

Dissociation of Presynaptic and Postsynaptic Dopaminergic Associations with Microstructural Alterations in Parkinson's Disease

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Abstract

Background

Parkinson's disease (PD) is characterized by a degeneration of dopaminergic neurons not only in the nigrostriatal pathways, but also in subcortical and cortical structures. Given the widespread dopaminergic innervation, PD dopamine-related dysfunction may contribute to microstructural alterations beyond the primary site of pathology. Multiparametric mapping (MPM) enables quantification of the longitudinal relaxation rate (R_1), the effective transverse relaxation rate (R_2^*), proton density, and magnetic transfer saturation (MTsat). We hypothesized that PD-related alterations in MPM would present with distinct spatial associations with pre- and postsynaptic dopaminergic markers.

Methods

31 patients with PD (PwPD) and 68 healthy controls (HCs) underwent a 3T MRI. Subsequently, MPM maps (R_2^* , R_1 , proton density, and MTsat) were used for voxel-wise group differences analysis. We used unthresholded t-maps to assess spatial correlation with PET-derived maps of the dopamine transporter (DAT), [^{18}F]-fluoro-L-DOPA (FDOPA), and dopamine D1 and D2 receptors.

Results

We observed spatially consistent dissociation between presynaptic markers. DAT was predominantly negatively associated with all MPM alterations in PwPD, while FDOPA demonstrated positive associations. Subcortical regions demonstrated the strongest in magnitude, heterogeneous, and predominantly iron content (R_2^*)-related associations, specifically in the substantia nigra, ventral pallidum, and the nucleus accumbens. Cortical regions, in turn, exhibited more subtle yet highly consistent, neuroinflammation (proton density)-related spatial associations. The strongest associations were between proton density and DAT in the supplementary motor area ($\rho = -0.841$, CI 95% = -0.844 to -0.837, $p_{\text{FDR}} = 0.0003$) and presupplementary motor area ($\rho = -0.800$, CI 95% = -0.803 to -0.796, $p_{\text{FDR}} = 0.0003$).

Conclusions

The observed spatial dissociation between DAT- and FDOPA-MPM associations in subcortical regions indicates that microstructural degeneration is associated with the loss of dopaminergic terminals, while dopamine synthesis capacity remains preserved or may reflect compensatory responses. The cortical motor areas yielded more subtle, spatially consistent, and neuroinflammation-related association signatures, revealing differential association patterns between subcortical and cortical regions.

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by the irreversible neuronal loss, primarily originating in the substantia nigra pars compacta (SNc)¹. Dopaminergic neurons are the primary population affected in PD due to their structural vulnerability, including highly branched, long axons, and metabolic vulnerability resulting from the toxic profile of dopamine synthesis². PD is primarily characterized by motor symptoms attributable to neurodegeneration of subcortical nuclei, such as the basal ganglia, which are innervated by dopaminergic projections from the SN^{3,4}. In addition to subcortical projections, there is widespread dopaminergic innervation of the neocortex through mesocortical and other midbrain dopaminergic pathways^{5,6}. The structural and metabolic profile of dopaminergic neurons makes them especially susceptible to iron accumulation-related cell death, believed to be the primary cause of SNc neurodegeneration in PD⁷. Additionally, dopaminergic depletion may cause pathological changes in dopamine-innervation regions, potentially underlying neurodegeneration extending beyond the primary site of neurodegeneration.

Using quantitative magnetic resonance imaging (MRI) techniques such as multiparametric mapping (MPM), the biophysical properties of the tissue can be investigated, including the effective transverse relaxation rate ($R2^*$), a biomarker of paramagnetic substances such as iron, allowing an *in vivo* spatial assessment of iron content in the brain^{8,9}. Additionally, MPM quantifies longitudinal relaxation rate ($R1$) and magnetic transfer saturation (MTsat), which serve as *in vivo* biomarkers of macromolecular and myelin content, as well as proton density, which reflects free-water content, thereby enabling *in vivo* investigation of demyelination/remyelination, neuroinflammation processes, and neuronal integrity^{10–12}.

The continuous advances and spatial cellular and molecular characterization of the brain enable further biological characterization of MRI-derived data, including positron emission tomography (PET)-derived maps of dopaminergic neurotransmission in the human brain¹³. The available PET-derived spatial maps of dopamine transporter (DAT), [¹⁸F]-fluoro-L-DOPA (FDOPA), and dopamine receptors D1 and D2 (D1 and D2), provide an additional layer to the biological characterization of pre- (FDOPA and DAT) and post-synaptic (D1 and D2) dopaminergic functions in the brain. Using MPM-derived differences in patients with PD (PwPD) and healthy controls (HCs), we examine their spatial correlation with PET-derived maps of FDOPA, DAT, D1, and D2 to investigate the *in vivo* relationship between the dopaminergic system and pathological processes underlying neurodegeneration, directly in the population of interest. We hypothesized that dopaminergic innervation would positively correlate with the MPM-derived markers of iron accumulation ($R2^*$), supporting the well-established view that iron accumulation is the primary cause of neurodegeneration in subcortical brain regions. Furthermore, we hypothesized that dopaminergic markers would positively correlate with proton density and negatively correlate with $R1$ and MTsat, indicating increased neuroinflammation and reduced myelin and neuronal integrity in the subcortical regions, reflecting additional pathological processes. We expected to observe divergent spatial correlation patterns between D1 and D2, given the functional specialization and innervation of these brain regions. Additionally, we performed an exploratory analysis of their spatial correlation within

the cortical motor regions to derive biologically driven findings and to expand our understanding of dopamine innervation and its relationship with pathological processes in PD beyond the basal ganglia and midbrain.

Methods

Experimental design and participants

Participants were recruited from our inpatient and outpatient clinics at the Department of Neurology of the University Hospital Schleswig-Holstein (Campus Luebeck) (Table 1). Parkinson’s disease was diagnosed as clinically established PD according to the Movement Disorder Society Clinical Diagnostic Criteria, representing the highest level of diagnostic certainty attainable on clinical grounds within this framework¹⁴. Our inclusion criteria comprised age between 50 and 80 years old and no concomitant neurological/psychiatric conditions. Exclusion criteria included comorbidities affecting the ability to provide written consent, MRI contraindications, diagnosis of atypical or secondary Parkinsonism, history of alcohol abuse, or history or presence of structural brain diseases. Every participant provided written informed consent. The study adhered to the Declaration of Helsinki and was approved by the local ethics committee at the University of Luebeck, Germany (AZ: 2024 – 302_2). Every participant underwent a clinical examination and one MRI session. PwPD were examined and imaged in the medication ON stage. The MRI dataset from this cohort has been previously reported^{15,16}, and present work reports a novel secondary analysis.

