrate highly specialized brainstem motor loops regulating laryngeal tension,⁸¹ their early structural failure drives the characteristic tremulous dysarthria. Consequently, this specific phenotype acts as a functional bridge, demonstrating that the clinical variant remains firmly anchored in a multisystemic network consolidation. This demonstrates that these rare, highly localized acoustic indicators represent predictable structural manifestations within a unified, nonlinear subcortical gradient—thereby bridging the gap between the epidemiological sensitivity derived from cohort studies and biological precision at the individual level.

4.4 Methodological implications for atypical proteinopathies

By shifting the diagnostic paradigm from absolute lesion densities to an onto-phylogenetic network matrix, this approach successfully isolates individual spatial dynamics from static diagnostic reference lines. Since these atypical courses remain strictly tied to their underlying, protein-agnostic topographies, it becomes possible to capture distinct pathodynamic states—ranging from classic hierarchical cascades to profound structural network inversions—without compromising diagnostic specificity.

This mathematical resolution offers a highly standardized, pre-mechanistic validation framework of significant utility for clinical trials. Standard linear clinical studies frequently encounter screening failures or false-negative results when atypical phenotypic variants are assessed using static staging scores, as such instruments misinterpret localized fractal shifts in vulnerability as global model dropouts or unstructured data noise. By applying the reverse-matching approach to the baseline OPC matrix, clinical investigators can objectively map individual kinetic trajectories to their precise biological compartments. This enables accurate single-subject stratification and ensures that therapeutic effects targeting disease progression can be accurately tracked along the true thermodynamic vector of least resistance, independent of clinical heterogeneity.

4.5 Translational validity and model robustness

4.5.1 *In vivo* biomarker validation and compartmental dominance

From a translational medicine perspective, these results indicate that atypical clinical anomalies are not stochastic outliers or statistical noise but highly sensitive, topographically determined early indicators of specific underlying systemic proteinopathies. The neurobiological validity of this compartmental architecture is directly confirmed by integrating individual tissue profiles with *in vivo* neuroimaging and molecular biomarkers, as demonstrated

by the hyperacute clinical manifestation within the already established picture of a multisystem disease in Case 5.³¹ Clinically, the patient presented with an established bilateral akinetic-rigid syndrome within a multisystem presentation, which was objectively reflected by independent *in vivo* biomarkers of striatal structural integrity: T2-weighted magnetic resonance imaging sequences revealed the classic hyperintense rim of the putamen, and postsynaptic iodine-123-iodobenzamide single-photon emission computed tomography imaging objectively confirmed a bilateral reduction in striatal dopamine D2 receptor density.

This multimodal *in vivo* profile confirms the presence of moderate degeneration within the putaminal architecture, reflecting the established pathology in this specific regional compartment. Crucially, however, the clinical presentation—rather than reflecting an isolated parkinsonian phenotype—was heavily dominated by severe, highly debilitating L-3,4-dihydroxyphenylalanine-resistant craniocervical dystonia manifesting as risus sardonicus. While routine molecular imaging lacks the resolution to provide specific neurochemical insights into the downstream medial globus pallidus, our network-based approach resolves this clinical stratification. The demonstrated involvement of the putamen explains why the entire trajectory exhibited complete spatial overlap within the systemic framework; nevertheless, the clinical phenotype remained dictated by the highly vulnerable, phylogenetically older substantia nigra and the pallidal networks, which both independently demonstrated maximal pathological vulnerability.

Furthermore, as the focal pallidal dystonia clinically overshadows and dominates the co-existing parkinsonian symptoms, this pooled matrix analysis successfully unmask how these highly vulnerable core structures dominate the overall phenotype, even when conventional *in vivo* markers focus primarily on the striatal changes. Identifying these specific network configurations elevates clinical anomalies from merely descriptive diagnostic

phenotypes—conventionally considered as rigid exclusion criteria in prospective trials—to predictive, pathophysiological windows.

4.5.2 Methodological rigor and sparse data principle

The methodology introduced here systematically decouples the spatial recruitment of neuronal networks from kinetic progression rates by translating nonlinear, semi-quantitative topographic distributions across various disease stages into mathematically standardized rank values. The mathematical robustness of this approach is particularly evident in its ability to accommodate historical reference data under the "sparse data principle," as illustrated by Case 6. Since Case 6 represents the landmark historical index case described by Niall Quinn³⁵—which formalized the clinical definition of disproportionate antecollis—the available clinical data are naturally more limited than data derived from modern, standardized assessment scales or prospective multicenter registries.

Crucially, the architecture of the "reverse-matching" approach functions effectively even in the absence of sophisticated, modern technical modalities or structured clinical indices. The model accommodates these clinical limitations, extracting the highly conserved pathodynamic signature directly from historical descriptions of the clinical phenomenon, by applying the standard mathematical procedure for averaging tied ranks—specifically for clinical rating scores—to account for non-linear scaling overlaps. Furthermore, a precise visual analysis of the published historical index photograph—which documents the patient's wide-based stance—makes it possible to demonstrate early, concurrent involvement of cerebellar networks along the disease validation trajectory (Trajectory 2). Thus, Case 6 underscores the clinical and translational utility of the sparse data principle embedded in the framework: it enables investigators to distill the true neuroanatomical essence from verified clinical observations and demonstrates that seminal historical reference cases can be seamlessly mapped onto modern quantitative systems-neurology matrices without introducing selection

biases or trajectory-specific intensity biases. In doing so, the framework accounts for dynamic, cell-type-specific depletion profiles across both proteinopathies.

