

Supplementary Material

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

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Section S1 Operationalization of the histopathological reference matrix

S1.1 Definition of the motor neuron disease (MND)/frontotemporal dementia (FTD) reference matrix (ranks)

To map the extra-motor target pathway of the TDP-43 spectrum (Track A/cortico-limbic trajectory) onto the invariant onto-phylogenetic coordinate (OPC) system—which comprises 25 nodes—the distinct multiregional histopathological target zones derived from the cross-sectional reference dataset by Geser et al.¹ were projected onto homologous anatomical coordinates in the OPC. To avoid statistical saturation artifacts—specifically the ceiling effect (100% cohort prevalence) observed in the classic motor nodes of Axis 1 (spinal cord, medulla, motor cortex)—the mathematical analysis focused strictly on the progressive cross-sectional frequencies of Axis 2, operationalized via three key onto-phylogenetic tiers:

Frontal neocortex → prefrontal cortex node: $V_{\text{node}} = 2.7921$ (OPC Rank 1.0). The frontal neocortex (middle frontal gyrus) is structurally matched to the macrofunctional prefrontal cortex hub within the 2026 OPC framework, since the middle frontal gyrus constitutes the canonical topographical representative of the dorsolateral prefrontal networks. Phylogenetically, the prefrontal cortex is the most highly differentiated and most recent neocortical structure; this corresponds to an exceptionally high intrinsic protective field tension (κ), which mathematically results in the lowest baseline vulnerability value ($V_{\text{node}} = 1/\kappa = 2.7921$) and, consequently, the lowest vulnerability rank within this trajectory.

Temporal neocortex → entorhinal cortex hub: $V_{\text{node}} = 6.7085$ (OPC Rank 2.0). The temporal neocortex (superior-mid temporal gyrus) is translationally operationalized via the hub of the entorhinal cortex, which functions as the critical entry hub and topographic gatekeeper to the temporal neocortical network. Phylogenetically, the entorhinal hub functions as an elegant proxy and serves as a crucial transitional bridge (periallocortex) between allocortical limbic structures and highly differentiated, six-layered neocortical areas.

Amygdala complex → amygdala node: $V_{\text{node}} = 6.9494$ (OPC Rank 3.0). The subcortical amygdala complex projects directly onto the invariant amygdala node of the 2026 architecture. As an archaic, early-developing component of the limbic core (allocortex), it possesses a very low phylogenetic shielding; this is reflected in the highest baseline vulnerability value ($V_{\text{node}} = 6.9494$) within this specific trajectory and distinguishes the cortico-limbic pathway from confounding factors associated with the subcortical basal ganglia.

To avoid cross-modality intensity bias, a direct correlation between clinical-radiological *in vivo* scores and post-mortem histopathological scores was deliberately avoided. Instead, this framework operationalizes population-wide post-mortem data by converting binary lesion frequency data (%) according to Geser et al.¹ into an ordinal topographic probability score (Ranks 1–3). This distribution-based approach ranks regional disease susceptibility within network pathways, assigning lower ranks to regions with lower lesion frequencies or chronologically delayed involvement, whereas regions with more pronounced or maximal lesion accumulation are assigned higher ranks. To ensure methodological consistency, raw cohort prevalence percentages are omitted from the main manuscript's summary tables and instead systematically integrated into the analytical narrative.

For Axis 1 (the MND axis), cross-sectional post-mortem data show that the network's core nodes reach absolute pathological saturation, with the primary motor cortex, the medulla oblongata, and the cervical spinal cord all exhibiting a maximum cohort prevalence of 100%. The operationalization of the ordinal reference matrix for Axis 2 was also based on the conversion of continuous, prevalence gradients derived from definitive cohort data¹. Crucially, this absolute ceiling effect creates a mathematical tie across all motor nodes, demonstrating that a continuous, differentiated ordinal graduation within this pathway is inherently impossible. This statistical saturation directly explains why Axis 1 functions strictly as a purely descriptive nosological anchor framework, rather than contributing to the continuous ranking matrices.

By charting the progressive increase in regional pathological penetrance on Axis 2, a robust hierarchy was established that aligns perfectly with the proportionality scaling rule, which reveals a perfect deterministic inversion against the OPC framework: the subcortical amygdala complex—exhibiting the lowest relative pathological burden with a cohort prevalence of 28.6%—was defined as the initial cohort tracking node ($R_X = 1.0$, mapping on the OPC $R = 3.0$); the temporal cortex gray matter—showing an intermediate vulnerability threshold with a prevalence of 38.5%—served as the second trajectory step ($R_X = 2.0$, mapping onto OPC $R = 2.0$); and the middle frontal cortex gray matter—representing the maximal disease node within this axis at a prevalence of 58.1%—was operationalized as the third central anatomical node ($R_X = 3.0$, mapping onto OPC $R = 1.0$).

S1.2 Definition of the multiple system atrophy (MSA) reference matrix (ranks)

To map the subcortical motor pathway of the α -synuclein/MSA spectrum (Track B/striatonigral trajectory) onto the invariant OPC framework—which comprises 25 nodes—the classic histopathological target regions defined by the cross-sectional reference dataset of Jellinger (2005) were projected onto homologous anatomical coordinates within the OPC.

S1.2.1 Striatonigral trajectory

S1.2.1.1 Putamen (dorsolateral) → Striatum node: $V_{node} = 4.8472$ (glial cytoplasmic inclusions [GCI] rank 3, primary epicenter; neuronal loss rank 2, OPC rank 1.0)

This region serves as the primary somatotopic receptive field for cortical motor projections. It represents the initial neuropathological focus of the striatonigral system when focusing on GCIs. Within the GCI framework, it functions as the definitive epicenter (cohort rank 3), which is structurally matched with the macro-functional node of the striatum within the 2026 OPC framework. Phylogenetically, this core subcortical input node exhibits high evolutionary protective field tension (κ), which mathematically results in a lower baseline

vulnerability value ($V_{\text{node}} = 1/\kappa = 4.8472$) and, consequently, the lowest vulnerability rank (OPC rank 1.0) within this trajectory.