Table 1
Demographic and clinical characteristics.

number	PwPD	HCs	p-value
	31	68	
male/female	13/18	28/40	1.000 ¹
age (years)	64.9 ± 9.3	65.6 ± 8.1	0.720 ²
MDS-UPDRS-III	28.6 ± 15.5	n.a.	
LEDD	512.6 ± 365.6	n.a.	
Disease duration (years)	4.5 ± 4.3	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. LEDD: levodopa equivalent daily dose. MoCA: Montreal Cognitive Assessment. MDS-UPDRS-III: Movement Disorders Society’s Unified Parkinson’s Disease Rating Scale (subscore III). n.a.: not available. PwPD: patients with Parkinson’s disease.			

Image acquisition and voxel-based quantification

MRI was performed at the Center for Brain, Behavior, and Metabolism Core Facility at the University of Luebeck, 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-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 $256 \times 176 \text{ mm}^2$ (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. Inline distortion correction (2D mode) and prescan normalization were enabled. The combination of T1-weighted acquisition (TR = 19.0 ms, flip angle = 20° , six echoes with TE = 2.20/4.70/7.20/9.70/12.20/15.00 ms, 8 minutes); the proton density-weighted acquisition (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, 11 minutes) and the magnetic transfer-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, 7 minutes), resulted in a total acquisition time of 26 minutes. A neuroradiologist reviewed all datasets to exclude concurrent conditions and to assess visual artifacts (e.g., extensive head motion). We also quantitatively evaluated the data quality using voxel-wise z-scores. Our exclusion criteria included participants with severe visible motion artifacts (ringing and blurring) and excessive quantitative measures, defined as z-scores greater than 2 standard deviations above the mean.

We processed the acquired images using the hMRI toolbox¹⁷ implemented in SPM25 (Statistical Parametric Mapping 25)¹⁸ and MATLAB (R2024b, The MathWorks Inc., Natick, MA, USA). We reconfigured the hMRI toolbox with scanner-specific settings using a custom-written MATLAB script. Acquired T1-, proton density-, and magnetic transfer-weighted images served as input. We generated MPM maps after B_1 correction using the UNICORT algorithm and after radiofrequency receive-sensitivity bias correction using unified segmentation. We preprocessed the created MPM maps using the hMRI toolbox pipeline, comprising segmentation (into gray matter, white matter, and cerebrospinal fluid tissue maps), nonlinear spatial registration to MNI space, and tissue-weighted smoothing^{19–21}. Our preprocessing settings included resampling to a voxel size of $1 \times 1 \times 1 \text{ mm}^3$, and spatial Gaussian smoothing with a $6 \times 6 \times 6 \text{ mm}$ FWHM kernel.

Multiparametric mapping group differences analysis

We performed the group-level analysis in SPM25 within MATLAB. Using a two-sample t-test and controlling for age and sex, we derived t-maps of PD-related differences across all four MPM modalities (R2*, R1, proton density, and MTsat). We assessed only one contrast, generating t-maps showing higher MPM-derived values in PwPD than in HCs (PwPD > HCs). All t-maps were generated using explicit masks, including the tissue probability mask for gray matter incorporated into the SPM25 environment, and masks derived from the HybraPD atlas²² and the Human Motor Area Template (HMAT)²³, thereby assessing group differences within specific regions of interest (ROIs).

Overall, we assessed group differences across 28 ROIs, including whole-brain gray matter (WBGm), 20 subcortical, and 6 motor cortical regions. Subcortical regions were defined by the HybraPD atlas, comprising caudate nucleus (CN), dentate nucleus of the cerebellum (DN), globus pallidus external/internal (GP, GPe/i), habenular nucleus (HN), nucleus accumbens (NAC), putamen, red nucleus (RN), SNc/SN pars reticulata (SNr), subthalamic nucleus (STN), and ventral pallidum (VeP, Supplementary Tables 1–16). Thalamic regions such as anterior (TH.AN), intralaminar (TH.IM), medial (TH.MN), posterior (TH.P), and ventral (TH.VN) thalamic nuclei were all combined into a single thalamus mask, used in the presented analysis. Assessed cortical motor regions include the primary motor area (M1), dorsal/ventral premotor cortex (PMd/v), the presupplementary and supplementary motor areas (preSMA and SMA), and the primary somatosensory cortex (S1). We generated four t-maps for each ROI, corresponding to PwPD > HCs R2*, R1, proton density, and MTsat values.

Voxel-wise spatial correlation of multiparametric mapping-derived t-maps and positron emission tomography-derived neurotransmitter receptor maps

Using the original unthresholded MPM-derived t-maps and PET-derived dopaminergic neurotransmission maps, we performed voxel-wise spatial correlation in Python (v3.13.9) using NumPy (v2.3.5), Pandas (v2.3.3), SciPy (v1.16.3), NiBabel (v5.3.2), and Statsmodels (v0.14.5). PET-derived maps of DAT, FDOPA, D1, and D2 were obtained from a previously published study¹³. We performed 16 correlation tests per ROI (four t-maps: R2*, R1, proton density, MTsat, and four dopaminergic maps: DAT, FDOPA, D1, D2). We restricted the analyses to voxels containing valid PwPD > HCs t-values and valid neurotransmitter receptor map values. For each analysis, we calculated Spearman's correlation coefficient (ρ), Cohen's f^2 effect size, and confidence intervals (CI 95%). We performed nonparametric testing ($n = 5000$) to obtain a numerical distribution under the assumption of no spatial correspondence between maps and report nominal p-values (p) and two-sided permutation-based p-values (p_{perm}). To control for multiple comparisons, we adjusted nominal p-values using the Benjamini-Hochberg false discovery rate (FDR, p_{FDR}) across all statistical tests, with $p_{\text{FDR}} < 0.05$ considered statistically significant. We report only ρ and p_{FDR} in the main text of the manuscript, and additionally Cohen's f^2 , CI 95%, p , p_{perm} in the Supplementary Tables. Visual presentations were generated in R (v4.5.3) using the ggplot2 package (v4.0.2) within RStudio (v2026.01.1 + 403; Posit Software, PBC, Boston, MA, USA).

Results

A consistent dissociation within presynaptic dopaminergic markers defines the global pattern.

The MPM-derived t-maps used for correlation analyses were obtained from group comparisons that identified significant PD-related alterations in a modest number of cortical clusters, reported elsewhere¹⁵. In this work, we observed a robust, directional dissociation within the presynaptic domain.

