Lesion-Independent Thalamic Degeneration Identifies Intrinsically Vulnerable Nuclei Associated with Cognitive Impairment in Multiple Sclerosis

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Abstract

Background: Cognitive impairment in multiple sclerosis (MS) is driven by both focal inflammation and compartmentalized neurodegeneration, yet the relative effect of lesion-independent thalamic atrophy on information processing speed (IPS) remains unclear.

Methods: This retrospective cohort study included 100 participants with MS. Automatic segmentation techniques quantified lesion load and delineated 26 thalamic regions of interest (ROIs). Linear models compared associations between ROI volumes and Symbol Digit Modalities Test (SDMT) performance in lesion-adjusted and unadjusted models.

Results: Twenty-one of 26 ROIs showed significant SDMT associations before lesion adjustment; twelve remained significant after adjustment. Lesion-independent associations were observed in the global thalamus, sensory relay nuclei (ventral posterolateral, medial and lateral geniculate), and associative hubs (pulvinar and mediodorsal-parafascicular complex). These intrinsically vulnerable nuclei exhibited significantly lower lesion-mediated effects (13.4%) than those losing significance after adjustment (34.2%, $p < 0.001$).

Conclusion: Our findings suggest that IPS impairment reflects heterogenous contributions from both primary and secondary degeneration, with nucleus-specific phenotyping potentially informing identification of higher risk individuals.

Keywords: multiple sclerosis, thalamus, information processing speed, lesions, cognitive decline, neuroimaging

Introduction

The prevailing view is shifting toward recognizing cognitive impairment in multiple sclerosis (MS) as the product of two parallel yet distinct pathological processes: focal inflammatory lesions that characterize relapsing disease activity, and compartmentalized neurodegeneration that occurs independently of inflammatory activity.[1] This distinction has important implications for persistent cognitive decline despite suppression of relapse activity. Numerous MRI and neuropathological studies demonstrate that deep grey matter (DGM) atrophy is strongly linked to lesion-mediated effects, which supports a secondary mechanism.[2–7] It has been shown that DGM structures, particularly the thalamus, atrophy earlier and faster than cortical regions and demonstrate strong associations with cognitive outcomes. [8–12]

Global and nucleus-specific thalamic atrophy have been demonstrated to be strong correlates of cognitive slowing in MS.[2,4,13–18] Information processing speed (IPS) is the most frequently impaired cognitive domain in MS. IPS demonstrates robust correlations with thalamic structural and microstructural integrity, reflecting lesion-mediated disconnection, microglial activation, and CSF-interface vulnerability.[1,3,4,6,7,19] The precise interplay and relative contribution of these mechanisms remain elusive and underexplored, and clarifying these pathways is critical given emerging therapeutic limitations. High-efficacy disease-modifying therapies (DMTs) can suppress new inflammatory lesions and global thalamic volume loss, yet they have not been shown to differentially protect thalamic nuclei or, crucially, mitigate nucleus-specific vulnerability linked to IPS deficits.[4,6,7,20–24]

Many studies continue to treat the thalamus as a uniform structure, neglecting the anatomical and functional heterogeneity that defines its nuclei.[3,9–11,21,24,25] The few studies examining nucleus-specific thalamic atrophy and cognitive performance,[6,7,26–28] have not accounted for lesion effects. To our knowledge, only one study directly compared models with and without lesion load as a covariate,[4] but that analysis relied on semi-manual lesion segmentation, omitted intracranial volume (ICV) correction, and reported no lesion-independent relationship between thalamic atrophy and IPS.[4] Therefore, this gap in the literature necessitates a more rigorous, nucleus-specific analysis to disentangle lesion-mediated versus lesion-independent thalamic degeneration by contrasting their associations with IPS.

In this work, we used automated segmentation to quantify thalamic regions of interest (ROIs) and lesion volumes, examining lesion-adjusted and unadjusted associations with IPS.[19,29,30] Differentiating these mechanisms may provide insights about the biological basis of cognitive slowing and its relationship to intrinsic grey matter pathology MS.[1]

Methods

This study was approved by the University of Western Ontario (Western University) Health Sciences Review Ethics Board (HSREB #11520). All participants provided written informed

consent prior to any study procedures taking place.

