Mapping the Microstructure of Human Cerebral Cortex In Vivo with Diffusion MRI

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Abstract

Despite advances in diffusion MRI, which have led to remarkable progress in mapping white matter of the living human brain, the understanding of cerebral cortical microstructure in vivo and its relationship to macrostructure, myeloarchitecture, cytoarchitecture, chemoarchitecture, metabolism, and function lag far behind. We present neuromaps of 21 microstructural metrics derived from diffusion tensor, diffusion kurtosis, mean apparent propagator, and neurite orientation dispersion and density imaging of the young adult cerebral cortex. We demonstrate how cortical microstructure follows cytoarchitectural and laminar differentiation, aligns with the macroscale sensory-fugal and sensorimotor-association axes, and contributes to functional brain networks, neural oscillatory dynamics, neurotransmitter receptor/transporter distributions, and cognition and behavior. We find cortical microstructural covariation across individuals to encode functional and structural connectivity as well as gene expression and neurotransmitter similarity. Finally, our exploratory analysis suggests cortical microstructure from diffusion MRI could prove useful in investigating a broad array of neuropsychiatric disorders.

Introduction

Most of our knowledge of mammalian brain microstructure and connectivity has traditionally derived from microscopic analysis of animal models and ex vivo human brain specimens. This historical state of affairs led Crick and Jones to call for the development of technologies to map the microarchitecture and connectivity of the in vivo human brain in their article "The Backwardness of Human Neuroanatomy"[1]. This perspective proved to be timely, since the following year saw the publication of the rank-2 tensor representation of diffusion magnetic resonance imaging (dMRI) by Basser et al.[2]. Over the past three decades, diffusion tensor imaging (DTI), and higher-dimensional representations such as the rank-4 tensor (diffusion kurtosis imaging: DKI) and mean apparent propagator (MAP-MRI) have enabled in vivo mapping of white matter microstructure and connectivity in the human brain with increasing power[3–6]. However, despite the remarkable progress in understanding white matter, "backwardness" remains in characterizing in vivo human cerebral cortex using dMRI due to limitations of signal-to-noise ratio (SNR), spatial and angular resolution, and microscale sensitivity. Hence, in vivo exploration of the human neocortex has been largely limited to macroscale measurements of volume, thickness, curvature, and surface area as well as a few cytoarchitectural or myeloarchitectural features, including iron content from susceptibility mapping[7] and myelin content from T1/T2 mapping[8].

The evolution of MRI hardware and software advances pioneered by the Human Connectome Project (HCP)[9] have broken the SNR barrier with millimeter spatial resolution and higher angular resolution at multiple diffusion-weighting strengths that interrogate the tissue architecture at smaller spatial scales than conventional DTI used for white matter mapping. This opened in vivo human cortical imaging to the full panoply of microstructural metrics available from low- and high-dimensional representations such as DTI, DKI, and MAP-MRI, and biophysical models such as neurite orientation dispersion and density imaging (NODDI)[10]. An initial study has outlined the regional variation of DTI and NODDI microstructural metrics

across the human cerebral cortex and its relationship with measures of macrostructure (cortical thickness), myelination (T1/T2 ratio) and cytoarchitecture (von Economo cell types)[11]. Recent clinical research also suggests advantages of cortical dMRI over traditional macrostructural measures such as thickness in disorders such as Alzheimer's disease[12–14].

In spite of this early progress, to our knowledge, there has not yet been a comprehensive investigation of how dMRI-derived cortical microstructural mapping relates to molecular, cellular, metabolic, electrophysiological, and functional variation across the human cerebral cortex. Recent breakthroughs have been achieved in generating multimodal maps of the cortex across spatial scales by integrating gene expression data and transcriptomics from the Allen Brain Atlas, neurotransmitter receptor and transporter densities as well as metabolic information from positron emission tomography (PET), electrophysiological data from magnetoencephalography (MEG), hemodynamic function from blood oxygenation level-dependent (BOLD) functional MRI (fMRI), myelination from T1/T2 ratio MRI, and macrostructure from MRI volumetrics[9,15–21]. However, conspicuously missing from these new "neuromaps" is the diversity of microstructural information available from state-of-the-art dMRI.

In this work, we leverage the latest advances in dMRI preprocessing, including machine learning-based denoising, motion and image artifact correction, and outlier replacement, to achieve cortical microstructural test-retest reliability comparable to traditional macrostructural metrics such as cortical thickness. We combine high-resolution DTI, DKI, MAP-MRI, and NODDI data with multimodal neuromaps to show how regional cortical microstructure corresponds to molecular features such as neurotransmitter receptor and transporter densities, mesoscale features such as Mesulam's hierarchy of laminar differentiation[22], the macroscale sensorimotor-association (SA) axis of evolutionary and childhood cortical development, electrophysiological oscillatory dynamics across the full spectrum of frequency bands, as well as cognition and behavior across many domains. These findings are a step forward in resolving the backwardness of human neuroanatomy. We also conduct an exploratory analysis of in vivo microstructural mapping for identifying abnormal cortex in neuropsychiatric disorders to help pave the way for clinical applications as cutting-edge dMRI becomes increasingly incorporated into a rapidly growing array of open access neuroimaging databases available worldwide[23].

Methods

All code and data used to perform these analyses can be found at https://github.com/ucsfncl/diffusion_neuromaps. Volumetric images are included in the neuromaps package[15].

Microstructural Data Acquisition

We used structural and diffusion preprocessed data from the S1200 release of the Human Connectome Project Young Adult (HCP-YA) dataset[9] to create cortical microstructural profiles. We exclude any subjects with quality control issues due to anatomical anomalies, segmentation and surface errors, temporal head coil instability, and model fitting irregularities[24]. As a result, our analysis comprises 962 subjects, 38 of whom also have retest data.