DAT predominantly showed negative associations (SN: all $p_{FDR} = 0.0003$; $R2^*$: $\rho = -0.169$; $R1$: $\rho = -0.196$; proton density: $\rho = -0.251$; MTsat: $\rho = -0.163$), while FDOPA showed positive associations with PwPD-derived MPM alterations (SN: all $p_{FDR} = 0.0003$; $R2^*$ $\rho = 0.510$; $R1$: $\rho = 0.459$; proton density: $\rho = 0.527$; MTsat: $\rho = 0.420$). Contrarily, postsynaptic markers D1 (SN: all $p_{FDR} = 0.0003$; $R2^*$: $\rho = 0.527$; $R1$: $\rho = 0.471$; proton density: $\rho = 0.533$; MTsat: $\rho = 0.420$) and D2 (SN: all $p_{FDR} = 0.0003$; $R2^*$: $\rho = 0.388$; $R1$: $\rho = 0.436$; proton density: $\rho = 0.458$; MTsat: $\rho = 0.443$) showed strong convergent associations, closely resembling FDOPA across all brain regions investigated (Fig. 1).

Dopaminergic-microstructural coupling is strongest within the nigrostriatal system and reveals region-specific organization of the basal ganglia.

The strongest and most coherent associations were observed within the nigrostriatal system, with the SN showing the highest overall effect sizes and clear differentiation between SNc and SNr (Fig. 2, Supplementary Tables 1–16). SNr showed positive correlations with FDOPA (all $p_{FDR} = 0.0003$; $R2^*$: $\rho = 0.515$; $R1$: $\rho = 0.449$; proton density: $\rho = 0.506$; MTsat: $\rho = 0.398$), D1 ($R2^*$: $\rho = 0.503$, $p_{FDR} = 0.0004$; $R1$: $\rho = 0.411$, $p_{FDR} = 0.0003$; proton density: $\rho = 0.473$, $p = 0.0003$; MTsat: $\rho = 0.345$, $p = 0.0003$), and D2 (all $p_{FDR} = 0.0003$; $R2^*$: $\rho = 0.423$; $R1$: $\rho = 0.459$; proton density: $\rho = 0.452$; MTsat: $\rho = 0.471$). SNc showed weaker and more variable findings (FDOPA: all $p_{FDR} = 0.0003$; $R2^*$: $\rho = 0.458$; $R1$: $\rho = 0.420$; proton density: $\rho = -0.454$; MTsat: $\rho = 0.430$. D1: all $p_{FDR} = 0.0003$; $R2^*$: $\rho = 0.510$; $R1$: $\rho = 0.488$; proton density: $\rho = -0.505$; MTsat: $\rho = 0.488$. D2: all $p_{FDR} = 0.0003$; $R2^*$: $\rho = 0.254$; $R1$: $\rho = 0.351$; proton density: $\rho = -0.371$; MTsat: $\rho = 0.361$). Contrarily, DAT negatively correlated with MPM modalities within the combined mask of SN, highlighting its divergence from FDOPA correlations (all $p_{FDR} = 0.0003$; $R2^*$: $\rho = -0.169$; $R1$: $\rho = -0.196$; proton density: $\rho = -0.251$; MTsat: $\rho = -0.163$).

Within the basal ganglia, association patterns were not uniform. While some regions, such as the SN, showed predominantly positive and convergent associations, the putamen and GPe exhibited more consistently negative profiles. However, the correlations between proton density, MTsat, and D2 in the GPe were the strongest (all $p_{FDR} = 0.0003$; proton density: $\rho = -0.408$; MTsat: $\rho = -0.341$). Negative associations in the putamen were more pronounced between $R1$ and FDOPA, D1 (all $p_{FDR} = 0.0003$; FDOPA: $\rho = -0.430$; D1: $\rho = -0.348$).

Dopaminergic-microstructural associations extend beyond the nigrostriatal system into limbic and associative subcortical circuits.

Several limbic and associative subcortical regions demonstrated strong, frequently convergent associations with dopaminergic markers and MPM modalities (Fig. 3). In multiple regions, the magnitude and consistency of these associations were comparable to those observed within the nigrostriatal system. NAC yielded one of the strongest positive associations between $R2^*$ and DAT ($\rho = 0.661$, $p_{FDR} = 0.0003$). VeP demonstrated the strongest positive associations between $R2^*$, $R1$, MTsat,

and DAT (all $p_{FDR} = 0.0003$; $R2^*$: $\rho = 0.506$; $R1$: $\rho = 0.617$; $MTsat$: $\rho = 0.782$), as well as D1 (all $p_{FDR} = 0.0003$; $R2^*$: $\rho = 0.324$; $R1$: $\rho = 0.432$; $MTsat$: $\rho = 0.645$). HN presented one of the strongest positive correlations between $R2^*$ and D2 ($\rho = 0.785$, $p_{FDR} = 0.0003$), while the remaining associations between MPM modalities and D2 in the HN were negative (all $p_{FDR} = 0.0003$; $R1$: $\rho = -0.579$; proton density: $\rho = -0.493$; $MTsat$: $\rho = -0.665$). RN yielded minor associations across MPM modalities, except for the positive associations between proton density, $MTsat$, and FDOPA (all $p_{FDR} = 0.0003$; proton density: $\rho = 0.463$; $MTsat$: $\rho = 0.504$); and D1 (all $p_{FDR} = 0.0003$; proton density: $\rho = 0.543$; $MTsat$: $\rho = 0.543$).

Motor cortical regions exhibited distinct presynaptic-associated patterns and modality-specific signatures.

We observed the strongest negative associations between proton density and DAT in the SMA ($\rho = -0.841$, $p_{FDR} = 0.0003$) and preSMA ($\rho = -0.800$, $p_{FDR} = 0.0003$, Fig. 4 and Supplementary Tables 17–20). The negative associations between proton density and FDOPA, and between proton density and D1 in the SMA, were among the strongest identified as well (all $p_{FDR} = 0.0003$; FDOPA: $\rho = -0.651$; D1: $\rho = -0.591$). Across all HMAT-derived ROIs, we observed consistently negative correlations between all MPM modalities and dopamine markers; however, the correlations were small in magnitude. preSMA showed the strongest correlations, especially between $R1$ and DAT, FDOPA, D1 (all $p_{FDR} = 0.0003$; DAT: $\rho = -0.319$; FDOPA: $\rho = -0.441$; D1: $\rho = -0.385$), which spatially overlapped with the associations between $MTsat$ and DAT, FDOPA, D1 (all $p_{FDR} = 0.0003$; DAT: $\rho = -0.483$; FDOPA: $\rho = -0.536$; D1: $\rho = -0.428$).