Participants

Participants with clinically definite MS aged 18 and older were recruited from the London (ON) MS clinic (London, ON Canada) between November 2020 and August 2022. Participants were excluded if they had binocular vision worse than 20/70, had relapsed within 90 days, had changed any medication within 30 days, or had an Expanded Disability Status Scale (EDSS) greater than or equal to 8.0.

Clinical Measures

The oral Symbol Digit Modalities Test (SDMT) was administered by a trained research coordinator.[31] The SDMT is a validated measure of IPS where participants are presented with a 8½ × 11 inch sheet of paper with nine symbols paired with corresponding symbols at the top of the page. Below this, the page contains a randomized, sequential assortment of these symbols. Participants are asked to verbally indicate the correct number for each symbol while the coordinator denotes their replies. Participants' score is the total number of correct responses in 90 seconds.

MRI

Participants were scanned on a 3 Tesla Siemens MAGNETOM Prisma Fit whole-body scanner using a 32-channel head coil. T1-weighted (T1w) images were acquired using a 3D magnetization prepared rapid gradient echo (MPRAGE) sequence (repetition time (TR) = 2400 ms, echo time (TE) = 2.28, flip angle = 9º, voxel size = 0.8 mm isotropic). A 3D T2-weighted fluid-attenuated inversion recovery (FLAIR) was acquired with TR = 5000 ms, TE = 387 ms, TI = 1800 ms, flip angle = 120°, voxel size = 0.8 mm isotropic.

Image Preprocessing

Lesion segmentation was performed using the Lesion Segmentation Toolbox's LST-AI.[30] LST-AI bias-corrected and co-registered T1w and FLAIR images and applied 3D U-Net convolutional neural networks trained on a large MS dataset to generate lesion probability masks.[30,32] The averaged probability map was then thresholded to produce individualized binary lesion masks in native space. Lesion load was defined as the total lesion volume and log-transformed to correct for right skew.

Thalamic nuclei were segmented using HIPS-THOMAS which extends the Thalamus Optimized Multi-Atlas Segmentation (THOMAS) framework to support MPRAGE images.[29,33] Following bias-correction, synthetic white-matter-nulled (WMn) images were generated to enhance grey-white matter contrast. The WMn image was non-linearly registered to the THOMAS template, and the resulting atlas labels were inverse warped into each participant's native space to obtain segmentations. This pipeline yielded 13 thalamic ROIs per hemisphere, including the global thalamus, 9 major nuclei (anteroventral, ventral anterior, ventral lateral

anterior, ventral lateral posterior, ventral posterolateral, central medial, pulvinar, lateral geniculate, and medial geniculate), two perithalamic structures (habenula and mammillothalamic tract), and a single ROI representing the mediodorsal-parafascicular (MD-Pf) complex.

Statistical Analysis

Descriptive statistics were used to summarize the demographic, clinical, and imaging variables. There was no missing cognitive or imaging data. The raw SDMT score served as the dependent variable. For each thalamic ROI, the THOMAS-derived volume was normalized to ICV to control head-size variability and was z-scored across all participants. All analyses were performed separately for left and right hemispheres to explore lateralization of effects.

Analysis of covariance (ANCOVA) models were fit with ROI volume as the independent variable, and age, sex, and years of education were included as covariates. A second set of models evaluated lesion-independent associations by adding lesion load as an additional covariate. Multiple comparisons across nuclei were controlled using the Benjamini-Hochberg procedure, and FDR-adjusted $p < 0.05$ was considered significant. Thalamic ROIs were classified as intrinsically vulnerable if their volumes remained significantly associated with IPS, independent of lesion effects.

Table 1: Demographic, clinical, and imaging characteristics of participants.

|	N = 100
Age in years, mean (SD)	46.2 (12.4)
Sex, female, N (%)	75 (75%)
Education in years, mean (SD)	14.2 (2.3)
Disease duration, mean in years (SD)	11.0 (8.8)
SDMT, mean (SD)	59.2 (10.9)
EDSS, median (IQR)	2.0 (1.5)
Total lesion volume in mL, mean (SD)	7.0 (6.8)
Intracranial volume in mL, mean (SD)	1582 (150)

Post hoc analysis further examined whether the associations between ROI volume and SDMT performance were mediated or explained by lesion burden. Single-level mediation models estimated the indirect effect of lesion load using bootstrap resampling with 5000 iterations. Additionally, nested ANCOVA models were compared to determine the change in explained variance (ΔR^2) attributable to adding lesion volume as a covariate. Group differences in mediation proportions and ΔR^2 between intrinsically vulnerable ROIs and those significant only in the unadjusted model were assessed using Student's t-test.