First, the diffusion data was denoised via Marchenko-Pastur Principal Component Analysis (MPPCA) denoising[25] followed by Rician debiasing[26]. We fit the diffusion tensor imaging (DTI)[2] model with only the b=1000 s/mm^2 shell and diffusion kurtosis imaging (DKI)[5], Neurite Orientation Dispersion and Density Imaging (NODDI)[10], and Mean Apparent Propagator-MRI (MAP-MRI)[6] models with the full dMRI acquisition. The DTI, DKI, and MAP-MRI fitting was performed via dipy[27]; the NODDI fitting was performed via AMICO[28]. We fit the DKI model with ordinary least-squares fitting using the Splitting Conic Solver from CVXPY[29]; the MAP-MRI model using a radial order of 6, Laplacian regularization of 0.05, and a positivity constraint; NODDI fitting using a modified parallel diffusivity value of 1.1×10^{-3} mm^2/s to better capture gray matter microstructure[30]. In total, we collected the following metrics: fractional anisotropy (FA), axial diffusivity (AD), radial diffusivity (RD), mean diffusivity (MD) from DTI; DKI-FA, DKI-MD, DKI-RD, DKI-AD, mean kurtosis (MK), radial kurtosis (RK), axial kurtosis (AK), mean kurtosis tensor (MKT), and kurtosis fractional anisotropy (KFA) from DKI; neurite density index (NDI), orientation dispersion index (ODI), and isotropic volume fraction (ISOVF) from NODDI; q-space inverse (QIV), mean-squared displacement (MSD), return-to-origin probability (RTOP), return-to-axis probability (RTAP), and return-to-plane probability (RTPP) from MAP-MRI; cortical thickness measured from freesurfer recon-all[31] and myelin as expressed in T1w/T2w MRI.

We used nilearn's vol_to_surf functionality to sample our volumetric microstructural maps uniformly between MSMall pial and white matter fsLR-32k surfaces, while masking out any voxels not in the cortical ribbon. For MAP-MRI derived values, we conducted additional outlier detection by excluding any voxels greater than 4.5 median absolute deviations from the median. For all microstructural values, we excluded any cortical voxels greater than one standard deviation away from the mean. We filled in any missing values via nearest neighbor sampling from known values on the MSMall midthickness surface. Finally, we parcellated the structural maps using the Glasser atlas[20], Desikan-Killiany (DK) atlas[32], Mesulam atlas[22], and von-Economo-Koskinas atlas[33,34] to reduce noise and improve interpretability.

To assess repeatability, we computed the test-retest coefficient of variation (CoV) and the two-way mixed, single measures, absolute agreement inter-class correlation (ICC). The test-retest CoV was computed as the subject-average standard deviation over sessions divided by the average value taken over the subjects and sessions. For the ICC, the variation between measurements was found using the test-retest portion and the variation between subjects was found using the whole dataset. To assess inter-subject variability, we computed the inter-subject CoV, taking the measurement error found in the test-retest dataset into account. Finally, the laterality index was computed as $\frac{x_{LH}-x_{RH}}{x_{LH}+x_{RH}}$, with positive values indicating left lateralization and negative values indicating right lateralization.

We found the structural covariance networks (SCNs)[35–38] for each metric by computing the correlation between pairs of gray matter regions across all subjects. We also computed an SCN that would encompass all metrics by z-scoring the microstructural data and then computing the correlation between pairs of grey matter regions across all subjects and metrics. We derived our structural gradients via degree-normalized Laplacian embedding[13,39,40]. We focused our analysis on the first two gradients, disregarding the first steady-state eigenvector.

Structural and Functional Networks

The structural and functional connectivity matrices used in this analysis were derived from the HCP-YA dataset and sourced from the enigma toolbox[41]. Functional connectivity was computed via pairwise correlations across time for each pair of gray matter regions with negative correlations clipped to zero. Subject connectivity matrices were then z-transformed, group-averaged, and min-max normalized. Structural connectivity was computed using MRtrix3[42]. Multi-shell, multi-tissue response functions were estimated[43], spherical deconvolution and intensity normalization were performed, and tractograms with 40 million streamlines were generated. Spherical-deconvolution informed filtering (SIFT2)[44] was applied, and a group-averaged structural connectome was computed by averaging the log-transformed streamline count, while preserving density and edge-length distributions. Edge weights were then min-max normalized.

MEG Maps

Magnetoencephalography (MEG) power across six frequency bands: delta (2-4 Hz), theta (5-7 Hz), alpha (8-12 Hz), beta (15-29 Hz), low gamma (30-59 Hz), high gamma (60-90 Hz) and intrinsic timescale were collected as part of the HCP-YA project[9] and sourced from the neuromaps library[15]. Previous publications have detailed the data collection and processing[18,45]. The maps were parcellated into Glasser regions.

PET Maps

Positron emission tomography (PET) maps were collected from multiple studies[46–86] and sourced from the neuromaps library[15]. For further information, see the following publication[17]. In all cases, only healthy controls were used. The maps are proportional to receptor/transporter density, and following convention, we refer to their values as receptor/transporter densities. Previous work has verified the consistency of the receptor/transporter densities via comparison with autoradiography data[17]. The maps were parcellated into Glasser regions.

Gene Analysis

Gene expression data was sourced from the Allen Human Brain Atlas (AHBA)[19] and generated using the abagen package[87]. Preprocessing included intensity-based filtering, probe selection for each gene, matching samples to each DK region, normalization, and aggregation across donors and within regions. Only genes with similarity ($r > 0.2$) across donors were kept, resulting in a total of 12,668 genes. Transcriptomics analysis was performed using the imaging-transcriptomics package[88]. Univariate spearman correlation tests were conducted, genes were ranked by their correlation coefficient, and gene set enrichment analysis (GSEA)[89] was used to compute normalized enrichment scores (NES) with respect to the null distribution derived using spin permutations. For all gene analysis, the DK parcellation was used.

Dominance Analysis

Dominance analysis was performed to determine the relative contribution of each variable to a multiple linear regression model[90]. This was conducted for each input variable by measuring the average increase in the coefficient of determination when adding the single input variable across

all possible combinations of input variable. The total dominance was expressed as a percentage of the adjusted coefficient of determination of the complete model. The robustness of the multiple linear regression model was assessed distance-dependent cross-validation, where the closest 75% of regions was taken to be the training set and the further 25% of regions was the test set[17].