A cortico-subcortical gradient distinguishes the magnitude and spatial consistency of dopaminergic-microstructural associations.

A clear gradient emerged between subcortical and cortical regions. Subcortical structures exhibiting higher magnitude and more heterogeneous associations; for example, strong positive associations between $R2^*$, $R1$, $MTsat$, and DAT in VeP ($R2^*$: $\rho = 0.661$; $R1$: $\rho = 0.617$; $MTsat$: $\rho = 0.782$) and a strong negative association between proton density and DAT in VeP ($\rho = -0.469$). While cortical regions showed lower magnitude but spatially consistent patterns across dopaminergic markers and MPM modalities (Figs. 1 and 5). For example, weak yet consistent negative associations across all dopamine markers and MPM modalities across the dorsal premotor cortex (PMd: all $p_{FDR} = 0.0003$. DAT: $R2^*$: $\rho = -0.165$; $R1$: $\rho = -0.271$; proton density: $\rho = -0.214$; $MTsat$: $\rho = -0.053$. FDOPA: $R2^*$: $\rho = 0.219$; $R1$: $\rho = -0.381$; proton density: $\rho = -0.064$; $MTsat$: $\rho = -0.143$. D1: $R2^*$: $\rho = -0.170$; $R1$: $\rho = -0.357$; proton density: $\rho = -0.035$; $MTsat$: $\rho = -0.080$. D2: $R2^*$: $\rho = -0.031$; $R1$: $\rho = -0.314$; proton density: $\rho = 0.184$; $MTsat$: $\rho = -0.073$).

Discussion

In this study, we investigated the spatial association between PwPD-derived MPM t-maps and PET-derived maps of DAT, FDOPA, D1, and D2 to examine the relationship between microstructural changes and the architecture of underlying dopaminergic neurotransmission in PD. The main finding was the identification of spatially consistent dissociation between the presynaptic markers DAT and FDOPA in

their associations with MPM-derived alterations in PwPD. DAT associations with MPM-derived data were consistently negative, whereas FDOPA frequently showed positive associations. The negative associations between DAT and MPM-derived findings indicate neurodegeneration of presynaptic dopaminergic terminals in regions with high iron content ($R2^*$), microstructural disruptions ($R1$ and $MTsat$), and increased water content (proton density), consistent with neuroinflammation. The positive associations between FDOPA and MPM-derived t-maps are suggestive of relatively preserved or upregulated dopamine synthesis capacity within the same regions. The observed spatial dissociation between DAT and FDOPA associations suggests a mismatch between presynaptic dopaminergic terminal loss and dopamine synthesis, possibly a compensatory mechanism within the dopaminergic system in response to ongoing neurodegeneration.

Within this framework, the consistently positive associations identified among $D1$, $D2$, and MPM-derived alterations can be interpreted as a postsynaptic adaptation to presynaptic dopaminergic neurodegeneration. Specifically, increased receptor availability in regions affected by structural alterations (e.g., iron accumulation and demyelination) may represent a compensatory mechanism to maintain dopaminergic signaling. This idea is supported by the observation that there were no expected differences between $D1$ and $D2$ association patterns across MPM modalities, indicating that the analysis captured a shared, system-level response of the dopaminergic system, rather than receptor-specific mechanisms.

The strongest magnitude associations were identified with the nigrostriatal systems. SN (SNc/SNr) consistently showed the strongest positive associations between dopamine markers and MPM modalities, with regional differences. As $R2^*$ is sensitive to paramagnetic substances such as iron, the positive associations between $R2^*$ and FDOPA, $D1$, and $D2$ likely reflect increased iron content within dopaminergic neurons, which is linked to oxidative stress and their vulnerability²⁴. We identified a similar pattern of associations between the dopaminergically enriched SNc and the predominantly GABAergic SNr ²⁵, suggesting that our observations may reflect network-level pathological processes within the SN rather than processes restricted to dopaminergic neurons.

Other basal ganglia structures, including the putamen and GPe , showed negative MPM-dopamine marker associations, suggesting reduced compensatory capacity or a greater pathological burden underlying the observed differences. These findings demonstrate a region-specific organization of dopaminergic-microstructural coupling, in which the observed associations reflect varying balances between neurodegeneration and preservation. Similar convergent findings across FDOPA, $D1$, and $D2$ associations were observed in the VeP and NAC , suggesting that dopaminergic-microstructural coupling is not confined to motor circuits but extends to subcortical systems, albeit with reduced magnitude.

Contrary to subcortical regions, where associations were more strongly linked to $R2^*$, cortical motor regions showed prominent associations with proton density, revealing a region-specific dopaminergic-microstructural signature. The strongest negative association between DAT and proton density in the $preSMA$ and SMA indicates a strong link between the loss of presynaptic dopaminergic terminals and

increased free water content, which is associated with neuroinflammatory processes. As preSMA and SMA play key roles in cortico-basal and ganglia-thalamo-cortical circuits involved in motor planning and execution, this observation represents a region-specific association between inflammation-related microstructural alterations and dopaminergic degeneration^{26,27}.

Additionally, we identified a subcortical-cortical gradient reflecting a hierarchical spatial organization of dopaminergic-microstructural associations. Subcortical regions such as SN and VeP exhibit focal, high-magnitude, and heterogeneous associations, whereas cortical regions, including preSMA and PMd, exhibit more spatially consistent yet lower-magnitude associations. The identified pattern could be influenced by disease stage, as the MPM differences were assessed in early- to mid-stage PwPD, in whom the cortical structure may be relatively preserved compared to subcortical areas. Some of the identified cortical associations included positive FDOPA, D1, D2, and MPM coupling, suggesting a continuation of compensatory responses from the subcortex. Based on our observations, subcortical regions were characterized by early, pronounced iron-related and degeneration-associated dopaminergic alterations, whereas cortical regions exhibit more subtle changes that may become more prominent in later disease stages, necessitating further longitudinal studies.

The limitations of this study include its cross-sectional design, which limits our ability to assess temporal and causal changes in the association between microstructure and dopaminergic innervation in PwPD. Future longitudinal studies addressing this issue would provide complementary insights into disease progression, compensatory mechanisms, and microstructure-dopamine interactions over time. Additionally, MPM modalities reflect tissue biophysical properties but lack histopathological specificity. R2*, R1, proton density, and MTsat are sensitive to multiple overlapping tissue properties, including myelin (R2*, R1, and MTsat), resulting in inherently nonspecific biological interpretation. Most importantly, the PET-derived dopaminergic maps were based on normative datasets rather than subject-specific PET acquisitions, limiting the investigation of the individual-level interface and biasing the derived correlations towards canonical distributions of dopaminergic markers. Therefore, the presented findings should be interpreted with caution and as reflecting population-level rather than subject-specific dopaminergic-microstructural coupling. Additional use of complementary approaches, including integrating genetic, molecular, and histopathological data, would strengthen and expand the biological interpretation of the derived data and the proposed approach.

