

Spatial Coupling between Parkinson's Disease-Related Quantitative MRI Alterations and Mitochondrial Brain Architecture

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Abstract

Background and Objectives:

Parkinson's disease (PD) is a degenerative disease caused by multiple pathogenic processes, including mitochondrial dysfunction. Multiparametric mapping (MPM) provides insights into tissue biophysical properties but has limited biological specificity. We investigated whether the MPM-derived PD-related microstructural differences spatially overlap with the underlying brain's mitochondrial architecture.

Methods

We performed MPM in 31 patients with idiopathic PD and 68 healthy controls, quantifying longitudinal relaxation rate (R1), effective transverse relaxation rate (R2*), proton density, and magnetic transfer saturation (MTsat). Using unthresholded group-differenced-derived t-maps, we performed spatial correlation with six mitochondrial brain atlas maps reflecting mitochondrial complex I, II, IV, mitochondrial density, and mitochondrial and tissue respiration capacity.

Results

Within gray matter, we observed weak but highly consistent spatial coupling between all four MPM modalities and mitochondrial features (all $p_{FDR} \leq 0.0004$), with the strongest association with proton density ($r = 0.265-0.320$, $p_{FDR} = 0.0002-0.0003$). Cortical motor areas and subcortical structures presented with region-specific MPM modality-mitochondrial feature association signatures.

Discussion

Our findings revealed region-specific spatial coupling between microstructural alterations and mitochondrial architecture in PD, providing *in vivo* evidence supporting a role for mitochondria in the spatial patterning of PD-related microstructural alterations.

INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disease, manifesting with heterogeneous motor and non-motor symptomatology¹. PD originates with dopaminergic neurodegeneration in the substantia nigra (SN) and subcortical nuclei such as the basal ganglia². However, widespread macro- and microstructural alterations in gray and white matter (GM and WM, respectively) beyond classical nigrostriatal degeneration are increasingly recognized to characterize PD³⁻⁶. PD pathogenesis comprises a complex interplay of processes, including alpha-synuclein aggregation, neuroinflammation, DNA damage, and mitochondrial dysfunction⁷. Mitochondrial dysfunction has been established as a key

contributor, leading to dysregulated energy metabolism and metabolic stress, thereby increasing neuronal susceptibility to neurodegeneration⁸.

Available neuroimaging techniques are limited in their ability to characterize microstructural alterations and to infer the pathogenic mechanisms underlying their formation *in vivo*, compared with post-mortem histological techniques. Meanwhile, post-mortem histology is limited to observing end-of-disease-stage pathogenic changes, underscoring the need for improved neuroimaging techniques. One such option is quantitative magnetic resonance imaging (qMRI), such as multiparametric mapping (MPM). MPM assesses biophysical properties of the imaged tissue, including longitudinal relaxation rate (R1), effective transverse relaxation rate (R2*), proton density, and magnetic transfer saturation (MTsat), allowing to assess the microstructure of the brain and biological processes resulting in its alterations, providing the equivalent of histology data, but from an *in vivo* perspective^{9,10}. R1 and MTsat are sensitive to myelin and macromolecular content; R2* to iron, myelin, and vascular content; and proton density reflects water content in the imaged tissue, thereby allowing assessment of demyelination, neuronal tissue loss, neuroinflammation, and iron accumulation^{11–13}.

Although MPM, in principle, provides biological interpretability, the derived insights reflect a combination of pathological cellular processes with overlapping etiologies, including mitochondrial dysfunction, which itself results from various dysfunctions across the organelle. Until recently, we lacked the *in vivo* techniques to map mitochondrial dysfunction to confirm its role in the MPM-derived changes. However, a recently published high-resolution mitochondrial brain atlas provides spatial maps of six mitochondrial features, creating a framework to assess spatial overlap between derived microstructural findings and these features, thereby increasing biological specificity in qMRI data^{14,15}. The mitochondrial brain atlas comprises spatial maps of electron transport chain protein complexes I, II, and IV (CI, CII, CIV), mitochondrial density (MitoD), mitochondrial and tissue respiration capacity (MRC and TRC, respectively)¹⁴. CI, CII, and CIV are markers of enzyme capacity, including nicotinamide adenine dinucleotide (NADH)-ubiquinone oxidoreductase (CI), succinate dehydrogenase (SDH, CII), and cytochrome c oxidase (COX, CIV), involved in the oxidative phosphorylation (OXPHOS) aimed at the adenosine triphosphate (ATP) production¹⁶. MitoD and MRC provide insights into the distribution and mitochondrial capacity within the tissue, reflecting its metabolic potential. While TRC accounts for how metabolic potential is expressed, accounting for heterogeneity in mitochondrial variability in oxidative capacity¹⁷.

Mitochondrial and energy metabolism dysfunctions are well-established contributors to PD pathogenesis, resulting in compensatory metabolic reprogramming; however, the tissue-specific etiology of the observed MRI-derived microstructural changes remains unclear¹⁸. In this study, using previously identified MPM-derived microstructural differences between patients with PD (PwPD) and healthy controls (HCs), along with spatial maps of six mitochondrial features, we assessed the spatial overlap between them¹⁹. We hypothesized that PD-related changes would spatially overlap with regions characterized by high mitochondrial density and capacity in the GM, reflective of systematic tissue

vulnerability due to metabolic capacity. Furthermore, we hypothesized that MPM-derived differences would reveal region-specific spatial coupling with mitochondrial features, demonstrating selective and local vulnerability.

MATERIALS AND METHODS

Experimental design and participants

We recruited participants from our inpatient and outpatient clinics at the Department of Neurology of the University Medical Center Schleswig-Holstein (Campus Lübeck). Participants with a clinically confirmed diagnosis of PD using the Movement Disorders Society Clinical Diagnostic Criteria were considered to be PwPD²⁰. Inclusion criteria included age between 50 and 80 years old and not concomitant neurological/psychiatric conditions, while exclusion criteria included MRI contraindications, history of alcohol abuse, diagnosis of atypical or secondary Parkinsonism, or history of structural brain diseases. The study protocol consisted of clinical assessment, including the Movement Disorders Society Unified Parkinson's Disease Rating Scale subscore III (MDS-UPDRS-III), and an MRI session for the PwPD group, and only an MRI session for HCs²¹. PwPD were assessed and measured always in the ON stage.

Standard Protocol Approvals, Registrations, and Patient Consents

Prior to study inclusion, every participant was required to provide an informed written consent. Participants with comorbidities that affected their ability to provide written consent were not included. The study was approved by the local ethics committee at the University of Lübeck, Germany (AZ: 2024 – 302_2) and adhered to the Declaration of Helsinki. Every participant provided written informed consent.