Permutation Testing

We used spin permutations, which preserves spatial autocorrelation, to generate null distributions for testing statistical significance[88]. We extracted Glasser and DK region centroid coordinates from the spherical projection of the fsLR-32k surface and then applied a random rotation and, for bihemispheric statistical testing, applied reflection before and after the rotation to the right hemisphere. Original parcels were reassigned to their closest rotated parcels for each permutation. To assess statistical significance for similarity matrices, we used Mantel's test. To generate the null distribution, the rows and columns of the similarity were permuted using the spin permutation method described above. All multiple hypothesis tests also underwent false discovery rate (FDR) correction. Unless otherwise stated, our significance level was set to 5%.

Cognitive Brain Maps

fMRI task-activation maps[91] were obtained using NeuroQuery[92], a meta-analytic machine learning tool that predicts the spatial distributions of neurological observations given an input string. We selected 123 cognitive terms from the Cognitive Atlas[93], previously used in the neuroscience literature[17,45].

Partial Least Squares Correlation Analysis

Partial least squares (PLS) correlation analysis[94,95] was used to relate microstructure to neurotransmitter receptor densities and functional activations via the pyls package. PLS projects two datasets onto orthogonal sets of latent variables with maximum covariance. The scores were computed by projecting the original data onto their respective weights and the loadings are the Pearson's correlation coefficient between the values and the scores. The significance of the latent variable was assessed via spin permutation testing. We restricted our analysis to only the first latent variable.

Results

To investigate cortical microstructure, we first took a group-averaged profile of the HCP-YA dataset, parcellated into 360 Glasser regions: FA, AD, RD, and MD from DTI; DKI-FA, DKI-AD, DKI-RD, DKI-MD, MK, AK, RK, MKT, KFA from DKI; ICVF, ODI, and ISOVF from NODDI, MSD, QIV, RTOP, RTAP, and RTPP from MAPMRI; cortical thickness (THICK) and myelin (MYL) (Fig. 1A). In addition to the group-average, we also measured the intersubject variability (Fig. S1) and the laterality index (Fig. S2) for each of the metrics.

Interrelatedness of Microstructural Metrics

To investigate the relationship between the microstructural metrics, region-wise Pearson correlation coefficients were computed between each metric and t-SNE maps were generated (Fig. 1B & 1C). Our analysis revealed the microstructural metrics to exist along a spectrum with the macrostructural metric of cortical thickness in the middle. At one end, we found metrics representative of isotropic structure, heterogeneous tissue environments, and higher rates of diffusivity, such as the DTI and DKI diffusivities (AD, MD & RD), QIV and MSD from MAP-MRI, and free water fraction (ISOVF) from NODDI. At the other end, we found metrics indicative of deviation from isotropy, such as the DTI and DKI anisotropies (FA & KFA), the DKI kurtoses (AK, RK, MK & MKT), and the MAP-MRI return probabilities (RTOP, RTAP & RTPP). These deviations from isotropy are positively correlated with NODDI indices of cellularity (ICVF) and fiber orientation dispersion (ODI) as well as with myelination. We conducted a similar analysis on structural covariance networks (SCNs), where region-to-region similarity was computed via subject-wise Pearson correlation coefficients for each microstructural metric (Figure S3). As SCNs, KFA became increasingly associated with the DKI diffusivities, the DKI and DTI diffusivities became increasingly disassociated, while cortical thickness and myelin become closely linked. However, patterns of similarity were highly conserved across SCNs as almost all pairs of SCNs had statistically significant associations. We stress that many of these associations likely only hold true in the cerebral cortex and do not reflect a more general relationship that should be extended into other tissues.

Laminar Differentiation and Cytoarchitecture Stratify Cortical Microstructure

Cortical microstructure was stratified by both cytoarchitectural and laminar differentiation, with the first two structural gradients (SG1) and (SG2) showing statistically significant differences across the von Economo cell type and the Mesulam laminar hierarchies (Figure 2). In the von Economo atlas, granular and agranular cortex were at opposite extremes of SG1, whereas polar cortex was distinguished from parietal and granular cortex by SG2. For the Mesulam atlas, SG2 best differentiated paralimbic and idiotypic cortices. Furthermore, SG1 was correlated with Thionin staining ($r = 0.38, p = 0.015$), specific for DNA and Nissl substance, while SG2 was correlated with Bielschowsky staining ($r = 0.39, p = 0.03$), a silver staining method used to demonstrate fibrous elements such as neurofibrils.

In addition to the structural gradients, each specific microstructural metric as well as the majority of intersubject CoVs and LIs showed statistically significant differences across both von Economo and Mesulam organizational hierarchies (Figures S4, S5). The paralimbic cortex was distinguished by higher diffusivities, anisotropies, kurtoses, and free water but lower KFA. DKI and NODDI measures were best at differentiating the other three levels of Mesulam's hierarchy, with progressively lower kurtoses (AK, MK & RK), cellularity (ICVF), and ODI along the sensory-fugal axis, a gradient extending from idiotypic to unimodal to heteromodal and ending at paralimbic cortex. This aligns with the well-known decrease of cortical myelination and increase

of cortical thickness along the sensory-fugal axis, a gradient extending from idiotypic to unimodal to heteromodal and ending at paralimbic cortex, that we also observed[22].

Much like Mesulam's paralimbic cortex, the von Economo polar regions were also distinguished by high diffusivities, high anisotropies, high kurtoses, high free water and strikingly low KFA, but not high thickness. Polar cortex was also more easily identified by high MSD and QIV, the two MAP-MRI metrics most associated with high rates of diffusivity in heterogeneous environments. Compared to agranular cortex, granular cortex was characterized by higher kurtoses (AK, MK & RK) and higher ICVF, ODI & ISOVF among the NODDI metrics as well as the lower cortical thickness and higher myelination that had been previously reported and that we also identified[33,34]. The higher ICVF in granular cortex agrees with previous findings in human and animal studies that reported higher neuron density in granular regions[96,97]. Synapse density, quantified via synaptic vesicle glycoprotein 2A (SV2A) binding density, was negatively correlated with ICVF ($r = -0.29, p = 0.013$) and myelin ($r = -0.30, p = 0.008$), confirming the inverse relationship between neuron density and synapse-to-neuron ratio[98].