Importantly, the presented spatial correlation analyses were based on the use of unthresholded PwPD > HCs t-maps derived from previously identified PD-related MPM alterations. Therefore, the reported associations reflect the spatial organization of PD-related tissue alterations, not the normative association between measured MPM and dopaminergic innervation. Additionally, PwPD were assessed in the ON state, and we have no means to quantify the possible contribution of symptomatic dopaminergic treatment to the reported findings; therefore, it should be considered when interpreting them. Further research with OFF-medication assessment may be needed to distinguish disease-related from medication-induced effects.

To conclude, we assessed the spatial relationship between the dopaminergic system and PwPD-derived MPM alterations. Our analysis revealed spatially structured and consistent dopaminergic-microstructural coupling in PD, characterized by dissociated presynaptic dopaminergic neurodegeneration and postsynaptic compensatory responses. Additionally, we observed a subcortical-cortical gradient, with high-magnitude, iron-associated alterations predominantly in subcortical regions and more subtle, neuroinflammation-associated alterations in cortical motor regions. Future longitudinal, subject-specific studies and integration of additional data are needed to assess the temporal and causal relationship in detail.

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Declarations

Funding declaration

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Authors contribution

Conceptualization: M.M.P., J.P.; Formal analysis: M.M.P., L.W.; Investigation: 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.

Competing interests statement

The authors declare that they have no competing interests.

Data availability

The data generated in this study is not publicly available. De-identified data may be provided by the corresponding authors upon reasonable request, subject to institutional approval.

Code availability

The code used in this study is not publicly available and may be provided by the corresponding authors upon reasonable request.

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Figures

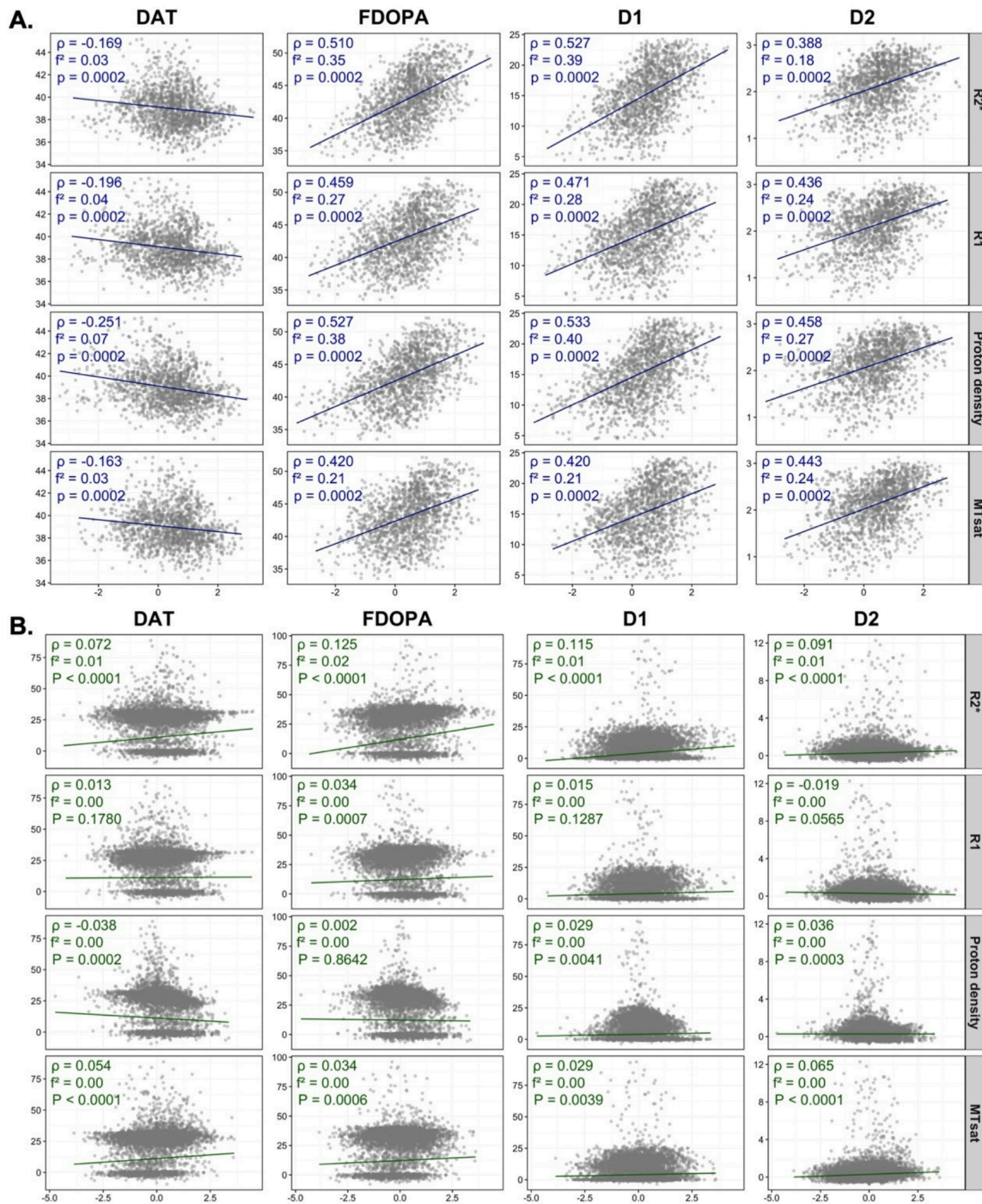


Figure 1

Spatial associations between patients with Parkinson's disease-derived multiparametric mapping measures and positron emission tomography-derived dopaminergic measures in the substantia nigra and across whole-brain gray matter. Representative scatter plots illustrate the spatial relationships between multiparametric mapping-derived t-values (rows: $R2^*$, $R1$, proton density, MTsat) and positron emission tomography-derived dopamine markers t-values (columns: DAT, FDOPA, D1, D2) in the

substantia nigra (A) and across the whole brain gray matter (B). D1: dopamine D1 transporter. D2: dopamine D2 transporter. DAT: dopamine transporter. f^2 : effect size. FDOPA: [^{18}F]-fluoro-L-DOPA. MTsat: magnetic transfer saturation. p: nominal p-values. R1: longitudinal relaxation rate. R2*: effective transverse relaxation rate. ρ : Spearman correlation coefficient.