Results

This population included 100 subjects who signed informed consent and completed the study visit (Table 1). Participants were on average 46.2 ± 12.4 years old with a mean disease duration of 11.0 ± 8.8 years. SDMT performance averaged 59.2 ± 10.9 points while median EDSS was 2.0 (IQR 1.5).

Lesion-Mediated Associations

In the models excluding lesion load as a covariate, 21 of the 26 thalamic ROIs were statistically significant after FDR correction. All significant correlations were positive, indicating that smaller ROI volume was associated with lower SDMT scores. In the left hemisphere, the strongest associations ($p < 0.001$) were observed for the global thalamus (THAL), pulvinar (Pul), ventral posterolateral (VPL), medial geniculate nucleus (MGN), lateral geniculate nucleus (LGN), and MD-Pf complex. Significant associations ($p < 0.01$) were detected in the central medial (CM) nucleus, with further associations ($p < 0.05$) in the anteroventral (AV), ventral anterior (VA), ventral lateral posterior (VLP) and ventral lateral anterior (VLa) nuclei. In the right hemisphere, significant associations ($p < 0.001$) were observed for THAL, Pul, and MD-Pf complex, with further significant effects ($p < 0.01$) in the VLa, VA, VLP, VPL, MGN, and LGN, and ($p < 0.05$) in the AV nucleus.
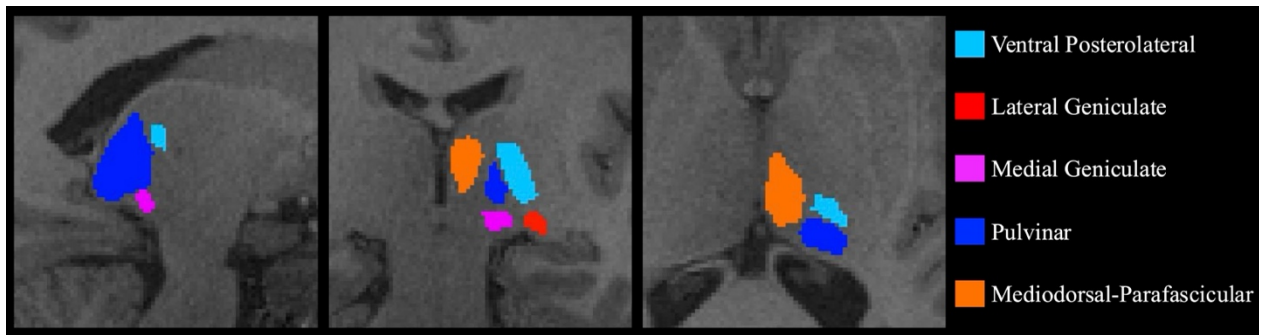

Figure 1: Spatial distribution of left-hemisphere thalamic ROIs exhibiting lesion-independent associations with IPS. ROIs are overlaid on a representative MS patient with sagittal (left), coronal (middle), and axial (right) views. Colour-coding represents nuclear groups: VPL (cyan), LGN (red), MGN (magenta), Pul (blue), and MD-Pf (orange).

Lesion-Independent Associations

Lesion adjustment isolated 12 ROIs whose volumes remained significantly associated with SDMT after FDR correction. As in the previous model, all surviving correlations were positive. In the left hemisphere (Figure 1), THAL, VPL, Pul, and MGN demonstrated the largest correlations ($p < 0.01$) with the LGN and MD-Pf complex remaining significant but with smaller effects ($p < 0.05$). In the right hemisphere, significant associations ($p < 0.01$) were observed for THAL, with further significant correlations in VA, VLa, Pul, LGN, and MD-Pf complex ($p <$