Intersubject CoV of dMRI-based metrics were lowest in idiotypic and granular regions, consistent with previous measures of intersubject variability, such as functional intersubject variability[99], and theories of developmental and evolutionary expansion[100–102]. Kurtoses (AK, MK & RK) were left-lateralized in the parietal cortex and right-lateralized in the polar and agranular cortices, possibly owing to the divergent hemispheric lateralization of visual and language processes[103].

Microstructure Diverges Along the Sensorimotor-Association Axis

The SA axis explains much of the microstructural cortical variation and provides a link to cellular, functional, and genetic markers (Fig. 2). Both SG1 and SG2 were stratified across the SA axis and SG2 had a statistically significant correlation with the SA axis ($r = 0.68, p = 0.004$) as well as the maps used to derive the SA axis: areal scaling ($r = 0.46, p = 0.012$), the principal component of gene expression ($r = -0.73, p = 0.002$), and the principal gradient of functional connectivity ($r = 0.50, p = 0.023$).

Individual measures of cortical microstructure and macrostructure also showed strong associations with variables closely aligned with the SA axis. Areal scaling was correlated with DKI-FA ($r = 0.66, p = 0.001$), DKI-AD ($r = 0.48, p = 0.007$), ODI ($r = -0.50, p < 0.001$), thickness ($r = 0.79, p < 0.001$), and myelin ($r = -0.46, p < 0.001$); functional intersubject variability was correlated with ICVF ($r = -0.51, p = 0.019$), RTOP ($r = -0.41, p = 0.029$), RTAP ($r = -0.37, p = 0.029$), and RTPP ($r = -0.34, p = 0.042$); the principal gradient of gene expression was correlated with DKI-AD ($r = -0.74, p = 0.016$), DKI-RD ($r = -0.67, p = 0.016$), DKI-MD ($r = -0.73, p = 0.016$), MSD ($r = -0.46, p = 0.022$), QIV ($r = -0.65, p = 0.016$), thickness ($r = -0.69, p = 0.008$), and myelin ($r = 0.74, p < 0.001$). The principal gradient of functional connectivity was correlated with myelin ($r = -0.48, p = 0.03$).

We confirm the known greater thickness and lower myelination of association versus sensorimotor cortex[100]. We further show higher DKI diffusivity (AD, MD & RD) as well as their higher-order counterparts (MSD & QIV) for association cortex compared to sensorimotor cortex, in contradistinction to its lower return probabilities (RTAP, RTOP & RTPP) as well as its lower

cellularity (ICVF) and orientation dispersion (ODI) (Figure S6). These results mirror the cortical microstructural transitions along the sensory-fugal axis.

All measures of microstructural intersubject CoV that showed statistically significant divergence across the SA axis (KFA, ICVF, ODI, and myelin), had lower intersubject variability in sensorimotor areas, reflecting its older phylogeny than the association areas[101]. We found myelin to be right-lateralized and ICVF and DKI higher-order metrics to be left-lateralized in the sensorimotor regions and vice-versa in association regions, possibly due to the divergent lateralization of visual and language centers[104] and mirroring the lateralization observed in microstructure of the parietal versus the polar and agranular cortices.

Microstructure Reflects Functional and Structural Connectivity

Microstructural metrics varied based on resting state fMRI networks (Fig. 3A) and on functional, structural, gene, and receptor similarity networks (Figures 3B & S7). The Yeo fMRI networks fell into two classes that mirrored the dichotomy of the SA axis. Visual, somatosensory and dorsal attention networks shared characteristics of sensorimotor cortex, whereas ventral attention, frontoparietal and default mode networks shared characteristics of association cortex. The limbic network showed more extreme kurtosis metrics (AK, MK, MKT, RK) and cellularity (ICVF) than other association areas due to its large component of paralimbic cortex. All microstructural values and intersubject CoVs and most LIs showed statistically significant divergence across Yeo functional networks under one-way ANOVA tests with FDR correction (Figure S8).

SCNs derived from every metric had significantly greater similarity for structurally connected gray matter region pairs than unconnected region pairs and for within-network region pairs as opposed to between-network region pairs under spin-permuted, distance corrected, one-sided t-tests with FDR correction (Figure S7). All SCNs had statistically significant correlations with structural, functional, receptor, and gene expression similarity networks under permutation testing, distance correction, and FDR correction. Finally, we found microstructure to follow functional, receptor density, and gene expression hubness under spin-permuted, distance corrected correlation analysis.

Microstructure Exhibits a Diversity of Organizing Principles

We computed adjusted coefficients of determination, expressed as a percentage, to measure the amount of variation the following organizations could explain for each microstructural metric: SA axis, Mesulam's hierarchy, Yeo functional networks, and the von Economo cell types (Figure S9). We found metrics to exhibit disparate organizational hierarchies. For instance, the SA axis was unable to capture the variation of the DKI higher-order metrics, whereas the other organizing principles were. Similarly, the von Economo-Koskinas cell types were unable to explain regional variation of the MAP-MRI return probabilities (RTAP, RTOP & RTPP) but the other organizations did. DTI and DKI FA variation was captured by only Mesulam's hierarchies and the Yeo networks; KFA was also expressed by both as well as the von Economo cell types. The diffusivities from DTI and DKI, ICVF and ODI from NODDI, MSD from MAP-MRI, and myelin and cortical thickness showcased universal organization across all parcellations. Importantly, the DKI diffusivities were more coherently organized across all hierarchies than the DTI diffusivities. Finally, we found most

microstructural metrics were best explained by the Yeo functional networks and/or Mesulam's hierarchy.