The Jellinger cohort metrics demonstrate an early, intermediate or maximal density of oligodendroglial inclusions (score 2/3+ in both Grade I and Grade II), followed by a decline to a lower density (2+) in the terminal stage of the disease (Grade III).² This deceleration from the pathological plateau is driven by the progressive breakdown of the tissue matrix and the loss of oligodendroglial cells. Crucially, under the alternative sensitivity mode—which focuses on structural cell death—this region falls back into the intermediate tier (cohort rank 2). Histopathologically, this downward shift is determined by the fact that the putaminal matrix remains largely spared during the early to intermediate stages of the disease (Grade I: score 0; Grade II: merely “+”) and exhibits severe neurodegenerative cell loss (2/3+) only in the terminal end stages (Grade III).

S1.2.1.2 Globus pallidus (medial) → septal nuclei proxy: $V_{\text{node}} = 7.4209$ (GCI rank 1, structural periphery; neuronal loss rank 1, OPC Rank 2.0)

As a passive, downstream component of the basal ganglia output network, this structure constitutes the structural periphery. To preserve topological invariance without introducing localized volume artifacts, the pallidum is translationally operationalized via the node of the septal nuclei, which occupies a homologous onto-phylogenetic trajectory within the transition zone between the basal forebrain and the striatum. With an intermediate value of ($V_{\text{node}} = 7.4209$), this proxy maps onto the intermediate vulnerability level within the OPC matrix (OPC rank 2.0).

Under the primary GCI density mode, the structure exhibits a consistently low GCI lesion load throughout the course of the disease (remaining unchanged at “+” across Grades I–III) and is thus clearly assignable to the initial trajectory step (cohort rank 1). In the alternative framework based on sensitivity to neuronal loss, the pallidum is classified correspondingly

(cohort rank 1), as histotopographically detectable neuronal depletion remains minimal (scoring $0/\pm$ in Grade II) or is limited to mild baseline features present at the terminal stage (scoring $+$ in Grade III); this ensures a stable multi-marker contrast, which is essential for the subsequent sensitivity analysis using dependent correlation comparisons.

SI.2.1.3 Substantia nigra pars compacta (dorsolateral) → locus ceruleus proxy: $V_{\text{node}} = 22.2627$ (GCI rank 2, intermediate node; neuronal loss rank 3, neuronal epicenter, OPC rank = 3]

In the primary framework tracking the dynamics of oligodendroglial inclusions, this central dopaminergic projection node is defined as an intermediate step (Cohort rank 2). Translational operationalization is achieved via the structurally anchored node of the locus coeruleus, as these two core catecholaminergic projection hubs of the brainstem share tightly parallelized catecholaminergic differentiation programs. From a phylogenetic perspective, this region possesses very little shielding in the face of advanced disease strain; this is reflected in the highest baseline vulnerability value ($V_{\text{node}} = 22.2627$) and the maximum vulnerability rank (OPC rank 3.0) within this track.

Within this pathway, GCIs exhibit an explicitly non-linear, bell-shaped accumulation kinetics: rising from a low baseline level ($+$) in Grade I to a peak during accelerated disease progression ($2+$ in Grade II), before declining again to a mild density ($+$) in the terminal end stages (Grade III). Crucially, however, in the alternative sensitivity framework based on structural cell death, this node undergoes a drastic pathophysiological expansion, ascending to the absolute pinnacle of the neurodegenerative hierarchy as a definitive neuronal epicenter (cohort rank 3). This upward ranking trajectory accounts for the fact that the presynaptic loss of dopaminergic cells constitutes a highly aggressive upstream driving force of the disease loop; it displays rapid acceleration ($0/2+$ in Grade I, $2/3+$ in Grade II) and reaches absolute, irreversible tissue exhaustion ($3+$ in Grade III).

S1.2.2 Olivopontocerebellar trajectory (qualitative nosological framework)

To maintain methodological consistency with the architecture of the primary manuscript—in which the olivopontocerebellar axis functions solely as a descriptive nosological framework rather than a quantitative predictive parameter—this trajectory is operationalized purely at a qualitative, spatiotemporal level. This qualitative synthesis is structurally required to contextualize the multi-systemic clinical features documented across the case series. Reviewing data from the Jellinger cohort² reveals a profound pathophysiological decoupling between the primary oligodendroglial inclusions (GCIs) handling and structural cell death within the infratentorial pathways. In contrast to the striatonigral degeneration pathway—which maintains a stable peripheral anchor point across markers—the olivopontocerebellar atrophy system exhibits highly asymmetric, non-linear changes. This directly illustrates why a continuous, linear ranking of this axis—which often recedes into the background—would lead to significant mathematical artifacts and variance inflation in the quantitative validation suites.

S1.2.2.1 Pontine basis

As the functional entry hub of the infratentorial network, the basis pontis (pontine nuclei) exhibits early maximal infiltration by oligodendroglial α -synuclein aggregates across Grade I and II. Consequently, based on cumulative GCI burden, it forms a prominent topographic landmark despite co-occurring structural tissue shifts (neuronal loss) in downstream elements. Within the shifting hierarchy of GCI density, the pontine pathway consistently functions as the temporally leading element of the circuit (pons > cerebellum $\geq$ inferior olive).

S1.2.2.2 Cerebellum

Although the moderate GCI load in the cerebellum matches the GCI burden of the inferior olive in Grades I-II, the cerebellum uniquely sustains a distinct, mild glial pathological

matrix into the advanced stage of the disease (Grade III). Crucially, this finer kinetic distinction is cross-validated by the early onset of Purkinje cell loss and demyelination. Regarding the structural hierarchy of neurodegenerative cell death, the cerebellar network exhibits a subtle, localized chronological lead over the inferior olive—a feature particularly evident at the intermediate Grade II (cerebellum > pons = inferior olive).