0.05). β was generally larger across left-hemisphere ROIs, most notably within the pulvinar nucleus (Figure 2).
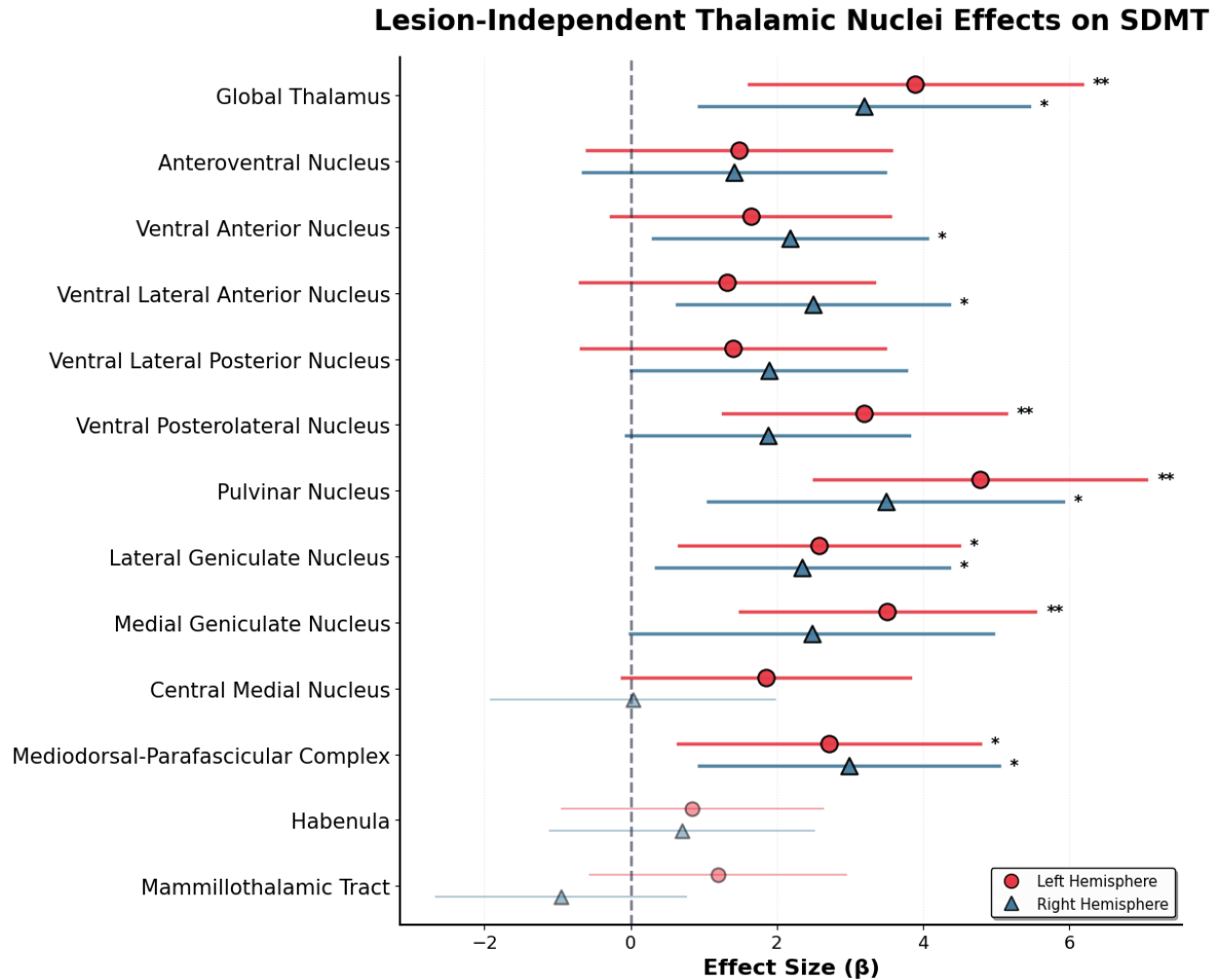
Figure 2: Coefficient plot of standardized regression coefficients (β) and 95% confidence intervals for the association of each ROI and SDMT performance after adjusting for age, sex, education, and lesion load. β coefficients reflect the change in SDMT per standard deviation increase in ROI volume. Thicker lines indicate significant associations in the baseline models, asterisks denote ROIs significantly associated after lesion adjustment (* FDR-adjusted $p < 0.05$, ** $p < 0.01$).