Image acquisition and voxel-based quantification

We conducted MRI at the Center for Brain, Behavior, and Metabolism Core Facility at the University of Lübeck, using a 3 Tesla Siemens Magnetom Skyra scanner with a 64-channel head/neck coil. Using a multi-echo 3D fast low-angle shot (FLASH) sequence, we acquired T1-, proton density-, and magnetization transfer (MT)-weighted images, as previously described¹⁰. All acquisitions were acquired in 3D with 240 contiguous slices, 1.0 mm isotropic resolution, a field of view of 256 × 176 mm² (phase FoV 68.8%), GRAPPA acceleration factor 2, and partial Fourier 6/8 in the slice direction. The receiver bandwidth for all echoes was 440 Hz/px. We enabled inline distortion correction (2D mode) and prescan normalization. The T1-weighted acquisitions (TR = 19.0 ms, flip angle = 20°, six echoes with TE = 2.20/4.70/7.20/9.70/12.20/15.00 ms) lasted approximately 8 minutes. The proton density-weighted acquisitions (TR = 24.0 ms, flip angle = 20°, eight echoes with TE = 2.20/4.70/7.20/9.70/12.20/15.00/17.50/20.00 ms) lasted approximately 11 minutes. The MT-weighted acquisition (TR = 37.0 ms, flip angle = 20°, six echoes with TE = 2.20/4.70/7.20/9.70/12.20/15.00 ms) required approximately 7 minutes, resulting in a total acquisition time of approximately 26 minutes.

All datasets were reviewed by a neuroradiologist to exclude concurrent conditions and to assess visual artifacts (e.g., extensive head motion). Additionally, we performed quantitative evaluations by calculating voxel-wise z-scores for each MPM-derived parameter. Exclusion criteria included participants with severe visible motion artifacts (ringing and blurring) and excessive quantitative measures, defined as z-scores more than 2 standard deviations above the mean.

Obtained images were processed utilizing the hMRI toolbox, within the Statistical Parametric Mapping 25 framework (SPM25, Wellcome Trust Center for Neuroimaging, London) in MATLAB software (R2025a, The MathWorks Inc., Natick, MA, USA)²². We reconfigured the hMRI toolbox with scanner-specific settings using a custom-written MATLAB script to reconstruct quantitative and semi-quantitative MPM maps. Utilizing obtained T1-, proton density-, and MT-weightings as input images, 'UNICORT' setting to correct for B1 bias and 'Unified segmentation' to correct for radiofrequency sensitivity bias, we created MPM quantitative maps. The maps were visually assessed for quality, followed by processing with the hMRI toolbox pipeline, comprising segmentation (into GM, WM, and cerebrospinal fluid maps), nonlinear spatial registration to MNI space, and tissue-weighted smoothing^{23–25}. We set the processing settings as follows: a resampled voxel size of $1 \times 1 \times 1 \text{ mm}^3$, a bounding box of 2×3 , and Gaussian smoothing with a $6 \times 6 \times 6 \text{ mm}$ full-width at half maximum (FWHM) kernel.

Group differences statistical analyses

We performed cluster-based second-level analyses comprising a two-sample t-test in SPM25 within MATLAB, to compare surrogate markers of microstructural integrity (e.g., MPM-derived maps) between PwPD and HCs. We assessed only one contrast, generating t-maps with higher MPM-derived values in PwPD than in HCs (PwPD > HCs), with age and sex as covariates. All analyses for R1, R2*, proton density, and MTsat were performed separately using explicit masks, including the tissue probability mask for GM incorporated into the SPM25 environment and masks derived from the HybraPD and Human Motor Area Template (HMAT) atlases, to assess group differences within disease-relevant regions of interest^{26,27}. Overall, we assessed group differences across 23 ROIs, generating four t-maps for each ROI, corresponding to differences in R1, R2*, proton density, and MTsat values between PwPD and HCs (Fig. 1). We performed correlation analyses across all ROIs, irrespective of whether we observed statistically significant group differences, to avoid introducing bias from thresholding and to detect all spatial pattern effects.

Spatial correlation analyses

For each ROI, we performed voxel-wise spatial correlation analyses between unthresholded t-maps derived from the group-differences analysis and six mitochondrial brain atlas maps, including CI, CII, CIV, MitoD, MRC, and TRC¹⁴. Given that we had four t-maps per ROI (R1, R2*, proton density, and MTsat), each correlated with maps of six mitochondrial features, we performed 24 spatial correlation tests per ROI (see Fig. 1). We restricted the analyses to voxels with finite PwPD > HCs t-values and valid mitochondrial

brain atlas map values. As our data was not normally distributed, we calculated Spearman’s correlation coefficients (ρ). Additionally, we calculated the effect size as Cohen’s f^2 to enhance the interpretation of the strength of spatial association. To account for spatial dependencies and multiple mitochondrial feature maps, we performed non-parametric permutation testing. For each mitochondrial feature map, t -values were randomly permuted across voxels within ROIs, simultaneously preserving the spatial distribution of PwPD > HCs t -values. We performed 5000 permutation tests for each mitochondrial feature map to generate null distributions of correlation coefficients. Additionally, to control for multiple comparisons across brain regions, we applied false discovery rate (FDR) correction across all ROIs.

RESULTS

Demographic and Clinical Assessment. Following the quality control procedure, we included thirty-one PwPD and sixty-eight HCs from a previously published study (Table 1)¹⁹. The age did not differ between the groups (PwPD: 65.5 ± 8.1 ; HCs: 65.0 ± 9.3 ; $p = 0.720$). We observed a comparable sex distribution between the groups (PwPD: females: 18/31; HCs: females: 40/68; $\chi^2 = 0.017$, $df = 1$, $p = 1.000$). The mean disease duration among PwPD was 4.5 ± 4.3 years. The severity of PD was assessed using MDS-UPDRS-III scores (mean $\pm$ SD: 28.6 ± 15.5) and Hoehn and Yahr stage 2 (median [range]: 2 [1–2]), measured in the ON state.

Table 1
Demographic and clinical characteristics.

	PwPD	HCs	p-value
number	31	68	
male/female	13/18	28/40	1.000 ¹
age (years)	64.9 ± 9.3 [60.00–72.00]	65.6 ± 8.1 [56.00–71.00]	.720 ²
MDS-UPDRS-III	28.6 ± 15.5 [19.00–34.00]	n.a.	
Disease duration (years)	4.5 ± 4.3 [1.50–7.00]	n.a.	
Hoehn and Yahr stage	2 [1–2]	n.a.	
Mean values and standard deviations are quoted. Values in square brackets represent the interquartile range. ¹ according to a χ^2 -test; ² two-sample t -test applied. HCs: healthy controls. MDS-UPDRS-III: Movement Disorders Society’s Unified Parkinson’s Disease Rating Scale (subscore III). PwPD: patients with Parkinson’s disease.			

Parkinson’s disease-related multiparametric MRI alterations exhibit weak yet consistent spatial coupling with mitochondrial features across the gray matter. We performed voxel-wise spatial correlation between MPM-derived unthresholded t -maps containing PwPD > HCs values (R_1 , R_2^* , proton density, MTsat) and six mitochondrial brain atlas features (CI, CII, CIV, MitoD, MRC, and TRC) within GM

(1,384,100 voxels, Fig. 2 and Table 2). Across all modalities and mitochondrial features, we observed weak yet highly consistent and significant spatial coupling (all $p_{\text{perm}} = 0.0002$, all $p_{\text{FDR}} = 0.0002-0.0004$). R1 showed consistent negative associations with mitochondrial features ($\rho = 0.088-0.143$, $p_{\text{FDR}} = 0.0002-0.0003$). R2* demonstrated the weakest associations with mitochondrial features ($\rho = 0.007-0.121$, $p_{\text{FDR}} = 0.0002-0.0004$). Contrarily, proton density demonstrated the strongest association across GM ($\rho = 0.265-0.352$, $p_{\text{FDR}} = 0.0002-0.0004$), while MTsat yielded weak negative associations with CI, CII, CIV, MitoD, and TRC only ($\rho = 0.017-0.128$, $p_{\text{FDR}} = 0.0003$).