S1.2.2.3 Inferior olive

In accordance with the multi-center cross-sectional reference data established by Jellinger ², the advanced histopathological end-stage (Grade III) is characterized by severe, maximum neuronal loss accompanied by marked tissue gliosis (both rated 3+). Similar to the structural changes observed in the cerebellar cortex, the density of GCIs within the olivary nuclei shows a relative drop to minimal levels at the end-stage. Within the qualitative framework of Track B, this synchronous combination of massive structural cell death and reduced local inclusion load defines the definitive neuropathological profile of advanced infratentorial MSA.

Section S2 Pathophysiologic rationale for the *in vivo* regional clinical-radiological scoring

S2.1 Group 1: Cortico-limbic (cortico-behavioral) cases

S2.1.1 Case 1³, amyotrophic lateral sclerosis with pseudobulbar affect/anxiety and amygdala atrophy

S2.1.1.1 Axis 1: MND (corticospinal/bulbar) axis

S2.1.1.1.1 Motor cortex

While upper motor neuron involvement was clearly demonstrated by hyperactive tendon reflexes and expanded reflex zones in the cervical and lumbar segments, the cortically mediated motor disturbance was submaximal. This topographically selective dysfunction of the upper

motor neuron system was further confirmed by motor-evoked potential studies, which revealed delayed response latencies and prolonged central motor conduction times to the lower limbs, but not to the upper limbs. The clinical examination noted the absence of the Babinski sign and ankle clonus, showing only mild bilateral upper-extremity spasticity. Furthermore, no macroscopic atrophy of the precentral gyrus was detected on the structural 1.5 T magnetic resonance imaging (MRI) sequences.

S2.1.1.1.2 Medulla oblongata

The bulbar region represents a prime clinical example of advanced, severe lower motor neuron degeneration. The patient exhibited rapid progression from barely understandable hypophonia necessitating written communication early on, to complete anarthria. Videofluoroscopic examinations revealed dysphagia coupled with tongue paresis that progressed rapidly, necessitating the early placement of a percutaneous endoscopic gastrostomy for nutritional support.

S2.1.1.1.3 Cervical spinal cord

The destruction of the lower motor neurons in the cervical spinal cord was severe and rapidly progressive. Electromyographic testing confirmed neurogenic changes and fasciculations within cervical spinal cord segments, accompanied by a significant reduction in amplitude of cervical somatosensory evoked potentials. This severe lower motor neuron denervation culminated in rapid generalized functional failure, rendering the patient completely unable to stand without assistance within a short period of time.

S2.1.1.2 Axis 2: Dementia (limbic-cortical) axis

S2.1.1.2.1 Medial frontal cortex [Severity score: 2 (moderate)]

Neuropsychological evaluation revealed psychomotor slowness, and concentration abilities were far below average, reflecting moderate frontal lobe involvement. However, global

cognitive function remained intact, as evidenced by a Mini-Mental State Examination score of 30. Concurrently, executive and visuospatial planning were preserved, as indicated by a non-demented clock-drawing test score (score: 2), thereby precluding a severe classification (score 3).

S2.1.1.2.2 Temporal cortex [Severity score: 2 (moderate)]

This neocortical temporal cortex score was based solely on objective structural neuroimaging metrics derived from T1- and T2-weighted 1.5-T MRI sequences. Coronal and axial scans showed clear macroscopic tissue loss, characterized by localized atrophy of the temporal lobe poles and an associated expansion of the adjacent temporo-polar subarachnoid space.

S2.1.1.2.3 Amygdala [Severity score: 3 (severe)]

As the central component of this clinical variant, the amygdala complex exhibited the most pronounced pathological changes. Structural coronal imaging revealed profound, bilateral asymmetric (right greater than left) atrophy of the amygdala and adjacent periamygdaloid cortical zones. This structural deterioration was clinically objectified by a severe neuropsychiatric phenotype, including an extreme elevation in baseline trait anxiety at the 95th percentile (score: 59) along with a highly elevated acute state anxiety score of 67 on the State-Trait Anxiety Inventory. The clinical severity was further evidenced by the manifestation of a pseudobulbar affect characterized by pathological crying (and laughing).

S2.1.2 Case 2⁴, progressive bulbar palsy with eccentric behavioral changes and channeled creativity

S2.1.2.1 Axis 1: MND axis (corticospinal/bulbar)

S2.1.2.1.1 Motor cortex

This score reflects the evident, multi-level impairment affecting cortical motor planning networks and descending execution pathways. The involvement of the motor network was demonstrated across multiple levels of the neuraxis. The progressive clinical course showed prominent spinal lower motor neuron features characterized by an asymmetric, predominantly left-sided, flaccid tetraparesis, accompanied by generalized muscle atrophy and weakness. The involvement of the upper motor neuron/corticospinal system was distinctly demonstrated by a specialized speech-language pathology finding, i.e., buccofacial apraxia. This deficit indicates an impairment in higher-level cortical motor planning and coordination of the upper motor network, extending beyond peripheral execution by the lower motor neuron. A maximum severity score of 3 was ruled out as the patient showed diminished—and not hyperactive—deep tendon reflexes in all extremities and no macroscopic atrophy of the precentral gyrus on the 1.5 T MRI.