Post-hoc analysis

The post-hoc analysis further quantified the contributions of lesion-mediated and independent thalamic atrophy to SDMT. In the lesion-mediated model (excluding lesion load as a covariate), 21 of 26 thalamic ROIs showed significant associations between volume and SDMT. 12 ROIs remained significant after adjusting for lesion load; these were classified as intrinsically

vulnerable nuclei. Mediation analysis revealed that ROIs whose SDMT associations did not survive lesion adjustment showed significantly higher lesion-mediated effects (34.2%) compared with the intrinsically vulnerable nuclei (13.4%, $p < 0.001$; Figure 3A). Similarly, the inclusion of lesion load explained a greater increase in variance for the nuclei whose SDMT associations did not survive lesion adjustment (5.5%) compared with the intrinsically vulnerable nuclei (2.4%, $p < 0.01$; Figure 3B).
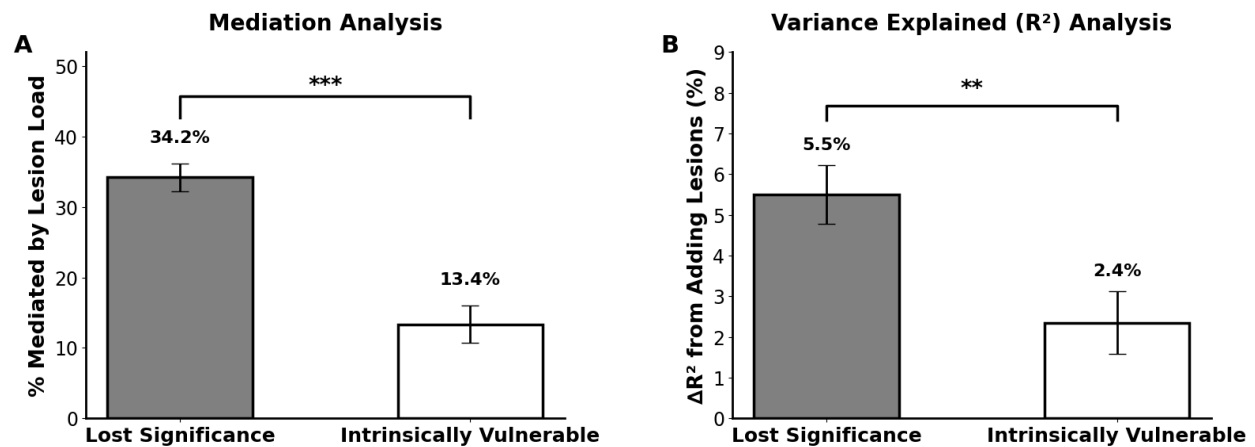
Figure 3: Group-level mediation and variance explained analyses. (A) Mean proportion of the ROI volume-SDMT association mediated by lesion volume for ROIs whose associations lost significance after lesion adjustment compared with intrinsically vulnerable nuclei. (B) Change in explained variance (ΔR^2) when lesion load was added to the ANCOVA models for these two groups. Error bars represent the standard error. ** $p < 0.01$, *** $p < 0.001$.

Discussion

In this work, we contrasted lesion-adjusted and unadjusted models to characterize lesion-mediated and lesion-independent thalamic atrophy associated with deficits in IPS. Nearly half of all thalamic ROIs maintained significant associations with SDMT after adjusting for lesion load, consistent with a heterogeneous contribution of lesion-mediated and lesion-independent factors to thalamic atrophy. We observed nucleus-specific patterns that aligned with distinct thalamocortical circuits. The intrinsically vulnerable nuclei were generally comprised of first-order sensory relays (VPL, LGN, MGN), and higher-order associative hubs (Pul, MD-Pf). These ROIs maintain significant associations after lesion adjustment, suggesting their vulnerability reflects intrinsic cellular or metabolic properties rather than network position. The ROIs whose SDMT associations did not survive lesion adjustment generally included the VA, VLa, VLP, AV, and CM nuclei. These structures support motor relay, limbic function, and arousal regulation through white matter projections to frontal motor and cingulate cortices. As their associations with SDMT lost significance after lesion adjustment, secondary degeneration may be a more substantial driver of IPS deficits than lesion-independent thalamic pathology in these structures.