Microstructure Shapes Dynamic Neuronal Oscillatory Activity

Given that microstructural profiles reflected hierarchical organization in the brain as well as both structural and functional connectivity, we next sought to identify whether they also shape neuronal oscillatory dynamics measured by MEG (Figure 4). Predictions for MEG power from every frequency band and timescale using cortical microstructure were statistically significant under FDR-corrected one-sided spin permutation testing ($0.79 < r < 0.92, p < 0.007$). Distance-dependent cross-validation analysis confirmed the robustness of our model (Figure S10). Divergence across the SA axis explained 28-47% of the variance of the prediction at different spectral types, except for the beta frequency band where it only explained 4%. Dominance analysis showed the predictions were mostly mediated by the DKI diffusivities, except for the beta frequency band, where DKI-FA played the strongest role.

Microstructure Captures Neurotransmitter Receptor and Transporter Densities

Along with neuronal dynamics, we found microstructure to also capture some of the distribution of neurotransmitter receptors and transporters (Figure S11). DKI measures were significantly correlated with the concentration of 5-HTT, D1, DAT, NMDA, and VAChT. Cortical thickness was significantly correlated with 5HT1a, 5HT4, 5HT6, CB1, D1, D2, H3, M1, mGluR5, and MOR while myelin was significantly correlated with 5HT4, CB1, M1, and MOR. Dominance analysis showed cortical thickness playing the largest role in multivariate prediction for receptor densities. Multivariate predictions of receptor or transporter density using microstructure were statistically significant for every receptor/transporter under FDR-corrected one-sided spin permutation testing ($0.64 < r < 0.85, p < 0.002$). Cross-validation test predictions confirmed the robustness of our models (Figure S12). We found stratification across Mesulam laminar differentiation to account for 2 to 50% of the variance of our predictions across receptors & transporters, with better explanatory power for transporters (5HTT, DAT, NET & VAChT) than their corresponding neurotransmitter receptors.

PLS correlation analysis revealed that a statistically significant principal gradient ($p = 0.002$) explained 65.4% of the covariance between neurotransmitter receptor/transporter densities and cortical microstructure (Figure 5). The structural and receptor/transporter scores had high spatial correspondence with each other ($r = 0.679, p = 0.0002$), revealing a divergence across the sensory-fugal axis with strong positive weighting in paralimbic regions and strong negative weightings in idiotypic and unimodal cortex. Both the receptor/transporter ($r = -0.62, p = 0.0036$) and structural ($r = -0.76, p = 0.0012$) values showed statistically significant correspondence with the first principal component of gene expression. Microstructural and receptor/transporter loadings showed uniformly positive weightings, except for KFA, myelin, and ODI as well as NET and GABAa, suggesting a mostly convergent relationship.

Mapping Microstructure to Cognition

We next considered the role microstructural distributions might play in cognition. PLS correlation analysis between meta-analytic task-activation maps and microstructural metrics revealed a statistically significant principal gradient ($p = 0.001$) that explained 78.9% of the covariance (Figure 5). Cognitive scores bore strong similarity to the corresponding structural scores ($r = 0.83,\ p = 0.0004$) as well as the receptor/transporter scores ($r = 0.62,\ p = 0.008$) and structural scores ($r = 0.84, p = 0.0004$) from the neurotransmitter receptor & transporter analysis. The cognitive ($r = -0.69, p = 0.006$) and the structural ($r = -0.72, p = 0.01$) values also showed statistically significant association with the first principal component of gene expression. Cognitive loadings were stratified across an attentive-affective axis. Cognitive processes associated with emotional and reward processing had strong positive loadings whereas those associated with sensory processing/integration, attention, judgement, and planning had strong negative loadings.

Microstructure Identifies Abnormal Cortex in Neuropsychiatric Disorders

Of the von Economo cell types, we found the microstructure of polar cortex measured from healthy young adults to be the least predictive of cortical thickness case versus control effect size for all six neuropsychiatric disorders investigated (Fig. 6), which is consistent with the contribution of von Economo neurons in polar cortex to the pathogenesis of these conditions[105–110]. The poorest correlation with normal young adult microstructure was for MDD, whereas ADHD had the best correlation, which also agrees with the relative importance of polar cortex to these disorders. In contradistinction, granular cortex had the highest correlation with normal young adult microstructure across the six disorders, especially for BD, SCZ and MDD. However, the lesser degree of correlation in granular cortex for ASD and ADHD is concordant with the known association of sensory processing dysfunction with both neurodevelopmental challenges[111–113]. The observation that granular cortex in OCD also has a lesser correlation with normative microstructure, similar to ASD and ADHD, suggests a pathogenic role in this disorder, too.

In the Mesulam hierarchy of laminar differentiation, the results for idiotypic cortex across the six neuropsychiatric disorders resemble that of granular cortex in the von Economo atlas, with high correlations for BD, MDD & SCZ but lower correlations for ASD & OCD, although ADHD had more intermediate results. Overall, the findings for both von Economo cell types and Mesulam laminar differentiation suggest the six neuropsychiatric disorders fall into two groups of three each with respect to the SA axis, in which SCZ, BD & MDD primarily involve association cortex whereas ADHD, ASD & OCD involve both association and sensory cortex. Most previous reports have focused on heteromodal and paralimbic cortex in psychiatric disease[100], but our results also point to early sensory areas as a key factor in ADHD, ASD & OCD which is more consistent with recent work employing cortical thickness covariance[114]. Furthermore, these findings indicate that, even among association regions, polar cortex is most affected in these neuropsychiatric disorders, especially MDD.

Dominance analysis did not show any specific microstructural metrics to be uniformly contributory across all disorders, indicating the need for a broad array of dMRI representations

and models to fully characterize abnormal cortex (Figure S14). MKT and ICVF played large roles in the prediction of MDD effect sizes for cortical thickness and surface area, respectively, whereas myelin was important for OCD cortical thickness. These exploratory findings will need to be validated in future studies of these patient populations that incorporate high-resolution dMRI for cortical mapping.