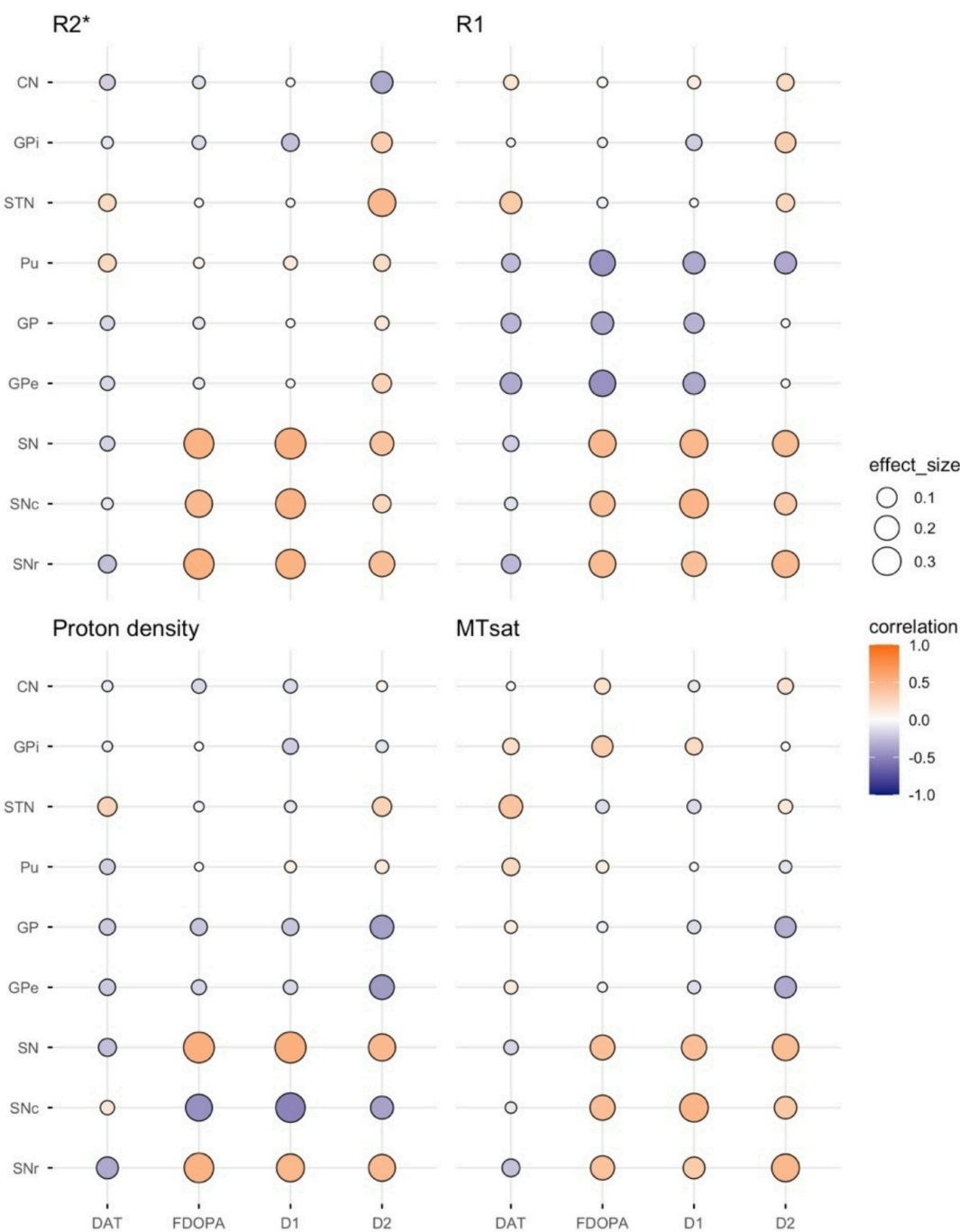


Figure 2

Regional association between patients with Parkinson’s disease-derived multiparametric mapping measures and positron emission tomography-derived dopaminergic measures within the basal ganglia.

Comparison plot demonstrating spatial correlation between multiparametric mapping-derived measures and positron emission tomography-derived dopaminergic markers. Each row of this comparison plot corresponds to a region of interest, and each column corresponds to a dopaminergic measure. Regions are ordered from bottom to top based on the cumulative strength of associations across all dopaminergic markers and multiparametric mapping modalities. CN: caudate nucleus. D1: dopamine D1 transporter. D2: dopamine D2 transporter. DAT: dopamine transporter. FDOPA: [¹⁸F]-fluoro-L-DOPA. GP(e/i): globus pallidus (external/internal). MTsat: magnetic transfer saturation. Pu: putamen. R1: longitudinal relaxation rate. R2*: effective transverse relaxation rate. SN (SNc/SNr): substantia nigra (pars compacta/pars reticulata). STN: subthalamic nucleus.