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We also noted a modest left-hemisphere dominance across several ROIs. Although this lateralization is subtle, the pattern is in line with the left hemisphere's specialization for symbolic mapping and rule-based attentional control.[34]

The persistence of SDMT associations among the sensory relay and high-order associative nuclei in the lesion-adjusted models suggests these structures share intrinsic vulnerabilities independent of lesion activity. First-order sensory nuclei exhibit tonic relay activity, and higher-order associative nuclei engage in sustained cortico-thalamic communication, potentially effecting substantial metabolic demands.[35,36] Within the chronically inflamed MS brain, even slight disruptions to mitochondrial efficiency or axonal energy supply may have disproportional effects on neuronal stability.[37] Electrophysiological studies have found that motor relay nuclei, however, fire in brief, movement-locked bursts,[38] which may impose comparatively lower oxidative stress than the continuous activity associated with sensory relay and higher-order nuclei. Collectively, these activity-dependent differences align with the lesion-independent associations observed in the sensory and associative nuclei. Trans-synaptic degeneration may also contribute to lesion-independent thalamic atrophy. Cortico-thalamic projections may propagate degenerative signals anterogradely or retrogradely, leading to further neuronal injury and grey matter atrophy. This mechanism is consistent with the cortical thinning[1,8,12,17] and white matter injury[3,7,13,26,27] characteristic of MS.

Moreover, IPS depends on rapid sensory encoding, attentional selection, and efficient visuoperceptual integration,[39–41] processes that are directly supported by our intrinsically vulnerable nuclei. The VPL, MGN, and LGN provide principal somatosensory and visual relays to the cortex, while Pul and MD-Pf regulate corticocortical communication and attentional control during goal-directed behaviour.[42,43] Atrophy in these nuclei suggests that nucleus-specific thalamic phenotypes could provide more informative markers of IPS dysfunction than global thalamic volume alone. With increasingly accessible automated pipelines for thalamic nuclei segmentation, such measures may screen individuals at greater risk for cognitive decline and may hold utility as endpoints in clinical trials targeting neuroprotection or compartmentalized inflammation in MS.

Differences in myelin organization and oligodendrocyte support may further shape lesion-independent vulnerability. Therefore, as the VPL, MGN, LGN, Pul, and MD-Pf participate in long-range thalamocortical loops that undergo high-frequency relay and integrative processing, these ROIs may be especially vulnerable to chronic inflammatory exposure. This glial dependence, together with microglial sensitivity to metabolic disturbance, may amplify maladaptive phagocytic activity.[44,45] These effects also point to the broader *inflammation versus neurodegeneration* debate: even in the absence of local lesions, chronic stress can initiate degenerative changes that exacerbate vulnerabilities in these nuclei.[1,7] Similarly, prior work has demonstrated that thalamic nuclei adjacent to the third ventricle, including the MD-Pf complex, exhibit accelerated neurodegeneration and an *ependymal-in* gradient of microglial activation.[6,27]

This study has several limitations. The cross-sectional design prevents inferences about the temporal relationship of thalamic atrophy and cognitive decline. The cohort was recruited

from one centre and exhibited mild disability which limits generalizability. Cognitive assessment was restricted to the SDMT and did not consider other domains such as memory, executive function, and language. Lesion burden was derived from total lesion volume without accounting for spatial localization. While all segmentations were manually reviewed, characterization of thalamic nuclei may have been hindered by partial volume effects and misclassification. Due to our sample size and statistical approach, this analysis may have limited power to capture nonlinear or subtle nucleus-specific effects. Nonetheless, this work presents the first demonstration that thalamic nuclei show differential correlations with IPS depending on whether their associations survive lesion adjustment. If validated, these findings implicate selective thalamic vulnerability as a correlate of the cognitive pathology in MS, potentially arising from multiple, converging mechanisms. We hope that this work motivates future imaging studies which further probe these mechanisms directly, both within the thalamus and across other regions that may exhibit similar trajectories.

In summary, this study differentiated lesion-dependent and lesion-independent thalamic contributions to IPS deficits in MS. Twelve thalamic ROIs showed significant associations with SDMT performance independent of lesion load. These nuclei exhibited significantly lower lesion-mediated effects than the ROIs whose associations did not survive adjustment, consistent with a framework involving contributions from primary and secondary degeneration. This nucleus-resolved separation of lesion-independent and lesion-dependent effects motivates further investigation of these mechanisms across vulnerable brain regions.

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