Consistency of Cortical Microstructure Metrics from Diffusion MRI

We used the test-retest portion of HCP-YA (n=38) to assess the consistency of our microstructural metrics, which we quantify via test-retest CoV and ICC over the Glasser parcellation (Figures S15, S16). Most of the microstructural metrics derived from the high quality, multi-shell dMRI acquisitions of the HCP-YA dataset have consistency equivalent to widely used macrostructural measures, such as cortical thickness. Every metric, except ISOVF and myelin, had a maximum regional CoV of 4%. Myelin had CoV above 4% only in the left and right posterior orbitofrontal cortical (OFC) complex. Other than ISOVF, which had a mean test-retest CoV of 9.4%, every other metric had a mean test-retest CoV less than 2%. We observed the lowest mean CoV in RTPP and the DKI diffusivities (AD, RD & MD), with CoV below 1%. All microstructural metrics maintained a regional ICC above 0.7, other than DKI-AD, MK, AK, RK, and MKT in fewer than four out of 360 regions each. All metrics had a mean ICC above 0.84, with DKI-FA, FA, ICVF, ODI, thickness, and myelin having mean ICCs above 0.9.

Discussion

Starting from the work of Brodmann[115], von Economo[34], and others[116–118], considerable effort has gone into cataloging the cytoarchitectural, myeloarchitectural, and laminar structure of the human brain. Recently, advanced imaging methods have enabled investigations into connectomics, where the cortex is modeled as a graph of homogeneous nodes with functional and/or structural edges. However, this simplification abstracts away the microstructural variation intrinsic to the mammalian brain. This research is an effort to add and integrate dMRI-derived microstructural information into a rich compendium of the cortex that includes molecular, cellular, laminar, dynamic, and functional attributes[15]. Assembling and combining the multimodal properties of the cortex will be essential to investigate how the complex microstructure and connectivity of the brain give rise to emergent properties and lead to cognition and complex behaviors.

We found prominent links between in vivo dMRI cortical metrics and cytoarchitecture and laminar differentiation. While previous literature found high-resolution ex vivo maps of DTI and MAP-MRI parameters to reveal laminar substructures[119] and show correlation with histological markers of cytoarchitecture[120], we now show that high-resolution in vivo human dMRI can discriminate among Mesulam's hierarchy of laminar differentiation and among von Economo cell types. In addition to the well-known increase of cortical thickness and decrease of myelination along the sensory-fugal axis, we additionally show decreasing kurtoses, cellularity and fiber orientation dispersion but increasing free water fraction. The histologically-based BigBrain cortical atlas illustrates that increasing thickness along the sensory-fugal axis is due to expanding layers III, V and, to a lesser extent, VI[121]. Our microstructural findings agree with microscopy studies of these

laminae in macaque brain demonstrating increasing axonal field size, dendritic arborization and number of synapses resulting in more neuropil along the sensory-fugal axis[122–125].

Interestingly, diffusivities derived from all three shells of the dMRI acquisition (DKI-AD, DKI-MD & DKI-RD) performed considerably better than their single-shell DTI equivalents in distinguishing between sensorimotor and association regions and among Mesulam's hierarchy, von Economo cell types, and Yeo functional networks (Figures S3 & S4). This observation differs from the prior diffusion MRI of white matter literature in which signal rectification effects at the higher diffusion-weighting factors due to strongly anisotropic tissue can distort diffusivity measurements[126] and suggests an advantage of applying high-b factor dMRI to cerebral cortex to better detect signal from smaller spatial scales, in agreement with recent work[127,128].

Cortical patterns of microstructure clearly divided the seven Yeo fMRI networks into a sensory group (somatosensory, visual and dorsal attention) and an association group (ventral attention, default mode, frontoparietal and limbic). This classification was not as clear with cortical thickness and was nonexistent with cortical myelination. These categorizations fit with the known functional roles of these networks, except for the two attention networks that are closely related to both sensory and higher-order cognitive functions[129]. The pronounced microstructural differences between the dorsal and ventral attention networks suggest the former is closer to the sensory pole of along the sensory-fugal axis whereas the latter is closer to the opposite pole of transmodal/heteromodal information processing. This result is concordant with a recent investigation demonstrating that maturation of the ventral attention network in childhood is crucial for attainment of adult cognitive and behavioral profiles[130]. Further research is needed to more definitively establish the functional significance of this microstructural dichotomy between the dorsal and ventral attention networks.

The dMRI-derived microstructural metrics were more predictive of MEG than were conventional measures such as cortical thickness and myelination. Dominance analysis showed the diffusivities (AD, MD, & RD) derived from DKI to be the most explanatory metrics across all MEG frequency bands and the intrinsic timescale, except for the beta band for which FA was dominant. The SA axis explained up to 47% of the variation of the multivariate prediction of MEG power and intrinsic timescale, except at the beta frequency band. Delta and gamma band power arise more strongly from association cortex, especially in the frontal lobes, than sensorimotor regions[131]. This leads to a strong positive correlation with the diffusivities. The reverse is true for the alpha band, which arises primarily from sensorimotor areas of occipital and parietal lobes; therefore, the correlation with the diffusivities is strongly negative. Theta band oscillations, which arise largely from the temporal lobes including the hippocampus, are intermediate, with a weaker positive correlation with the diffusivities than delta or gamma bands. The overall negative correlation of beta band oscillatory power with the diffusivities is consistent with its sources from sensorimotor planning regions; however, beta band activity has no significant correlation with the SA axis. It is notable that high gamma band activity has a stronger positive correlation with the diffusivities than low gamma band activity. This presumably mirrors the known greater bias of high gamma band activity towards the frontal lobes compared to the low gamma band. This also helps explain the strongly positive correlation of the diffusivities with the MEG intrinsic timescale. These findings are

consistent with recent work showing that the temporal hierarchy of intrinsic timescales in MEG converges with the spatial hierarchy along the SA axis, with longer timescales in "core" association regions and shorter timescales in "peripheral" sensorimotor regions[132].