S2.1.2.1.2 Medulla oblongata

The bulbar compartment represents the clinical and diagnostic hallmark of this patient. He exhibited rapidly progressive speech and bulbar dysfunction that had been present for one to two years, characterized by slurred, strained, and slowed articulation, accompanied by difficulties with swallowing and chewing. A specialized speech-language pathology examination revealed dysarthrophonia, moderate-to-severe dysphagia, and orofacial impairments with tongue fasciculations. The degeneration of vital bulbar nuclei and lower motor neuron components in the medulla oblongata was underscored by intermittent, extremely

distressing clinical episodes with a “feeling of suffocation” and associated rapid weight loss of 5 to 6 kg within one year. This clinical picture corresponds to the highest classification for critical brainstem failure.

S2.1.2.1.3 Cervical spinal cord

The destruction of the lower motor neuron within the spinal cord was severe, anatomically extensive, and functionally catastrophic. The patient exhibited progressive generalized muscle wasting, which was particularly pronounced in the small hand muscles, reflecting severe cervical anterior horn cell degeneration. Quantitative electromyography provided objective electrophysiological evidence of active denervation and chronic neurogenic changes, demonstrating widespread pathological spontaneous activity (muscle fasciculations) across all examined muscle regions, including the cervically innervated right biceps brachii and left abductor pollicis brevis, as well as the lumbar- innervated right vastus medialis and the lumbosacral-innervated left tibialis anterior. Electrophysiologically, the transformation of motor units was underlined by a polyphasia rate of 50% to 60%, and ongoing denervation was evidenced by the presence of positive sharp waves in the left tibialis anterior muscle. Biomechanically, this severe multi-segmental loss of lower motor neurons led to a profound loss of structural stability, resulting in an unsteady gait, severe postural instability on the Romberg test, and an omnidirectional tendency to fall, culminating in an asymmetric, predominantly left-sided, flaccid tetraparesis over the disease course.

S2.1.2.2 Dementia (limbic-cortical) axis

S2.1.2.2.1 Medial frontal cortex [Severity score: 1 (mild)]

This score reflects a mild, subtle dysfunction that was strictly circumscribed. Objective, standardized neuropsychological test batteries (Consortium to Establish a Registry for Alzheimer's Disease-Plus) documented only mild, isolated impairments in executive control

and visuoconstructive abilities, as evidenced by the standardized Z-score profile. Notably, critical frontal and global indices, such as the Mini-Mental State Examination (30/30) and the Trail Making Test Part A remained within normal limits. The Trail Making Test Part B indicated an executive vulnerability characterized by a "loss of concept." However, the preservation of frontally mediated cognitive flexibility was clinically confirmed by the patient's excellent response to cognitive behavioral therapy. Leveraging his intact metacognition, he successfully recognized and reframed distorted attributions about alcohol's effect on creativity through logical reinterpretation. 1.5 T MRI did not show frontal atrophy, a finding consistent with mild, early-stage network involvement.

S2.1.2.2.2 Temporal cortex [Severity score: 2 (moderate)]

The degeneration of the neocortical and paralimbic temporal lobe was demonstrated by objective structural neuroimaging parameters and by corresponding functional cognitive deficits. Coronal and axial 1.5-T MRI sequences revealed right-sided atrophy of the medial temporal lobe, encompassing the temporal pole, hippocampus, and adjacent entorhinal cortex. This structural decline was functionally validated by neuropsychological testing, which objectively identified impairment in semantic verbal fluency (animal naming test) on the Consortium to Establish a Registry for Alzheimer's Disease-Plus battery, demonstrating a moderate disturbance in the temporal lobe-mediated access to the semantic network.

S2.1.2.2.3 Amygdala [Severity score: 3 (severe)]

The amygdala complex exhibited the most advanced pathological changes, with structural imaging revealing significant macroscopic tissue atrophy, most pronounced in the amygdala relative to the surrounding temporal structures. This tissue destruction was reflected in an extreme, chronic, and severe neuropsychiatric phenotype during his clinical course spanning many years. This presentation was characterized by severe, treatment-resistant depressive episodes, persistent suicidal ideation, acute suicidal crises, and a massive,

maladaptive alcohol dependence utilized as a dysfunctional coping mechanism. Such profound affective disinhibition within the limbic network culminated in bizarre, morbid behaviors, such as placing a real coffin in his private room (utilized for T-shirt storage) as a preparation for his death.

This behavior contrasted with his lifelong artistic activities, which varied in intensity but remained a canalized, intact cognitive resource for expressing and navigating his inner world throughout the disease course (Supplementary Fig. S1). Due to a long-standing misattribution crediting alcohol for his personal, professional, and artistic endeavors, the patient failed to recognize this contrast until undergoing psychotherapy.

S2.1.3 Case 3⁵, FTD with depression, socially inadequate behaviors, and eruptive, stylistically altered creativity

S2.1.3.1 Axis 1: MND axis (corticospinal/bulbar)

S2.1.3.1.1 Motor cortex

The long-term clinical observation documented a late transition to parkinsonian features. These deficits manifested as a bound posture, an increasingly unsteady gait, and falls, culminating in wheelchair dependence (“largely wheelchair bound”) alongside a supranuclear gaze palsy. Since these features indicate an infiltration of the subcortical extrapyramidal system rather than pyramidal upper motor neuron failure with widespread spasticity, they were excluded from this motor cortex analysis. However, radiological evidence showed of a progressive, bilateral, left-predominant frontotemporal atrophy that anatomically eventually also encompasses the motor cortex.

S2.1.3.1.2 Medulla oblongata

In the advanced stage of the disease, the brainstem region showed clinical involvement, characterized by the onset of dysphagia, in the context of the switch from melperone and

aripiprazole to low-dose quetiapine due to extrapyramidal concerns. Clinically, this bulbar dysfunction was not due to a primary lower motor neuron degradation of the brainstem nuclei themselves; rather, it represented a pseudobulbar supranuclear deafferentation caused by the dysfunction of frontomoto-cortical inputs from above, closely tracking the patient's atypical, co-occurring extrapyramidal features and vertical gaze palsy.