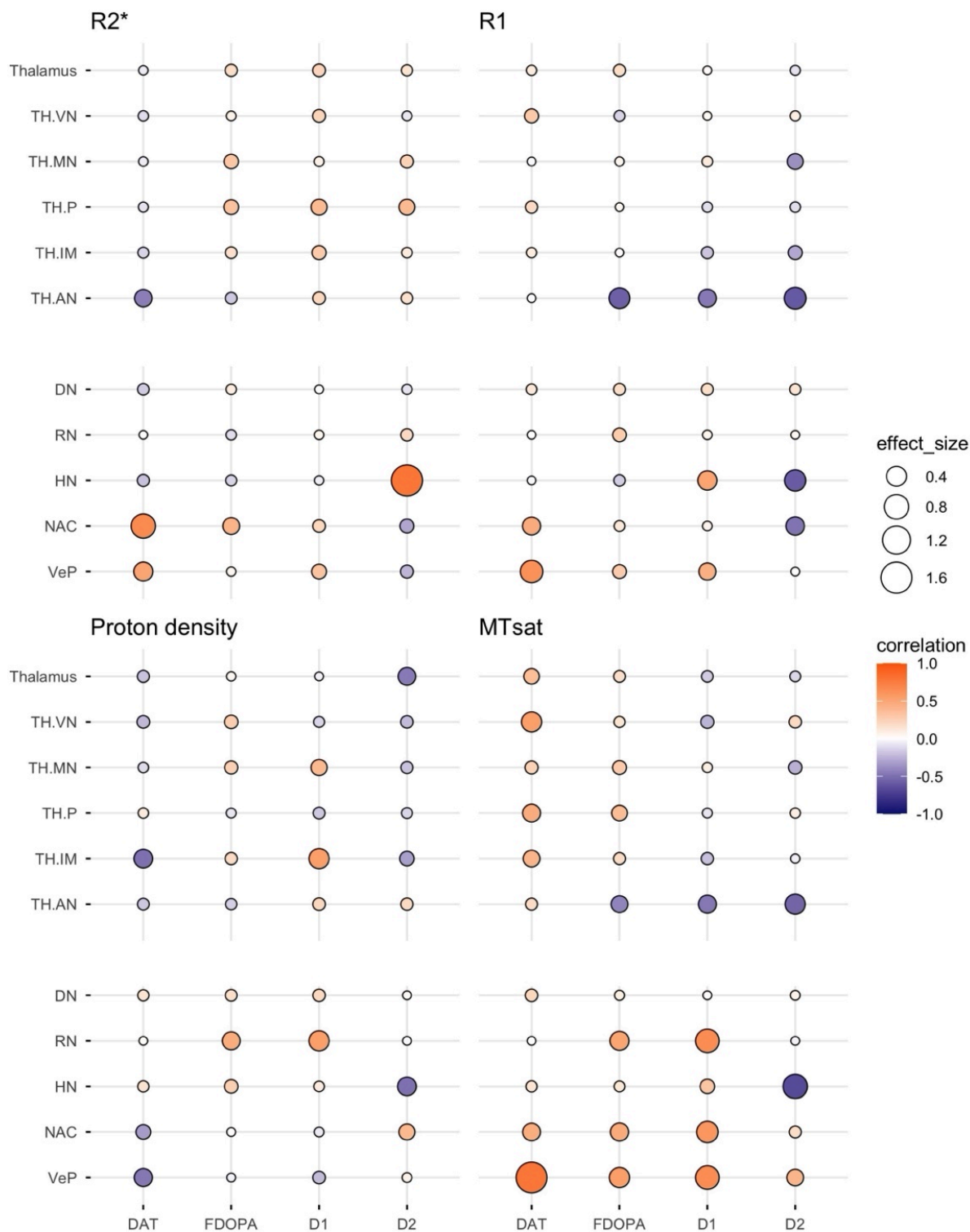


Figure 3

Regional association between patients with Parkinson's disease-derived multiparametric mapping measures and positron emission tomography-derived dopaminergic measures within the subcortical regions and thalamic nuclei. Comparison plot demonstrating spatial correlation between multiparametric mapping-derived measures and positron emission tomography-derived dopaminergic markers. Each row corresponds to a region of interest, and each column corresponds to a dopaminergic

measure. Within each anatomical section, regions are ordered from bottom to top based on the cumulative strength of associations across all dopaminergic markers and multiparametric mapping. D1: dopamine D1 transporter. D2: dopamine D2 transporter. DAT: dopamine transporter. DN: dentate gyrus of the cerebellum. FDOPA: [^{18}F]-fluoro-L-DOPA. HN: habenular nucleus. MTsat: magnetic transfer saturation. NAC: nucleus accumbens. R1: longitudinal relaxation rate. R2*: effective transverse relaxation rate. RN: red nucleus. TH.AN: thalamic anterior nucleus. TH.IM: thalamic intralaminar nucleus. TH.MN: thalamic medial nucleus. TH.P: thalamic posterior nucleus. TH.VN: thalamic ventral nucleus. VeP: ventral pallidum.