4.6 Study limitations and outlook

Several limitations of the present study must be considered. Firstly, the architecture of this retrospective mapping relies on the phenomenological and radiological details extracted from published reports on index cases; subtle, subclinical multisystem symptoms or signs may be inherently overlooked, particularly within the comparatively brief reports of Cases 4 and 6. However, the model robustly accounts for the clinical reality of sparse data, where rapid and accurate diagnosis is vital and the "red flag" serves as a crucial non-cardinal warning sign in early, clinically paucisymptomatic disease phases.

Secondly, the sample size (consisting of six highly characterized index patients) is constrained by the relative rarity of precisely documented, purely atypical disease courses evaluated with consistent investigation and methodology. Crucially, however, this compact cohort size does not compromise the statistical validity of the conclusions. Since the framework applied here derives its analytical power from the robust consolidation of pooled data pairs ($n = 9$ per analytical track, $N = 18$ for the entire study cohort, reflecting the universal concept of tissue vulnerability within the OPC framework), statistical significance relies on the consistent intra-individual hierarchy across neuroanatomical nodes rather than on a large epidemiological sample size. Widespread stochastic noise or random outliers would inevitably result in chaotic, highly variable data distributions. In sharp contrast, the seamless alignment of these complex, atypical phenotypes with their respective, biologically plausible macro-vectors provides strong mathematical evidence for a deterministic biological principle. The systematic resolution of conventional staging discrepancies into a unified, non-linear gradient demonstrates that these phenotypic variants—regardless of the limited cohort size—reflect highly conserved systemic states.

Furthermore, conventional descriptive metrics often encounter severe limitations, as the quantitative density of protein inclusions does not consistently or uniformly parallel the actual rate of neuronal loss across different syndromic populations. This conceptual dilemma becomes heavily apparent when comparing large-scale post-mortem datasets within the specific cortical and limbic compartments of the matrix utilized here (TDP-43 group, Axis 1). In mixed syndromic cohorts that include FTD, ALS, and ALS-FTD combined, the pronounced consolidation of the neocortex leads to high correlations in the frontal and temporal cortex, driven by early tissue saturation and structural ceiling effects. In contrast, the analysis of the identical neocortical matrices collapses in classic ALS cohorts, where rapid neuromuscular failure limits survival. This underscores the strong cohort dependency of conventional linear tracking. Crucially, only the highly vulnerable mesiotemporal core (encompassing the amygdala/periamygdaloid cortex and the entorhinal cortex) presents a stable, highly significant architectural signal across both divergent study populations, although the associated correlation coefficients remain heavily constrained. This demonstrates that the total aggregate burden is mathematically insufficient to capture localized tissue death. This systematic decoupling is consistent with experimental models showing that the cytoplasmic aggregate load can mechanistically dissociate from active neurodegeneration.^{82,83} By utilizing the OPC reference matrix to capture multi-compartmental structural vulnerabilities—rather than volatile, linear lesion densities—the approach applied here successfully bypasses these cohort-specific and intensity-driven pathological mismatches, thereby ensuring robust translational validity.

Furthermore, it must be acknowledged that the static nature of cross-sectional mathematical analysis does not track future, real-time kinetic rates. Mechanistically, a longitudinal analysis is required to definitively distinguish between a transient, transitional state and a theoretically possible stationary focal arrest within localized tissue compartments.

Future research should focus on prospectively validating this reverse-matching approach. To this end, automated, high-resolution quantitative imaging and novel molecular *in vivo* biomarkers—including highly specific positron emission tomography tracers for tau,⁸⁴ recently validated radioligands targeting pathological α -synuclein aggregates,⁸⁵ as well as emerging tracers targeting pathological TDP-43 conformations⁸⁶—can be utilized to track the pathodynamics of neuronal networks in real time, starting from the earliest prodromal disease stages.

5 Conclusion

This study links individual variance and population statistics through systemic-level anatomical mapping, demonstrating the biological plausibility of rare and atypical neurodegenerative variants. Instead of treating individual clinical anomalies as stochastic phenotypic outliers, it is warranted to consider them as highly organized, reproducible tissue susceptibility states that expose localized fractal vulnerabilities. A scalable, predictive framework for early disease detection is established by mapping *in vivo* phenotypes onto standardized post-mortem datasets.

Crucially, resolving these individual anomalies represents the definitive stress test for the baseline framework: since the OPC matrix was originally validated against cohort statistics at the population level, its ability to seamlessly integrate and explain these singular, extreme variants without modification provides strong mathematical validation of its universal biological applicability. Consequently, this study advocates a conceptual shift: translational research should move away from inflexible, descriptive categorization toward dynamic, spatiotemporal network mapping. Redefining rare clinical phenomena as highly sensitive non-cardinal early warning signals ("red flags") and supportive features of systemic proteinopathies opens new avenues for timely diagnosis and targeted therapeutic intervention at the earliest

stages of disease progression. The "reverse-matching" approach introduced herein does not require case-specific autopsy data and enables a precise translational prediction of the disease course. This mathematical resolution offers a standardized, pre-mechanistic validation tool that paves the way for precise stratification at the single-subject level in future therapeutic trials targeting atypical neurodegenerative diseases.

Funding

No funding was received towards this work.

Conflict of interest

The author declares no conflicts of interest associated with his manuscript.

Supplementary material

Supplementary material is available online.

Author contribution

FG conceptualized the study, performed the mathematical modeling and statistical analysis, and drafted the manuscript.

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