S2.1.3.1.3 Cervical spinal cord

Signs of peripheral motor instability and secondary spinal cord network involvement were functionally manifest. Indeed, longitudinal observation documented a worsening overall mobility characterized by an increasingly unsteady gait and recurrent falls, including a major fall at age 80 years. Since these falls were exacerbated by a supranuclear gaze palsy and subcortical extrapyramidal motor dysfunction, rather than by a localized paraplegic syndrome with lower motor neuron denervation, they cannot serve as primary indicators for advanced spinal failure.

S2.1.3.2 Axis 2: Dementia (limbic-cortical) axis

S2.1.3.2.1 Medial frontal cortex [Severity score: 2 (moderate)]

Impairment of the executive frontal network was pronounced, as evidenced by cranial CT scans revealing bilateral, left-predominant frontal lobe atrophy. This structural decline was clinically confirmed by executive dysfunction on the Consortium to Establish a Registry for Alzheimer's Disease-Plus test battery, encompassing deficits in goal setting, planning, and coordination, as well as by marked behavioral disinhibition, logorrhea, and a lack of insight and social awareness of the illness. However, a maximum severity score of 3 was ruled out due to a characteristic neuropsychological dissociation; while the patient's semantic verbal fluency was significantly impaired, her phonemic verbal fluency (S-words) remained entirely intact, even scoring above average. This preservation indicates that the frontocortical networks

required for speech generation and specific cognitive-executive loops were structurally and functionally operational, thereby confirming a moderate rating of 2.

S2.1.3.2.2 Temporal cortex [Severity score: 3 (severe)]

The temporal corridor represented the pathodynamic epicenter of this phenotype. On cranial CT imaging, a pronounced, progressive bilateral tissue loss—accentuated on the left—was observed. A marked decline in semantic verbal fluency, severe deficits in verbal new memory formation, and a profound failure in retrieving non-verbal content functionally corroborated this morphological disintegration. Over two decades, there was an artistic transformation, during which three-dimensionality and fine structural geometric details were increasingly abandoned, while contrast and the color spectrum broadened. Taken together, a maximum score of 3 is justified.

S2.1.3.2.3 Amygdala [Severity score: 3 (severe)]

Structural involvement of this subcortical limbic node was morphologically embedded within the radiologically verified, advanced medial temporal atrophy. In parallel to the severe degeneration of the surrounding temporal neocortex, this subcortical nuclear complex exhibited a profound loss of functional integrity. This structural disintegration gave rise to a persistent psychiatric phenotype spanning many years, characterized by intolerance to criticism and chronic, maladaptive alcohol consumption, serving as a dysfunctional coping mechanism. At clinical presentation, these symptoms intensified into a depressive-behavioral phenotype marked by profound emotional lability, pervasive suspiciousness, irritability, and socially inappropriate verbal outbursts or verbal aggressiveness that ultimately required targeted psychopharmacological intervention. Later in the clinical disease course, the advanced breakdown of amygdalar network modulation culminated in a dramatic behavioral and affective shift, transitioning from a hostile, defensive attitude toward a childlike, excessively affectionate euphoria. Given the inextricable alignment between macrostructural tissue loss and profound

clinical and psychiatric impairment, classification at the maximum severity level (score 3) is justified.

S2.2 Group 2: Subcortical/brainstem-striatal-cerebellar cases

S2.2.1 Case 4^{6,7}, multiple system atrophy (MSA) with risus sardonicus and quivering dysarthria

S2.2.1.1 Trajectory 1: Striatonigral trajectory

S2.2.1.1.1 Putamen [Severity score: 2 (moderate)]

The patient exhibited a clinically confirmed parkinsonian syndrome, explicitly documented by marked hypomimia. This characteristic masking of facial expression directly reflects an advanced, established dysfunction of the primary striatal motor circuits. Since photographic evidence demonstrated that the patient was still able to sit upright, maintain fixation, and actively cooperate during clinical examinations, a maximum functional severity of 3 was ruled out. These findings also exclude a state of total motor collapse or an end-stage akinetic crisis. Thus, a moderate severity score of 2 is justified.

S2.2.1.1.2 Pallidum [Severity score: 3 (severe)]

The prime clinical feature and critical warning sign of this case was severe, highly debilitating cranial and cervical dystonia. Photographic analysis confirmed marked, asymmetric orofacial distortion presenting as a classic "risus sardonicus," combined with severe cervical dystonia affecting the platysma. Given that this massive hyperkinetic manifestation dominated the regional physical presentation and reflects profound functional dysregulation of downstream basal ganglia projection pathways, classification at the highest level of severity (Score 3) is justified.

S2.2.1.1.3 Substantia nigra [Severity score: 3 (severe)]

Building on the clinical phenotype of the progressive parkinsonian syndrome, the accompanying marked hypomimia clinically indicates advanced dysfunction of the presynaptic nigrostriatal system. To maintain pathophysiological consistency with the pronounced neurodegenerative architecture of the striatonigral pathway and to account for the fact that presynaptic dopaminergic loss constitutes the obligatory, upstream driving force of the profound striatal network dysfunction—which secondary unbalances basal ganglia projection pathways and manifests as severe dystonia—a maximum severity grade of 3 is assigned.

S2.2.1.2 Trajectory 2: Olivopontocerebellar trajectory

S2.2.1.2.1 Cerebellum

Although classic appendicular limb ataxia was not reported in the brief clinical case description, the specialized neurological examination documented a highly characteristic tremulous component within the patient’s speech, specifically presenting as a distinct quivering dysarthria. From a network perspective, this vocal tremor reflects a rhythmic instability in the real-time fine-tuning of the laryngeal and orofacial muscles, which is a classic functional manifestation of disrupted cerebellar-brainstem loops.