Mesulam's hierarchy of laminar differentiation explained up to 50% of the variation in some neurotransmitter receptor densities. In addition, PLS correlation analysis suggests that the sensory-fugal axis shapes the relationships between microstructure, cognition, and neurotransmitter receptor/transport distributions. Microstructural metrics with the highest divergence across the sensory-fugal axis, such as the DKI diffusivities and myelin, had the greatest loading magnitudes. The density of neurotransmitter receptors/transporters closely linked with mood regulation were highest in fugal areas, including 5-HTT, 5-HT1a, cholinergic, dopaminergic, cannabinoid, and opioid receptors. In addition, affective processes were positively weighted while attentive processes were negatively weighted in paralimbic and insular regions. Finally, structural, cognitive, and receptor/transmitter scores were all closely aligned with the sensory-fugal axis and significantly correlated with the principal component of gene expression, hinting at the importance of gene expression architecture behind these relationships.

Microstructural SCNs were significantly associated with structural and functional connectivity as well as neurotransmitter receptor/transporter and gene expression similarity. This association across multiple modalities demonstrates that microstructurally similar cortical regions may not only be structurally connected into functional networks, but also linked via neurotransmitter and gene expression architecture. In addition, we found microstructure was related to functional, receptor, and gene expression hubness. The close association between microstructure and functional hubness reflects organization across the SA axis, while the association between microstructure and neurotransmitter & gene hubness reflects organization across the sensory-fugal axis. Structural hubness, which does not align with either the SA or sensory-fugal axes, shows no significant association with cortical microstructure.

While we did not find any statistically significant univariate relationships between microstructure and case-control cortical thickness and surface area effect sizes in the neuropsychiatric disorders investigated, we did find the association to be significant in a multivariate framework. Dominance analysis demonstrated that MKT & QIV and ICVF contributed the most to the prediction of MDD effect sizes for cortical thickness and surface area, respectively, possibly due to the large role ICVF plays in serotonin receptor density prediction and the statically significant association between MKT and serotonin transporter density. This exploratory finding requires further investigation in larger MDD cohorts with high-quality dMRI data.

Due to the difficulty in modeling gray matter microstructure, we mostly used signal representations such as DTI, DKI, and MAP-MRI, which do not make many underlying assumptions. The only tissue model we did make use of is NODDI, which we recognize is ill-posed to fully capture gray matter microstructure due to the short time scale of diffusion across cell membranes. However, we believe that because NODDI continues to be widely used across dMRI literature, particularly in the clinical context, its inclusion is merited. Furthermore, models more specific to the underlying biology of gray matter, such as NEXI[127,128], require acquisitions with multiple diffusion times and ideally at a greater number of b-values with greater diffusion weighting. High-dimensional q-space

representations such as MAP-MRI could also benefit from greater diffusion weighting and sampling, but current clinical applications are limited to acquisitions similar to the HCP-YA[133]. This is currently impractical for any large patient cohort for which microstructural measures can be derived. While NODDI is suboptimal for gray matter, we found that its metrics of cellularity, fiber orientation dispersion and free water content were still often correlated with structural and functional properties of human cerebral cortex. The dominance analysis we utilized to gauge the relative importance of the various microstructural metrics is limited to linear relationships, as is the PLS correlation analysis for cognitive and neurotransmitter receptor/transporter associations. Future work in larger and more diverse datasets is needed to investigate nonlinear interactions across subjects.

As dMRI progresses to ultra-high fields with higher performance gradients and radiofrequency systems, greater spatial resolutions will allow for laminar-specific examination of neural microstructure[134], while greater q-space resolutions will allow for fitting to more complex and more faithful models of the gray matter. Integrating mesoscale T1 and T2 relaxometry with dMRI in a multidimensional framework might also offer improved microstructural visualization of cortical laminae, as recently demonstrated for ex vivo human neocortex[135]. Advances in generative artificial intelligence show promise in leveraging high-quality dMRI data collected on specialized MRI hardware for improved imaging speed, quality and reproducibility on lower performance clinical MRI scanners for both white matter and gray matter[136]. This should enable high-resolution cortical dMRI in larger patient cohorts for improved diagnosis, prognosis and treatment monitoring.