Table 2

Voxel-wise spatial correlation between Parkinson's disease-related differences derived from multiparametric mapping and the six mitochondrial brain atlases features across the gray matter.

	r	Cohen's f^2	P_{uncorr}	P_{perm}	P_{FDR}
R1					
CI	-0.143	0.014	< 0.0001	0.0002	0.0003
CII	-0.088	0.015	< 0.0001	0.0002	0.0003
CIV	-0.138	0.016	< 0.0001	0.0002	0.0002
MitoD	-0.100	0.013	< 0.0001	0.0002	0.0003
MRC	-0.134	0.021	< 0.0001	0.0002	0.0003
TRC	-0.137	0.018	< 0.0001	0.0002	0.0003
R2*					
CI	-0.143	0.025	< 0.0001	0.0002	0.0003
CII	-0.012	0.027	< 0.0001	0.0002	0.0003
CIV	-0.082	0.025	< 0.0001	0.0002	0.0004
MitoD	-0.007	0.028	< 0.0001	0.0002	0.0002
MRC	-0.121	0.028	< 0.0001	0.0002	0.0003
TRC	-0.085	0.026	< 0.0001	0.0002	0.0003
Proton density					
CI	0.304	0.049	< 0.0001	0.0002	0.0003
CII	0.320	0.054	< 0.0001	0.0002	0.0003
CIV	0.289	0.053	< 0.0001	0.0002	0.0002
MitoD	0.352	0.053	< 0.0001	0.0002	0.0003
MRC	0.265	0.052	< 0.0001	0.0002	0.0002

We assessed the group differences in R1, R2*, proton density, and MTsat using t-maps containing PwPD > HCs values and six mitochondrial feature maps: CI, CII, CIV, MitoD, MRC, and TRC. After masking for finite values, n = 1,384,100 voxels were included in the analysis. For each analysis type, we report nominal, permutation-derived, and false discovery rate (FDR)-adjusted p-values. CI, CII, CIV: mitochondrial electron transport chain protein complexes I, II, and IV. Cohen's f^2 : standardized effect size measure. HCs: healthy controls. MitoD: mitochondrial density. MTsat: magnetic transfer saturation. MRC: mitochondrial respiration capacity. PwPD: patients with Parkinson's disease. p_{FDR} : false-discovery rate-adjusted p-value. p_{perm} : non-parametric p-value derived from permutation testing. p_{uncorr} : nominal p-value. r: correlation coefficient. R^2 : coefficient of determination. R1: longitudinal relaxation rate. R2*: effective transverse relaxation rate. TRC: tissue respiration capacity.

	r	Cohen's f²	P_{uncorr}	P_{perm}	P_{FDR}
R1					
TRC	0.309	0.048	< 0.0001	0.0002	0.0003
MTsat					
CI	-0.028	0.002	< 0.0001	0.0002	0.0003
CII	-0.119	0.001	< 0.0001	0.0002	0.0003
CIV	-0.017	0.001	< 0.0001	0.0002	0.0003
MitoD	-0.128	0.002	< 0.0001	0.0002	0.0003
MRC	-0.002	0.001	< 0.0001	0.0002	0.9966
TRC	-0.024	0.001	< 0.0001	0.0002	0.0003
<p>We assessed the group differences in R1, R2*, proton density, and MTsat using t-maps containing PwPD > HCs values and six mitochondrial feature maps: CI, CII, CIV, MitoD, MRC, and TRC. After masking for finite values, n = 1,384,100 voxels were included in the analysis. For each analysis type, we report nominal, permutation-derived, and false discovery rate (FDR)-adjusted p-values. CI, CII, CIV: mitochondrial electron transport chain protein complexes I, II, and IV. Cohen's f²: standardized effect size measure. HCs: healthy controls. MitoD: mitochondrial density. MTsat: magnetic transfer saturation. MRC: mitochondrial respiration capacity. PwPD: patients with Parkinson's disease. p_{FDR}: false-discovery rate-adjusted p-value. p_{perm}: non-parametric p-value derived from permutation testing. p_{uncorr}: nominal p-value. r: correlation coefficient. R²: coefficient of determination. R1: longitudinal relaxation rate. R2*: effective transverse relaxation rate. TRC: tissue respiration capacity.</p>					

Cortical motor and premotor regions exhibit convergent multimodal associations with mitochondrial features. Utilizing HMAT atlas we performed regional voxel-wise spatial correlation analysis, demonstrating that cortical motor and premotor regions, specifically the primary motor area (M1, 60176 voxels), dorsal premotor cortex (PMd, 52792 voxels), presupplementary motor area (preSMA, 17468 voxels), and primary somatosensory cortex (S1, 34304 voxels), yielded convergent multimodal spatial coupling with mitochondrial features (Supplemental Tables 1–6, Fig. 3). M1, PMd, and preSMA demonstrated negative associations between R1 (M1: rho = 0.180–0.280, p_{FDR} = 0.0002–0.0003; PMd: rho = 0.320–0.377, p_{FDR} = 0.0003; preSMA = 0.119–0.222, p_{FDR} = 0.0002–0.0003), R2* (M1: rho = 0.019–0.048, p_{FDR} = 0.0002–0.0004; PMd: rho = 0.077–0.123, p_{FDR} = 0.0003–0.0004; preSMA: rho = 0.076–0.201, p_{FDR} = 0.0002–0.0004), MTsat (M1: rho = 0.064–0.092, p_{FDR} = 0.0003–0.0004; PMd: rho = 0.092–0.125, p_{FDR} = 0.0003–0.0004; preSMA: rho = 0.053–0.198, p_{FDR} = 0.0003–0.0004) and mitochondrial features. Meanwhile, the association between proton density and mitochondrial features within M1 and PMd was positive (M1: rho = 0.205–0.318, p_{FDR} = 0.0002–0.0003; PMd: rho = 0.201–0.290, p_{FDR} = 0.0002–0.0003). Regions including preSMA, supplementary motor area (SMA, 21712 voxels), and ventral premotor cortex (PMv, 46704 voxels) demonstrated consistent coupling within specific modalities. For instance, negative coupling between R1, R2*, MTsat, and mitochondrial features in the preSMA (R1: rho =

0.119–0.222, $p_{\text{FDR}} = 0.0002–0.0003$; $R2^*$: $\rho = 0.076–0.201$, $p_{\text{FDR}} = 0.0002–0.0004$; MTsat: $\rho = 0.053–0.198$, $p_{\text{FDR}} = 0.0003–0.0004$). Additionally, negative coupling between $R2^*$, MTsat, and mitochondrial features in the SMA ($R2^*$: $\rho = 0.028–0.084$, $p_{\text{FDR}} = 0.0002–0.0004$; MTsat: $\rho = 0.052–0.081$, $p_{\text{FDR}} = 0.0003–0.0004$) and positive coupling between proton density and mitochondrial features in the PMv ($\rho = 0.178–0.195$, $p_{\text{FDR}} = 0.0002–0.0003$). The identified associations within S1 were of the opposite nature, with negative coupling between R1 and positive coupling between $R2^*$, proton density, MTsat, and mitochondrial features ($R1$: $\rho = 0.038–0.096$, $p_{\text{FDR}} = 0.0002–0.0003$; $R2^*$: $\rho = 0.006–0.101$, $p_{\text{FDR}} = 0.0002–0.0004$; proton density: $\rho = 0.124–0.243$, $p_{\text{FDR}} = 0.0002–0.0003$; MTsat: $\rho = 0.031–0.156$, $p_{\text{FDR}} = 0.0003–0.0004$).