S2.2.1.2.2 Basis pontis

The involvement of the pontine projection networks and the pontine gray nuclei is objectively evidenced by the distinct, strangled, high-pitched dysarthria. This mixed speech pattern reflects a marked dysregulation of the pontokinetically mediated pathways that control phonatory coordination, representing a pathophysiologically distinct dysfunction. This phonatory constriction reflects the convergence of the coexisting MSA parkinsonian-type (MSA-P) phenotype and cerebellar network dysfunction, alongside the involvement of the pyramidal tract at the level of the brainstem. In particular, degeneration of the corticobulbar

fibers passing through the basis pontis results in a pronounced spastic component of the speech pattern. This mixed spastic-rigid and ataxic phonatory pattern overlays the tremor-like (quivering) component of the dysarthria.

S2.2.1.2.3 Inferior olive

The inferior olivary nucleus represents a synchronized downstream component within the climbing fiber loop. From a purely clinical perspective, isolated network dysfunction of the inferior olive does not present as a classic coordination deficit but rather manifests through specific, positive hyperkinesias of the lower brainstem associated with a disorder of the Guillain-Mollaret triangle. There was no atypical lower brainstem hyperkinesia that would complicate assessment—such as rhythmic palatal tremor, palatopharyngolaryngeal myoclonus, or localized vertical ocular oscillations indicative of disruption of the Guillain-Mollaret triangle—thereby reflecting that the quivering dysarthria is fully explained by the pontocerebellar interface nodes (basis pontis and cerebellum), and establishing a pure, non-confounded MSA phenotype.

S2.2.2 Case 5⁸, MSA with risus sardonicus

S2.2.2.1 Trajectory 1: Striatonigral trajectory

S2.2.2.1.1 Putamen [Severity score: 2 (moderate)]

Multimodal structural and functional neuroimaging demonstrated robust involvement of the striatal network. Specifically, T2-weighted MRI sequences showed a characteristic hyperintense rim lateral to both putamina, while diffusion-weighted imaging revealed regional apparent diffusion coefficients near the upper limit. Additionally, an ¹²³I-iodobenzamide SPECT examination confirmed a bilateral, right-dominant decrease in dopamine D2 receptor density. Because the patient was still able to push herself up with her arms when attempting to

rise from a chair, a terminal state of complete kinetic collapse was ruled out, thereby justifying a moderate severity rating of 2.

S2.2.2.1.2 Pallidum [Severity score: 3 (severe)]

The definitive clinical red flag in this patient was marked, highly disabling craniocervical dystonia. The patient showed a noticeable, symmetric distortion of the lower face and anterior neck muscles, a hyperkinetic phenomenon that persisted even after levodopa discontinuation. Because this focal dystonia dominated the regional physical appearance and caused severe functional impairment, a maximum severity rating of 3 was assigned.

S2.2.2.1.3 Substantia nigra [Severity score: 3 (severe)]

A widespread degeneration of the presynaptic nigrostriatal projection system manifested clinically as an early onset of asymmetric stiffness and slowness in the right lower limb associated with falls to the front. This syndrome progressively expanded into a severe, bilateral akinetic-rigid syndrome characterized by generalized bradykinesia and pronounced axial and limb rigidity (right > left). This structural failure was further confirmed by a negative levodopa test showing no response as measured by the Unified Parkinson's Disease Rating Scale. Given that the pronounced presynaptic dopamine deficiency constitutes the obligatory pathophysiological driver of the functional collapse of the striatonigral loop, secondarily enabling the severe focal dystonia through downstream basal ganglia dysregulation, a maximum severity score of 3 is fully warranted.

S2.2.2.2 Trajectory 2: Olivopontocerebellar trajectory

S2.2.2.2.1 Cerebellum

The patient showed definitive signs of cerebellar network failure, including pronounced limb ataxia and a characteristic wide-based stance during clinical evaluation in the early-to-mid

stage of the disease. This presentation indicates an established, submaximal disruption of the cerebellar cortex and Purkinje cell proprioceptive feedback loops.

S2.2.2.2.2 Pons

Involvement of the brainstem network within the basis pontis projection tracts and the associated gray matter nuclei was objectively evidenced by several independent oculomotor deficits. The patient exhibited broken-up smooth pursuit eye movements, gaze-evoked nystagmus at an eccentric eye position exceeding 45 degrees, and slowed vertical saccadic eye movements. Taken together, these findings indicate a well-established dysregulation of the paramedian pontine reticular formation and related tracking circuitry traversing the pontine brainstem.

S2.2.2.2.3 Inferior Olive

The inferior olivary nucleus functions as a synchronous downstream node within the ascending olivocerebellar climbing fiber loop. There are no documented isolated, hyperkinetic signs originating intrinsically from the medulla oblongata—such as a rhythmic palatal tremor, palatopharyngeal-laryngeal myoclonus, or localized vertical ocular oscillations indicative of active dysfunction of the Guillain-Mollaret triangle.

S2.2.3 Case 6⁹, MSA with disproportionate antecollis

S2.2.3.1 Trajectory 1: Striatonigral trajectory

S2.2.3.1.1 Putamen [Severity score: 2 (moderate)]

The patient presented with a clinically confirmed parkinsonian syndrome, leading to a clinical diagnosis of probable MSA-P.¹⁰ This diagnostic status inherently implies marked dysfunction of the primary striatal motor circuits that is poorly responsive or unresponsive to levodopa therapy. A maximum severity score of 3 was ruled out based on objective clinical-

functional findings: the patient was still able to stand freely and unsupported, thereby excluding terminal motor immobility or an end-stage akinetic crisis. Thus, an intermediate severity score of 2 is justified.