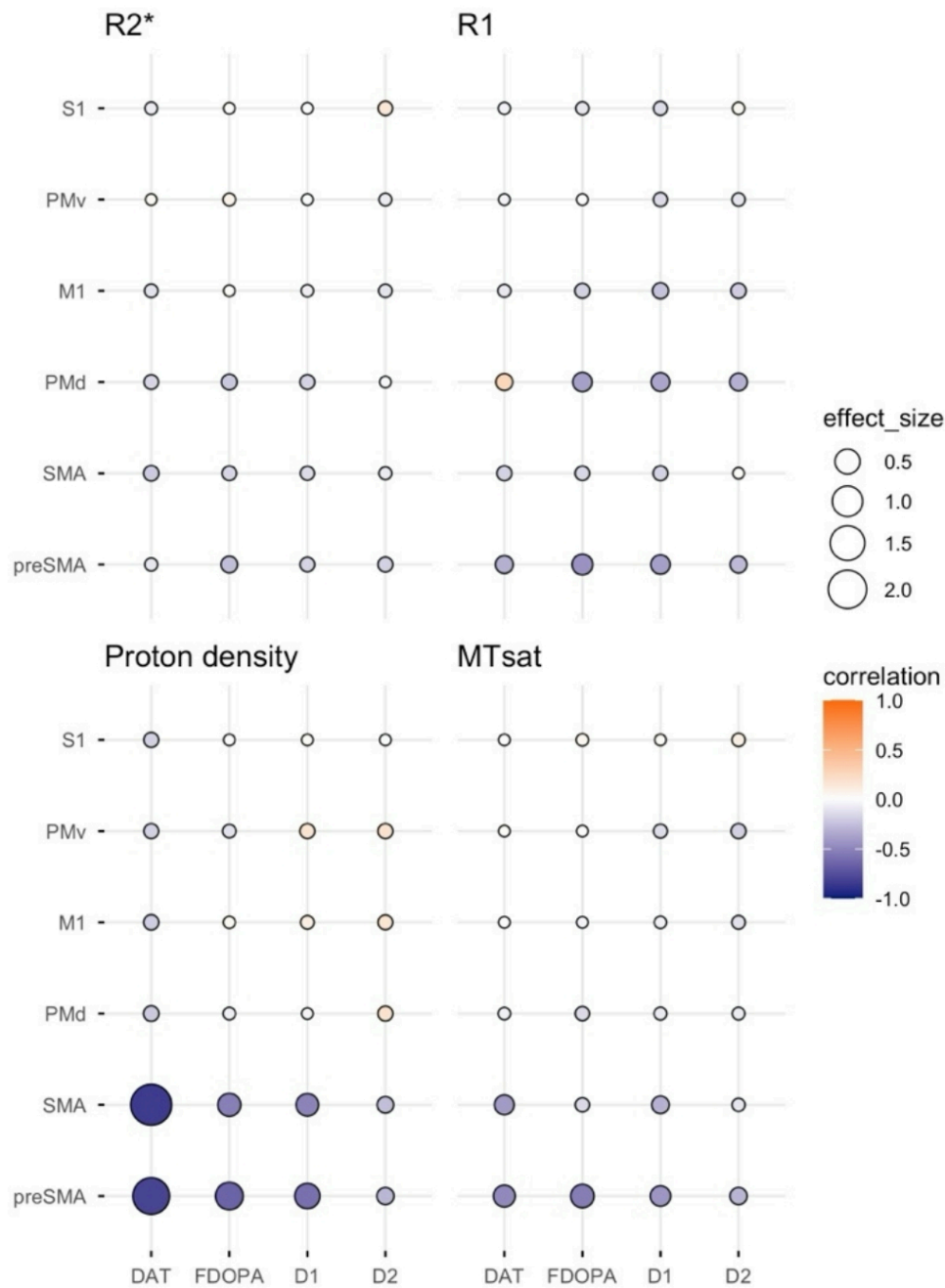


Figure 4

Regional association between patients with Parkinson's disease-derived multiparametric mapping measures and positron emission tomography-derived dopaminergic measures within cortical motor-related areas. Comparison plot demonstrating spatial correlation between multiparametric mapping-derived measures and positron emission tomography-derived dopaminergic markers. Each row corresponds to a region of interest, and each column corresponds to a dopaminergic measure. D1:

dopamine D1 transporter. D2: dopamine D2 transporter. DAT: dopamine transporter. FDOPA: [¹⁸F]-fluoro-L-DOPA. M1: primary motor cortex. MTsat: magnetic transfer saturation. PMd/v: dorsal/ventral premotor cortex. preSMA: presupplementary motor area. R1: longitudinal relaxation rate. R2*: effective transverse relaxation rate. S1: primary somatosensory cortex. SMA: supplementary motor area.

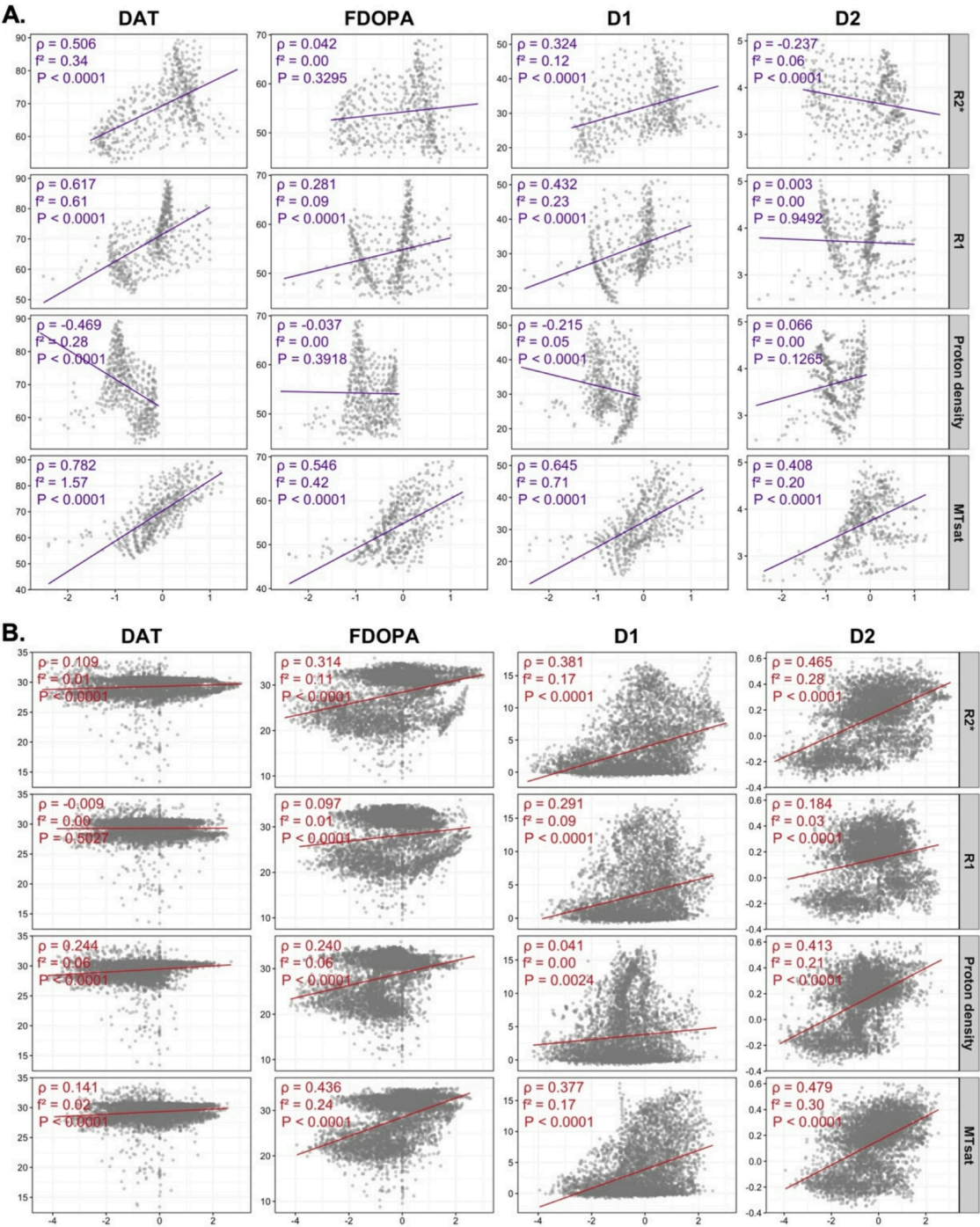


Figure 5

A cortical-subcortical gradient of magnitude and consistency of spatial associations between patients with Parkinson's disease-derived multiparametric mapping measures and positron emission tomography-derived dopaminergic measures. Representative scatter plots illustrate the identified cortical-subcortical gradient that distinguishes the magnitude and consistency of dopaminergic-microstructural associations, using the ventral pallidum (A) and lingual gyrus (B) as examples. The scatter plots demonstrate the associations between multiparametric mapping modalities t-values (rows: R2*, R1, proton density, MTsat) and positron emission tomography-derived dopaminergic markers t-values (columns: DAT, FDOPA, D1, D2). D1: dopamine D1 transporter. D2: dopamine D2 transporter. DAT: dopamine transporter. Cohen's f^2 : Cohen's effect size. FDOPA: [^{18}F]-fluoro-L-DOPA. MTsat: magnetic transfer saturation. p: nominal p-values. R1: longitudinal relaxation rate. R2*: effective transverse relaxation rate. ρ : Spearman correlation coefficient.

Supplementary Files

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