Basal ganglia and midbrain-related structures exhibit region-specific, partially divergent

mitochondrial–microstructural profiles. Using the HybraPD atlas, we observed less convergent spatial coupling within the basal ganglia and subcortical structures, although some modality-specific associations were strongest in certain structures (Supplementary Tables 7–16 and Fig. 4). For example, putamen (14838 voxels) and nucleus accumbens (NAC, 12181 voxels) demonstrated the strongest negative coupling between R1 and mitochondrial features (Putamen: $\rho = 0.237–0.358$, $p_{\text{FDR}} = 0.0002–0.0003$; NAC: $\rho = 0.204–0.337$, $p_{\text{FDR}} = 0.0002–0.0003$), among all ROIs investigated. Additionally, NAC demonstrated the strongest negative associations between $R2^*$ and mitochondrial features ($\rho = 0.270–0.461$, $p_{\text{FDR}} = 0.0003–0.0004$). Red nucleus (RN, 1101 voxels) demonstrated the strongest positive coupling between $R2^*$ and mitochondrial features ($\rho = 0.133–0.202$, $p_{\text{FDR}} = 0.0003–0.0049$), while SN (1499 voxels) demonstrated the strongest positive coupling between $R2^*$ and specific mitochondrial features. Examples include spatial coupling between $R2^*$ and CI ($\rho = 0.168$, $p_{\text{FDR}} = 0.0003$), CII ($\rho = 0.234$, $p_{\text{FDR}} = 0.0003$), and TRC ($\rho = 0.106$, $p_{\text{FDR}} = 0.0003$). The caudate nucleus (CN, 13224 voxels) presented with the strongest spatial positive coupling between proton density and negative coupling between MTsat and mitochondrial features (Proton density: $\rho = 0.131–0.370$, $p_{\text{FDR}} = 0.0002–0.0003$; MTsat: $\rho = 0.249–0.374$, $p_{\text{FDR}} = 0.0003–0.0004$). Other structures also demonstrated the modality-specific spatial couplings with mitochondrial features, however, with a smaller effect size, including negative coupling between R1 and mitochondrial features in the globus pallidus (GP, 5361 voxels, $\rho = 0.108–0.261$, $p_{\text{FDR}} = 0.0002–0.0003$) and negative coupling between R1 and mitochondrial features in the ventral pallidum (VeP, 8266, $\rho = 0.174–0.235$, $p_{\text{FDR}} = 0.0002–0.0003$). Habenular nucleus (HN, 228 voxels) and dentate nucleus of the cerebellum (DN, 2485 voxels) revealed statistically divergent results across all mitochondrial features and MPM modalities.

Thalamic nuclei demonstrated selective vulnerability, with the strongest effects in intralaminar regions.

We assessed spatial correlation using all thalamic nuclei combined into a single mask (Supplementary Table 17) and for separate thalamic nuclei (Supplementary Tables 18–22, Fig. 4), with detailed statistics provided. The analysis of the combined mask revealed consistent positive spatial coupling between R1 and negative coupling between MTsat and mitochondrial features ($R1$: $\rho = 0.085–0.123$, $p_{\text{FDR}} = 0.0002–0.0003$; MTsat: $\rho = 0.046–0.329$, $p_{\text{FDR}} = 0.0002–0.0004$). Some separate nuclei yielded

modality-specific coupling with mitochondrial features, such as positive coupling between R2* and negative coupling between proton density and mitochondrial features in the thalamic posterior nucleus (5340 voxels; R2*: $\rho = 0.060\text{--}0.178$, $p_{\text{FDR}} = 0.0002\text{--}0.0004$; Proton density: $\rho = 0.001\text{--}0.195$, $p_{\text{FDR}} = 0.0002\text{--}0.0003$) and negative associations between proton density, MTsat and mitochondrial features in the thalamic ventral nucleus (8260 voxels, proton density: $\rho = 0.035\text{--}0.237$, $p_{\text{FDR}} = 0.0003\text{--}0.0149$; MTsat: $\rho = 0.093\text{--}0.277$, $p_{\text{FDR}} = 0.0003\text{--}0.0003$). Regions such as the anterior thalamic nucleus (965 voxels) and medial thalamic nucleus (5110 voxels) demonstrated no consistent couplings across all mitochondrial features. Notably, the intralaminar thalamic nucleus demonstrated the strongest positive coupling between proton density and mitochondrial features across all regions of interest (ROIs) investigated ($\rho = 0.185\text{--}0.412$, $p_{\text{FDR}} = 0.0002\text{--}0.0003$).

Integration of findings reveals region-specific multimodal mitochondrial signatures across the Parkinson's disease brain. Some ROIs showed consistent, highly significant associations across multiple MPM modalities and all mitochondrial features (Fig. 5). For instance, M1, PMd, and VeP consistently revealed negative associations between R1, R2*, MTsat, and mitochondrial features, and positive associations between proton density and mitochondrial features. Areas such as preSMA and NAC revealed consistent negative associations between R1, R2*, and mitochondrial features, consistent with M1, PMd, and VeP. Both RN and putamen showed consistent positive associations between R2*, MTsat, and mitochondrial features. Additionally, S1 demonstrated consistent positive associations between R2*, proton density, MTsat, and mitochondrial features, whereas SN showed consistent positive associations across all MPM modalities and mitochondrial features.

DISCUSSION

In this study, we investigated whether MPM-derived PD-related microstructural alterations spatially overlap and associate with mitochondrial features across GM and disease-relevant regions. We identified weak magnitude but highly consistent and significant spatial overlaps between observed MPM differences and all mitochondrial features. Our findings demonstrate that the identified microstructural changes are associated with underlying mitochondrial architecture and capacity, providing *in vivo* evidence supporting a mitochondrial role in PD-related brain changes and complementary insights into MPM findings. Within the GM, the observed changes are highly significant but of small magnitude, possibly due to the large voxel count. The consistency of the identified associations suggests that MPM-derived alterations are driven by broad metabolic vulnerability, rather than by a single mitochondrial feature.

At the regional level, we observed multiple region-specific patterns and various directions of associations across all four modalities. Given the complex and multifactorial nature of PD, such inconsistency is expected, with genetic factors, disease stage, and region-specific cellular compositions and connectivity differentially affecting structural susceptibility to various pathogenic processes, explaining why PD is better characterized by a combination of multiple region-specific patterns rather than a uniform change.