S2.2.3.1.2 Pallidum [Severity score: 3 (severe)]

The clinical centerpiece and red flag of this case was a highly disproportionate antecollis, characterized by severe, involuntary forward flexion of the head and neck, with comparatively minor flexion elsewhere. This severe segmental axial dystonia reflects profound, disruptive hyper-recruitment and dysregulation of the pallidal output pathways (specifically the internal segment of the globus pallidus). Given that this specific phenomenon was the most debilitating and physically dominant feature driving the patient's biomechanical instability, assigning the maximum severity score of 3 is fully justified.

S2.2.3.1.3 Substantia nigra [Severity score: 3 (severe)]

Advanced dysfunction of the presynaptic nigrostriatal projection system was clinically evidenced by overall motor impairment and—crucially—by a poor or negligible response to levodopa therapy consistent with Quinn’s criteria for a diagnosis of probable MSA-P. A lack of therapeutic response to high-dose levodopa serves as a reliable *in vivo* marker for profound, irreversible neurodegenerative loss of dopaminergic projections originating in the substantia nigra, driving downstream collapse of the striatal loop. While the published case photograph shows the patient still able to stand unaided, this preserved biomechanical function of the lower extremities underscores the highly compartmentalized, segmental nature of the axial motor disorder rather than indicating a moderate overall disease burden; thus, a maximum score of 3 is warranted.

S2.2.3.2 Trajectory 2: Olivopontocerebellar trajectory

S2.2.3.2.1 Cerebellum

Because this historically significant case presented phenotypically as a predominantly striatonigral variant (probable MSA-P), there was no evidence of widespread cerebellar degeneration in the written report that would have met the full, core diagnostic criteria for the cerebellar variant of MSA. However, visual analysis of the published index photograph clearly documents a wide-based stance. This localized widening of the base of support reflects an early, subtle disturbance of the cerebellar cortex (Purkinje cells), impairing the real-time integration of proprioceptive feedback loops during unassisted standing.

S2.2.3.2.2 Pons

Regarding the pontine pathways, there was a complete absence of documented clinical or neuroimaging signs indicating functional impairment or structural pontine network failure.

S2.2.3.2.3 Inferior olive

The inferior olivary nucleus constitutes a downstream component within the ascending olivocerebellar climbing fiber loop. No signs of localized lower brainstem hyperkinesia—such as a rhythmic palatal tremor or involuntary orofacial movements—were reported.

Section S3 Supplementary Tables S1 to S6: Network susceptibility mapping and rank correlation matrix for Case 1 to Case 6

Table S1: Network susceptibility mapping and rank correlation matrix for Case 1 (amyotrophic lateral sclerosis with amygdala atrophy)³

Anatomical Axis	Region of Interest	Case Recruitment (0/1)	Case Severity Score (0-3)	Conventional Cohort Rank (R_X)	OPC Framework (R)	Case Rank (R_Y)
Axis 2	Middle frontal cortex	1	2	3 (58.1%)	1 ($V_{\text{node}} = 2.7921$)	1.5
Axis 2	Temporal cortex	1	2	2 (38.5%)	2 ($V_{\text{node}} = 6.7085$)	1.5
Axis 2	Amygdala	1	3	1 (28.6%)	3 ($V_{\text{node}} = 6.9494$)	3.0

Statistical metrics:

Jaccard Similarity Index: Axis 2 (limbic-cortical), $J = 1.00$.

The conventional cohort ranks (R_X) are derived from the post-mortem reference dataset by Geser et al.¹, whereas the fractally invariant ontogenetic-phylogenetic coordinate system (OPC) ranks (R) are extracted from the Geser et al.¹¹ framework. Detailed neuroanatomical and clinical descriptions of the cohort hierarchies, structural proxies, and individual patient profiles are provided in the Supplementary Material, Sections S1 and S2.

Table S2: Network susceptibility mapping and rank correlation matrix for Case 2 progressive bulbar palsy with eccentric behavioral changes and channeled creativity⁴

Anatomical Axis	Region of Interest	Case Recruitment (0/1)	Case Severity Score (0-3)	Conventional Cohort Rank (R_X)	OPC Framework (R)	Case Rank (R_Y)
Axis 2	Middle frontal cortex	1	1	3 (58.1%)	1 ($V_{\text{node}} = 2.7921$)	1.0
Axis 2	Temporal cortex	1	2	2 (38.5%)	2 ($V_{\text{node}} = 6.7085$)	2.0
Axis 2	Amygdala	1	3	1 (28.6%)	3 ($V_{\text{node}} = 6.9494$)	3.0

Statistical metrics:

Jaccard Similarity Index: Axis 2 (limbic-cortical), $J = 1.0$.

The conventional cohort ranks (R_X) are derived from the post-mortem reference dataset by Geser et al. ¹, whereas the fractally invariant ontogenetic-phylogenetic coordinate system (OPC) ranks (R) are extracted from the Geser et al. ¹¹ framework. Detailed neuroanatomical and clinical descriptions of the cohort hierarchies, structural proxies, and individual patient profiles are provided in the Supplementary Material, Sections S1 and S2.

Table S3: Network susceptibility mapping and rank correlation matrix for Case 3 FTD with depressive-behavioral phenotype and eruptive, stylistically altered creativity⁵

Anatomical Axis	Region of Interest	Case Recruitment (0/1)	Case Severity Score (0-3)	Conventional Cohort Rank (R_X)	OPC Framework (R)	Case Rank (R_Y)
Axis 2	Middle frontal cortex	1	2	3 (58.1%)	1 ($V_{\text{node}} = 2.7921$)	1.0
Axis 2	Temporal cortex	1	3	2 (38.5%)	2 ($V_{\text{node}} = 6.7085$)	2.5
Axis 2	Amygdala	1	3	1 (28.6%)	3 ($V_{\text{node}} = 6.9494$)	2.5

Statistical metrics:

Jaccard Similarity Index: Axis 2 (limbic-cortical), $J = 1.0$.