PMd and M1 demonstrated significant associations across all four modalities, including negative associations between R1, R2*, and MTsat; and positive associations between proton density and mitochondrial features. R2* is commonly attributed to iron; however, several studies have demonstrated its sensitivity to myelin and vasculature^{28,29}. Collectively, these findings suggest that composite microstructural alterations, consistent with reduced macromolecular and structural integrity, as well as neuroinflammation, occur in regions of metabolic vulnerability. Interestingly, S1 reported positive associations between R2*, proton density, MTsat, and mitochondrial features, demonstrating that PD-related iron accumulation and neuroinflammation occur in regions with high mitochondrial capacity, highlighting the mitochondrial contribution to these processes *in vivo*^{30,31}.

Furthermore, we identified correlation signatures for subcortical structures in the basal ganglia, one of the primary structures affected in PD³². The observed heterogeneity and divergence in the findings can be explained by the differences in regional architecture and functional specialization. Despite the consistency of associations, certain mitochondrial features demonstrated particularly strong associations within specific ROIs. The SN demonstrated consistent positive associations across all MPM modalities and most mitochondrial features. However, only proton density revealed a consistent positive association with all mitochondrial features. Interestingly, the associations with CI and CII were the strongest among all mitochondrial features, indicating that regional neuroinflammation is associated with a high density of electron transport chain protein complexes involved in ATP production. This suggests that energy production and oxidative stress are more significant drivers of the observed structural changes in this region. The CN demonstrated consistent and relatively strong associations between proton density and mitochondrial features. As higher proton density in PwPD reflects neuroinflammation and gliosis, the observed spatial associations demonstrate CN's susceptibility to neuroinflammation-induced microstructural alterations, in part due to its underlying mitochondrial architecture. Additional subcortical areas, such as RN, showed some of the strongest associations between R2* and mitochondrial features, indicating iron accumulation in regions of high metabolic activity, consistent with previous findings of iron accumulation in the RN in PwPD³³.

Interestingly, the strongest positive associations between proton density and mitochondrial features were detected in the intralaminar thalamic nuclei, providing evidence of regional vulnerability to neuroinflammation due to the tissue's metabolic capacity. Intralaminar thalamic nuclei play roles in attention and motor control and have been identified as affected in preclinical models of PD, with emerging *in vivo* evidence of their susceptibility to pathogenic processes^{34,35}. Furthermore, a recent study demonstrated a moderate association between creatine-weighted MRI-derived metabolic alterations in the intralaminar thalamic nuclei and motor severity in PwPD³⁶.

Several limitations should be considered when interpreting our findings, including the nature of the mitochondrial maps used, which were derived from transcriptomic and metabolomic data from healthy brains and lack PD-specific mitochondrial alterations. The observed spatial correlations had modest strength and effect sizes, highlighting the complexity of PD pathogenesis and the potential contributions

of additional pathogenic mechanisms, including calcium dysregulation, protein aggregation, oxidative stress, and DNA damage. Our study is cross-sectional, and future research should use longitudinally collected neuroimaging data to investigate dynamic changes and the effects of disease stage on the observed findings.

To summarize, we demonstrated that PwPD-specific MPM-derived microstructural changes converge with mitochondrial architecture in a region- and modality-specific manner. We provide direct *in vivo* evidence of the mitochondrial role in PD-specific microstructural alterations. The use of MPM provides more detailed insights into the underlying processes and causation of the observed microstructural alterations, while the additional interpretation alongside mitochondrial features provides more biologically grounded insights, demonstrating the link between PD-driven microstructural alterations and metabolic vulnerability, all within one MRI scan.

Declarations

Funding declaration

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Authors contribution

Conceptualization: M.M.P., J.P.; Formal analysis: M.M.P., M.G.; Investigation: L.S., H.S.W., L.D., L.A., N.G., J.U., J.H.; Writing – Original Draft: M.M.P.; Writing – Editing & Review: M.G., N.B., J.P.; Visualization: M.M.P., Supervision: J.P.; Project Administration: J.P.; Funding Acquisition: N.B., J.P.

Competing interests statement

The authors declare that they have no competing interests.

Data availability

All the data needed to evaluate the conclusions in this paper are presented in the paper and/or the Supplementary Materials. Additional anonymized imaging data are available from the corresponding author upon reasonable request.

Code availability

The underlying code for this study is not publicly available but may be made available to qualified researchers on reasonable request from the corresponding author.

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Figures

FIGURES:

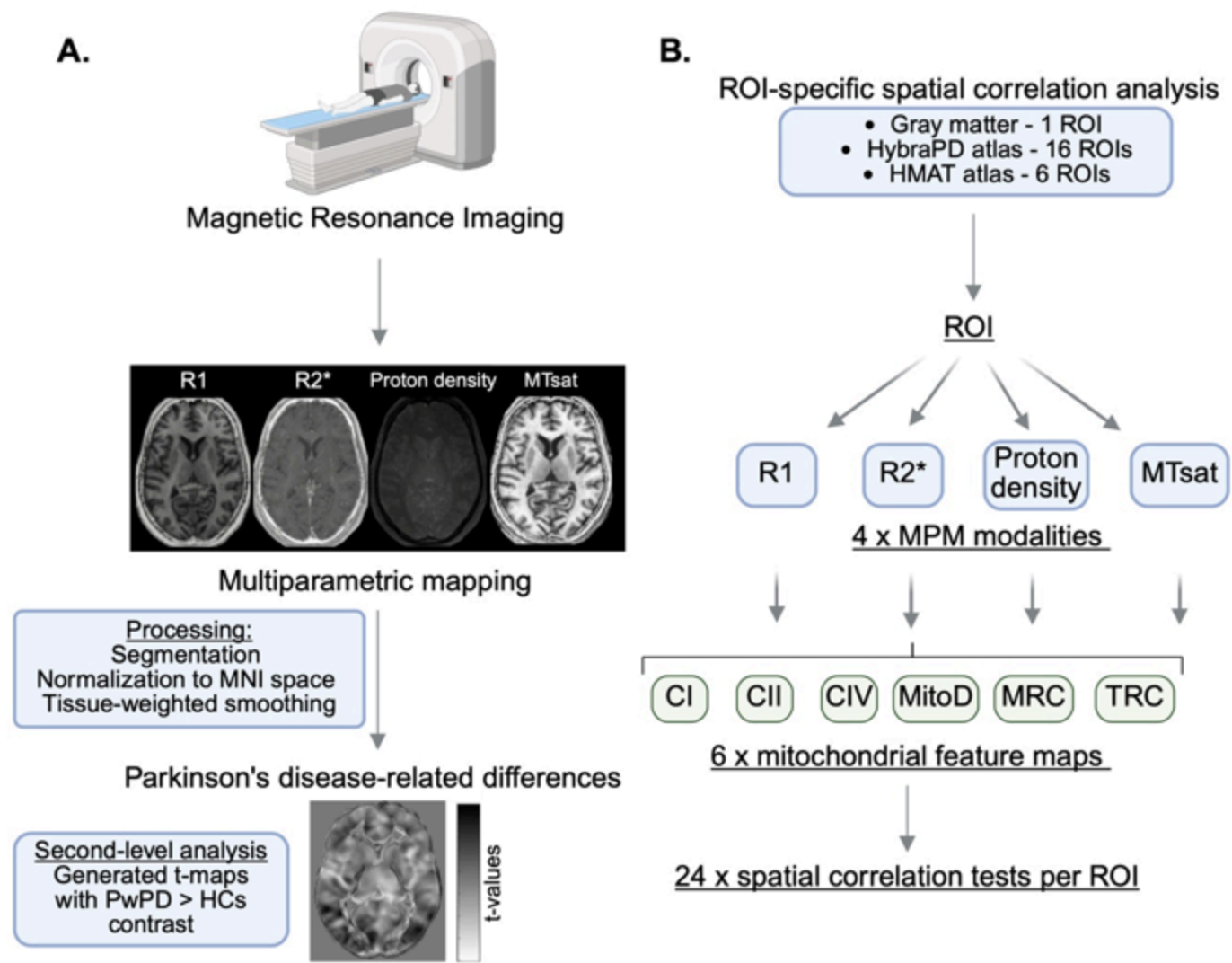


Figure 1

Data processing and analytical workflow of this study. (A) Following magnetic resonance imaging, the derived images are used to generate multiparametric mapping comprising R1, R2*, proton density, and MTsat maps. Generated maps are processed, comprising tissue segmentation, normalization to MNI space, and tissue-weighted smoothing. Processed maps are used in the second-level analysis to assess group differences, yielding t-maps with higher t-values in PwPD than in HCs (PwPD > HCs). **(B)** Generated t-maps are used for ROI-specific spatial correlation analysis. For each ROI, we performed 24 spatial correlation tests, correlating R1, R2*, proton density, and MTsat with 6 mitochondrial features. We performed analysis within 23 ROIs, comprising gray matter and brain structures derived from the HybraPD and HMAT atlases. CI, CII, CIV: mitochondrial electron transport chain protein complexes I, II, and IV. HCs: healthy controls. HMAT: human motor area template. MitoD: mitochondrial density. MPM:

multiparametric mapping. MRC: mitochondrial respiration capacity. MTsat: magnetic transfer saturation. PwPD: patients with Parkinson's disease. R1: longitudinal relaxation rate. R2*: effective transverse relaxation rate. ROI(s): region(s) of interest. TRC: tissue respiration capacity.

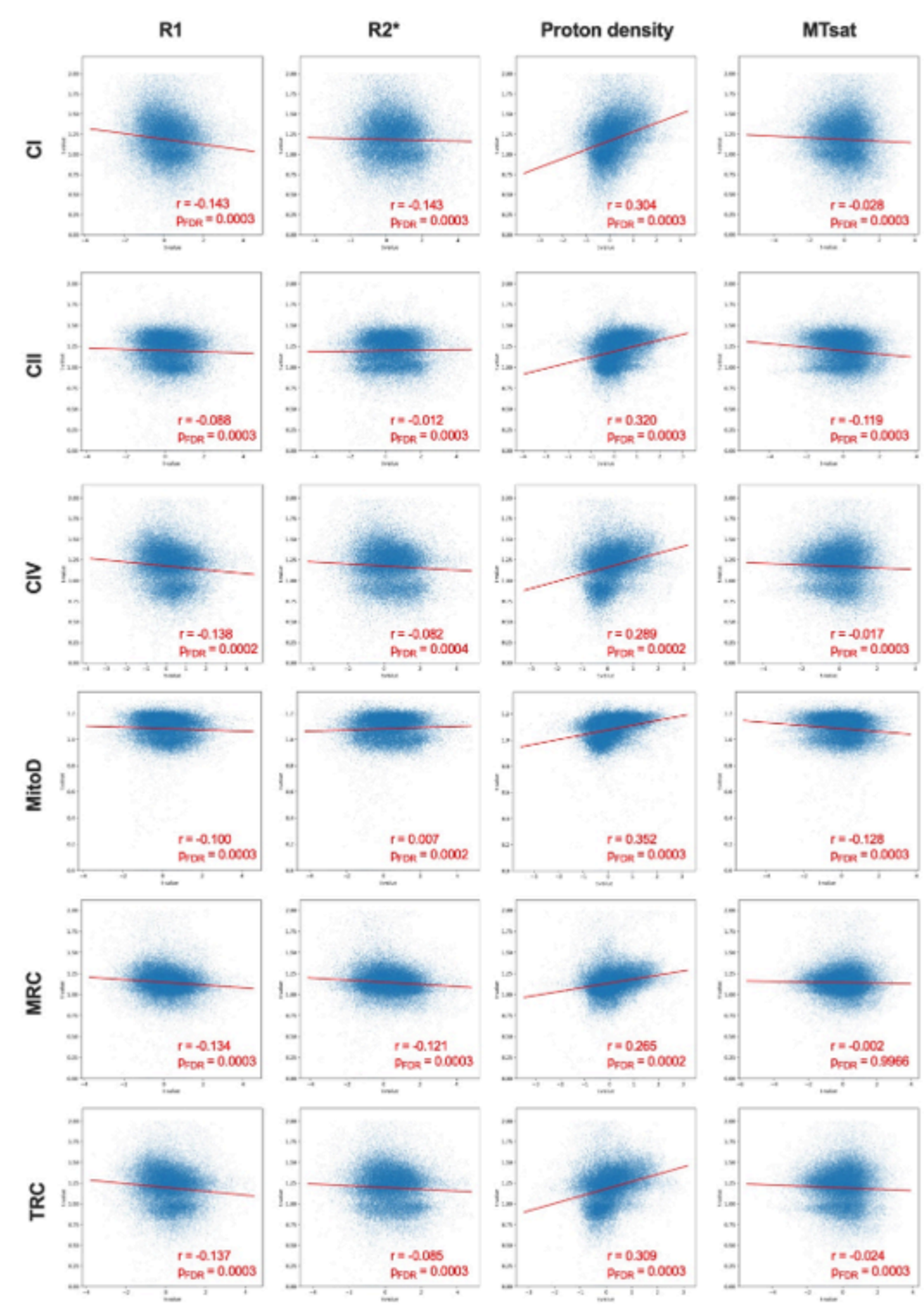


Figure 2

Scatter plots of spatial associations of voxel-wise t-values across quantitative multiparametric values and mitochondrial features in the gray matter. We present voxel-wise correlations of higher R1, R2*, proton density, and MTsat values in PwPD compared to HCs, and six mitochondrial features: CI, CII, CIV, MitoD, MRC, and TRC. Spearman correlation coefficients and false-discovery rate-adjusted p-values are reported for each association. CI, CII, CIV: mitochondrial electron transport chain protein complexes I, II, and IV. HCs: healthy controls. MitoD: mitochondrial density. MTsat: magnetic transfer saturation. MRC: mitochondrial respiration capacity. p_{FDR} : false-discovery rate adjusted p-values. PwPD: patients with Parkinson's disease. r: correlation coefficient. R1: longitudinal relaxation rate. R2*: effective transverse relaxation rate. TRC: tissue respiration capacity.