The conventional cohort ranks (R_X) are derived from the post-mortem reference dataset by Geser et al.¹, whereas the fractally invariant ontogenetic-phylogenetic coordinate system (OPC) ranks (R) are extracted from the Geser et al.¹¹ framework. Detailed neuroanatomical and clinical descriptions of the cohort hierarchies, structural proxies, and individual patient profiles are provided in the Supplementary Material, Sections S1 and S2.

Table S4: Network susceptibility mapping and rank correlation matrix for Case 4 (multiple system atrophy with risus sardonicus)^{6,7}

Anatomical Trajectory	Region of Interest	Case Recruitment (0/1)	Case Severity Score (0-3)	Cohort Rank (R_X)	OPC Framework (R)	Case Rank (R_Y)
Trajectory 1	Putamen	1.0	2.0	3	1 ($V_{\text{node}} = 4.8472$)	1.0
Trajectory 1	Pallidum	1.0	3.0	1	2 ($V_{\text{node}} = 7.4209$)	2.5
Trajectory 1	Substantia nigra	1.0	3.0	2	3 ($V_{\text{node}} = 22.2627$)	2.5

Statistical metrics:

Jaccard similarity index: Trajectory 1 (striatonigral degeneration), $J = 1.0$.

The conventional cohort ranks (R_X) are derived from cumulative ordinal glial cytoplasmic inclusion severity profiles across three distinct disease grades within the post-mortem reference dataset by Jellinger et al.², whereas the fractally invariant ontogenetic-phylogenetic coordinate system (OPC) ranks (R) are extracted from the Geser et al.¹¹ framework. Detailed neuroanatomical and clinical descriptions of the cohort hierarchies, structural proxies, and individual patient profiles are provided in the Supplementary Material, Sections S1 and S2.

Table S5: Network susceptibility mapping and rank correlation matrix for Case 5 (multiple system atrophy with risus sardonicus)⁸

Anatomical Trajectory	Region of Interest	Case Recruitment (0/1)	Case Severity Score (0-3)	Cohort Rank (R_X)	OPC Framework (R)	Case Rank (R_Y)
Trajectory 1	Putamen	1.0	2.0	3	1 ($V_{\text{node}} = 4.8472$)	1.0
Trajectory 1	Pallidum	1.0	3.0	1	2 ($V_{\text{node}} = 7.4209$)	2.5
Trajectory 1	Substantia nigra	1.0	3.0	2	3 ($V_{\text{node}} = 22.2627$)	2.5

Statistical metrics:

Jaccard similarity index: Trajectory 1 (striatonigral degeneration), $J = 1.0$.

The conventional cohort ranks (R_X) are derived from cumulative ordinal glial cytoplasmic inclusion severity profiles across three distinct disease grades within the post-mortem reference dataset by Jellinger et al.², whereas the fractally invariant ontogenetic-phylogenetic coordinate system (OPC) ranks (R) are extracted from the Geser et al.¹¹ framework. Detailed neuroanatomical and clinical descriptions of the cohort hierarchies, structural proxies, and individual patient profiles are provided in the Supplementary Material, Sections S1 and S2.

Table S6: Network susceptibility mapping and rank correlation matrix for Case 6 (multiple system atrophy with disproportionate antecollis)⁹

Anatomical Trajectory	Region of Interest	Case Recruitment (0/1)	Case Severity Score (0-3)	Cohort Rank (R_X)	OPC Framework (R)	Case Rank (R_Y)
Trajectory 1	Putamen	1.0	2.0	3	1 ($V_{\text{node}} = 4.8472$)	1.0
Trajectory 1	Pallidum	1.0	3.0	1	2 ($V_{\text{node}} = 7.4209$)	2.5
Trajectory 1	Substantia nigra	1.0	3.0	2	3 ($V_{\text{node}} = 22.2627$)	2.5

Statistical metrics:

Jaccard similarity index: Trajectory 1 (striatonigral degeneration), $J = 1.0$.

The conventional cohort ranks (R_X) are derived from cumulative ordinal glial cytoplasmic inclusion severity profiles across three distinct disease grades within the post-mortem reference dataset by Jellinger et al.², whereas the fractally invariant ontogenetic-phylogenetic coordinate system (OPC) ranks (R) are extracted from the Geser et al.¹¹ framework. Detailed neuroanatomical and clinical descriptions of the cohort hierarchies, structural proxies, and individual patient profiles are provided in the Supplementary Material, Sections S1 and S2.



Supplementary Fig. S1: Channeled creativity of Case 2

This surrealistic-to-abstract multimedia collage was created from weathered waste materials (such as rusted metal parts and objects with peeling paint) by Case 2, a male patient with progressive bulbar palsy and a secondary, frontotemporal-like phenotype⁴). Driven by an internal need for communication approaching death, he presented this artwork as a gift to his physician late in the disease course. The patient conceptualized his artworks as “makings,” rather than artistic achievements, aiming to visualize the “beauty of the evanescent.” He was reluctant to assign titles to his artwork, since he did not want to restrict the viewer’s imagination.

The collage features a heavy, ornate picture frame enclosing a central, prison-like cage grid that conceals a colorful humanoid figure, hidden behind iron bars, set against a deep blue and greenish background. A sun-like circular disk, shining in gold, dips into the cage, while a pipe and a metal-like tuft occupy the bottom corners, and a single puzzle piece is situated in an upper corner. From a network-anatomical perspective, this expressive act reflects the profound extra-motor target-network recruitment observed in this case variant. In particular, it demonstrates that the phylogenetic shielding of the highly protected prefrontal structure leaves the structural integrity of these high-level cortical architectures relatively intact long enough to facilitate—in the face of the severe, catastrophic degeneration of bulbar neurons—a powerful channel for the patient's inner life and coping mechanisms ("self-healing"). The patient gave full informed consent and kindly agreed to the public release of his artwork and his medical history.

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