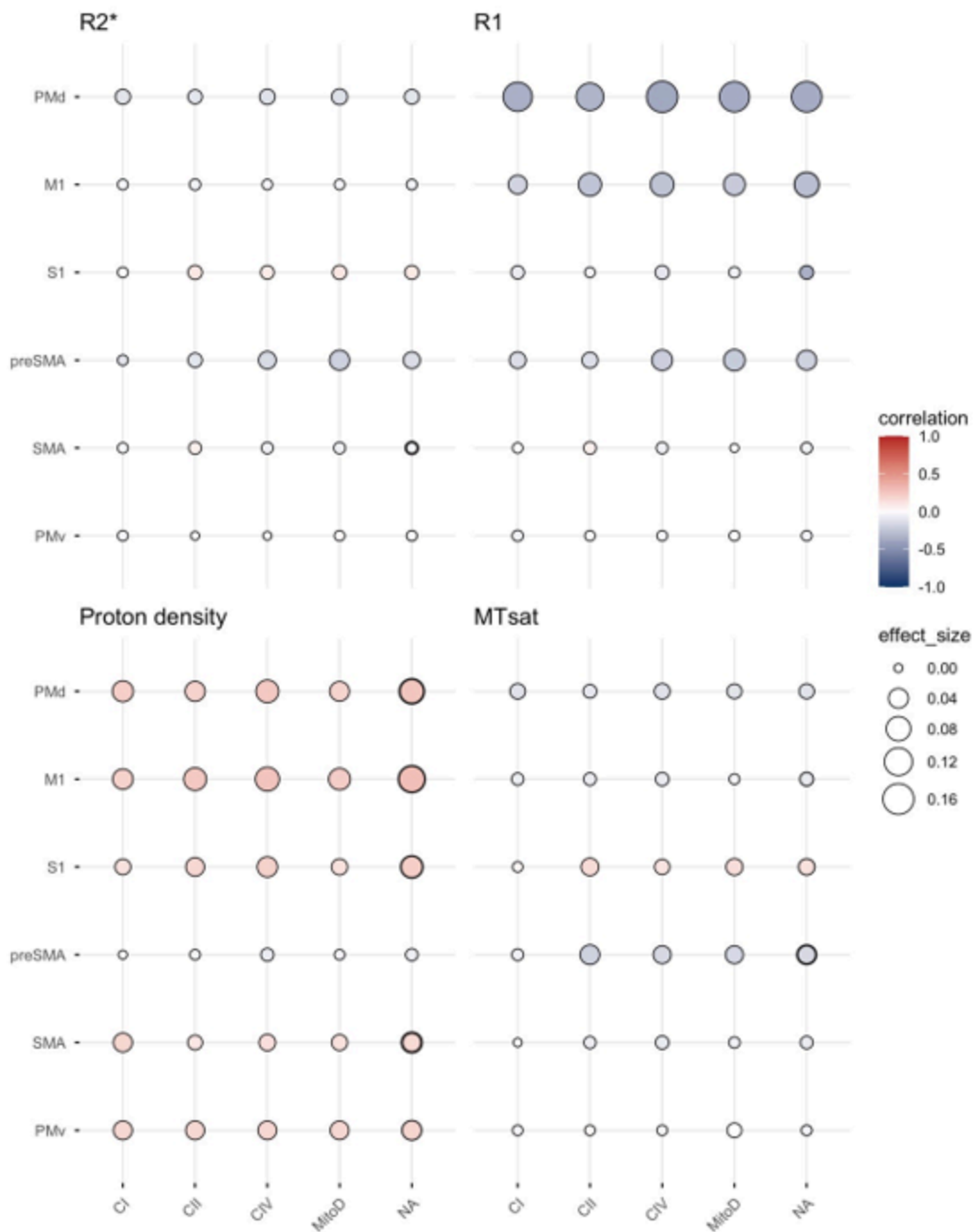


Figure 3

Regional spatial associations between patients with Parkinson’s disease-derived multiparametric mapping measures and mitochondrial features within the Human Motor Area Template. Comparison plot demonstrates spatial correlation between multiparametric mapping-derived measures and mitochondrial features. Each row corresponds to a region of interest, and each column corresponds to a mitochondrial feature. Within each anatomical section, regions are ordered from bottom to top based on the cumulative strength of associations across all mitochondrial features and multiparametric mapping results. CI, CII, CIV: mitochondrial electron transport chain protein complexes I, II, and IV. M1: primary

motor area. MitoD: mitochondrial density. MRC: mitochondrial respiration capacity. PMd/v: dorsal/ventral premotor cortex. preSMA: presupplementary motor area. S1: primary somatosensory cortex. SMA: supplementary motor area. TRC: tissue respiration capacity.

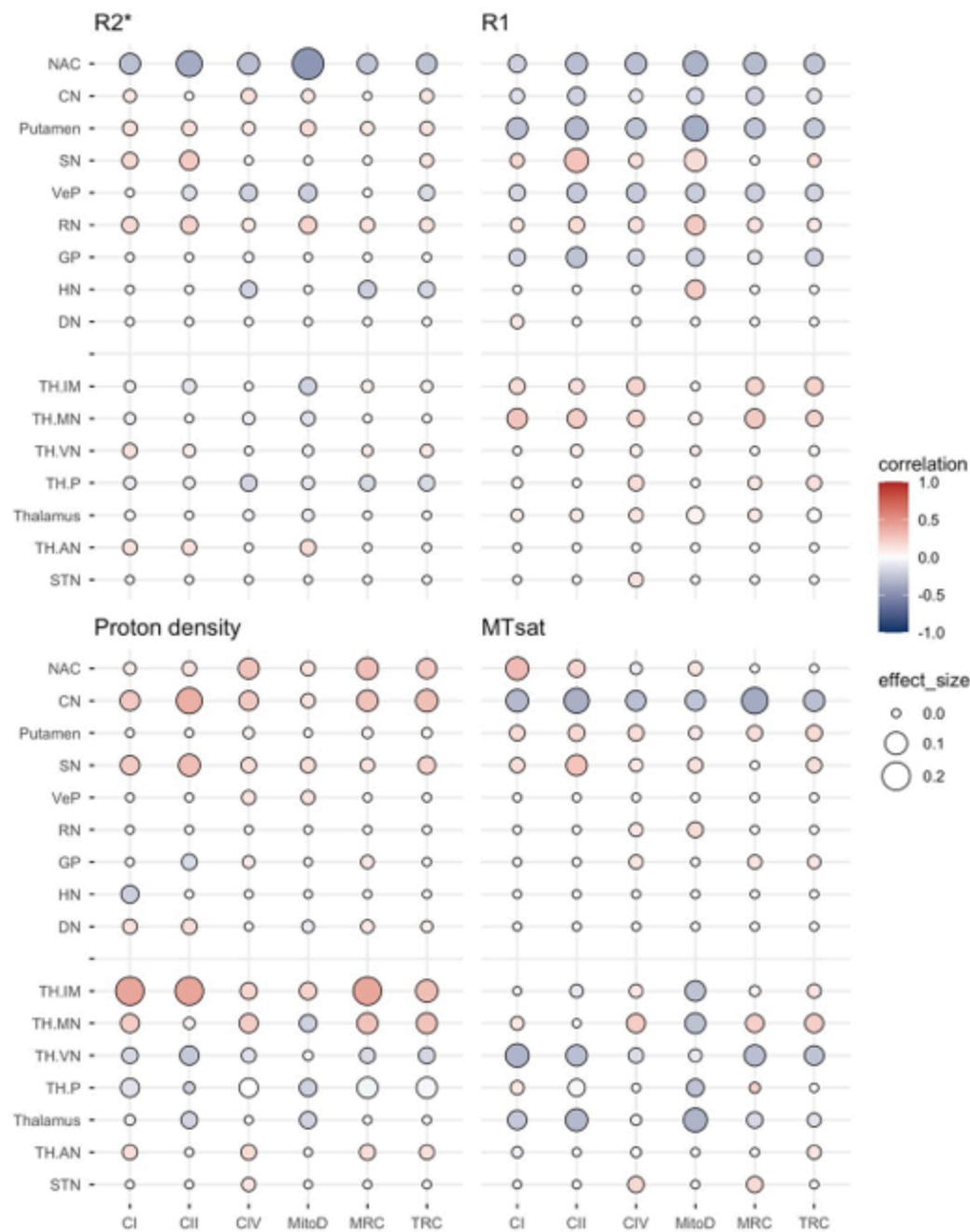


Figure 4

Regional spatial associations between patients with Parkinson’s disease-derived multiparametric mapping measures and mitochondrial features within the HybraPD atlas. Comparison plot demonstrates spatial correlation between multiparametric mapping-derived measures and mitochondrial features. Each row corresponds to a region of interest, and each column corresponds to a mitochondrial feature. Within each anatomical section, regions are ordered from bottom to top based on the

cumulative strength of associations across all mitochondrial features and multiparametric mapping results. CI, CII, CIV: mitochondrial electron transport chain protein complexes I, II, and IV. CN: caudate nucleus. DN: dentate nucleus. GP: globus pallidus. HN: habenular nucleus. MitoD: mitochondrial density. MRC: mitochondrial respiration capacity. NAC: nucleus accumbens. RN: red nucleus. SN: substantia nigra. STN: subthalamic nucleus. TH.AN: anterior thalamic nucleus. TH.IM: intralaminar thalamic nucleus. TH.MN: medial thalamic nucleus. TH.P: posterior thalamic nucleus. TH.VN: ventral thalamic nucleus. TRC: tissue respiration capacity. VeP: ventral pallidum.

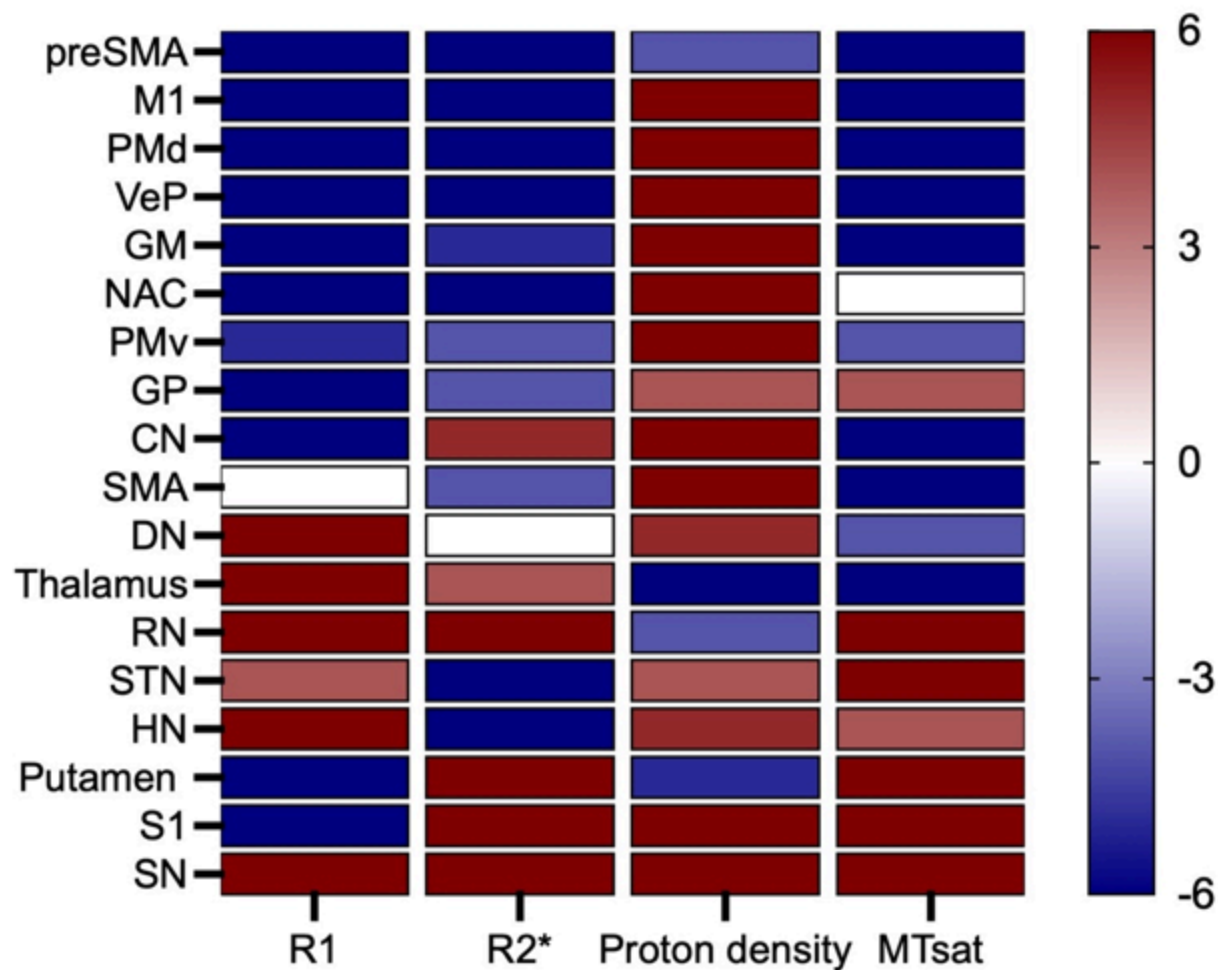


Figure 5

The consistency of spatial couplings between multiparametric alterations in patients with Parkinson’s disease and mitochondrial brain atlas features across regions of interest. The presented heatmap summarizes the directional consistency of spatial coupling between mitochondrial brain atlas features (CI, CII, CIV, MitoD, MRC, and TRC) and multiparametric mapping-derived values (R1, R2*, proton density, and MTsat) in patients with Parkinson’s disease, across predefined regions of interest. For each structure investigated and multiparametric mapping parameter, values indicate the number of mitochondrial features presenting consistent positive (in red) or negative (in blue) associations. CN:

caudate nucleus. DN: dentate nucleus. GM: gray matter. GP: globus pallidus. HN: habenular nucleus. M1: primary motor area. MTsat: magnetic transfer saturation. NAC: nucleus accumbens. PMd: dorsal premotor area. PMv: ventral premotor area. preSMA: presupplementary motor area. R1: longitudinal relaxation rate. R2*: effective transverse relaxation rate. RN: red nucleus. S1: primary somatosensory cortex. SMA: supplementary motor area. SN: substantia nigra. STN: subthalamic nucleus. VeP: ventral pallidum.

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