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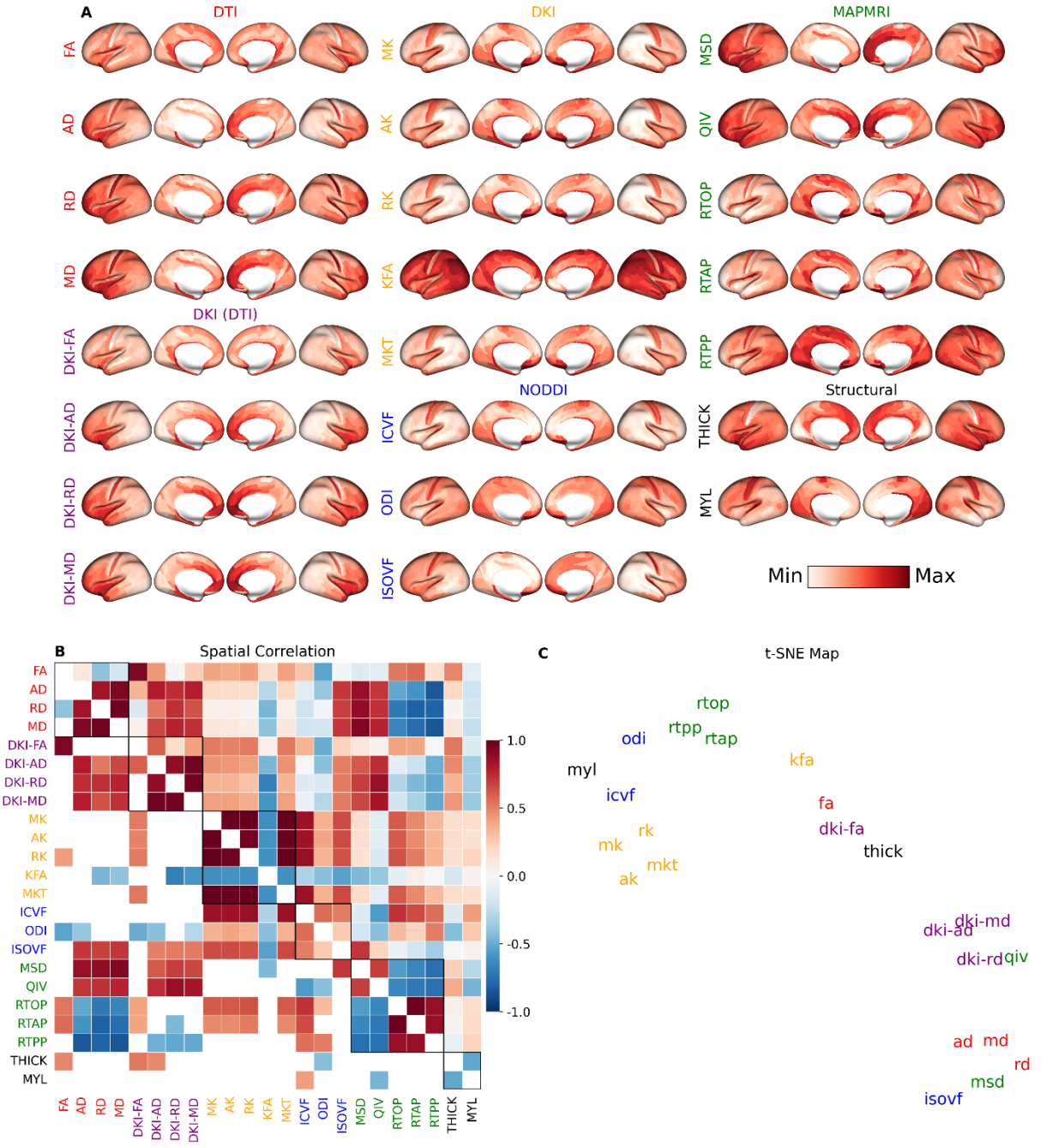
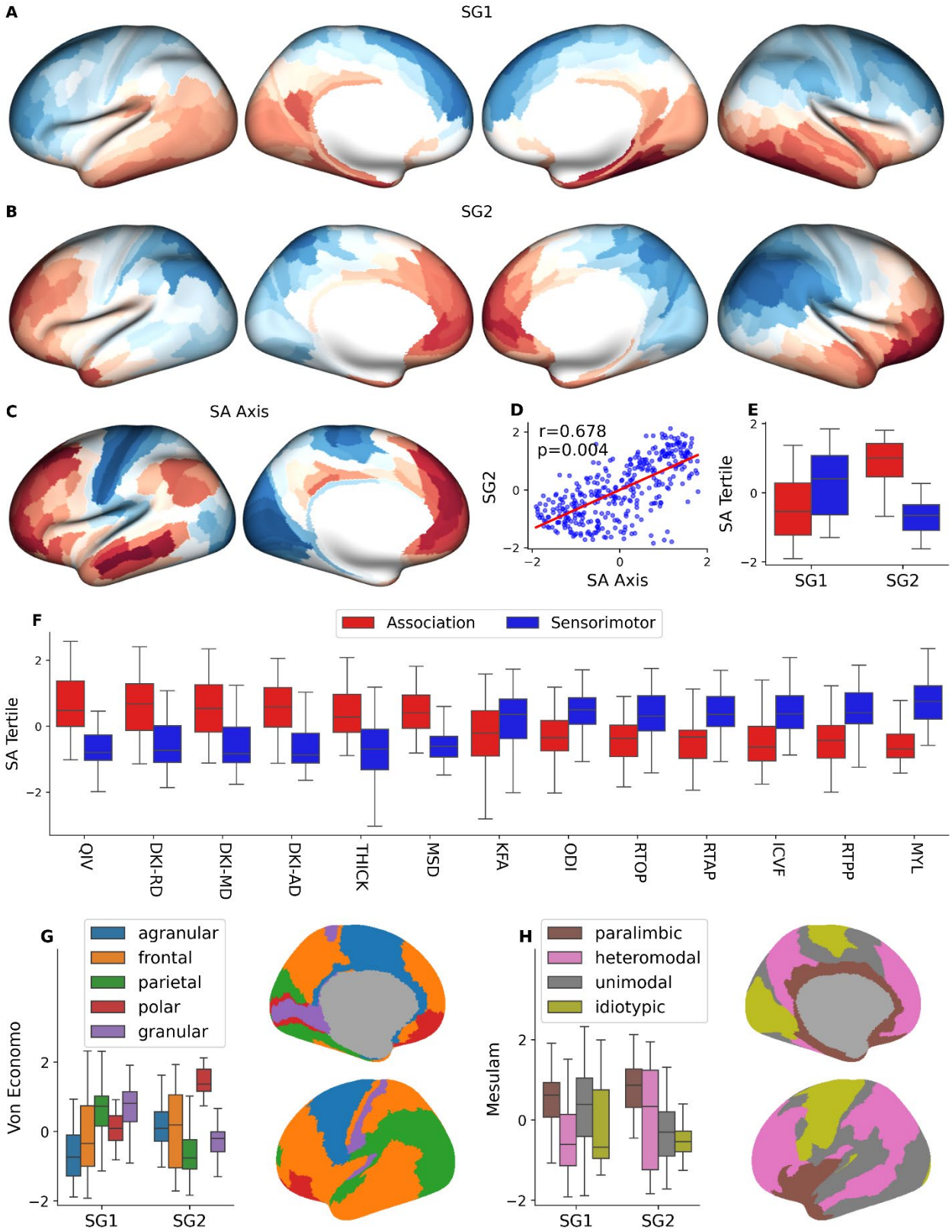
Fig. 1: The group-averaged cortical microstructural profile of the HCP-YA dataset



(A) Microstructural metrics were collected for each subject of the Human Connectome Project Young Adult (HCP-YA) cohort (n=962) following quality control and group-averaged. We present fractional anisotropy (FA), axial diffusivity (AD), radial diffusivity (RD), and mean diffusivity (MD) from DTI; DKI fractional anisotropy (DKI-FA), DKI axial diffusivity (DKI-AD), DKI radial diffusivity (DKI-RD), DKI mean diffusivity (DKI-MD), mean kurtosis (MK), axial kurtosis (AK), radial kurtosis (RK), kurtosis fractional anisotropy (KFA), mean kurtosis tensor (MKT) from DKI; intracellular volume fraction (ICVF), orientation dispersion index

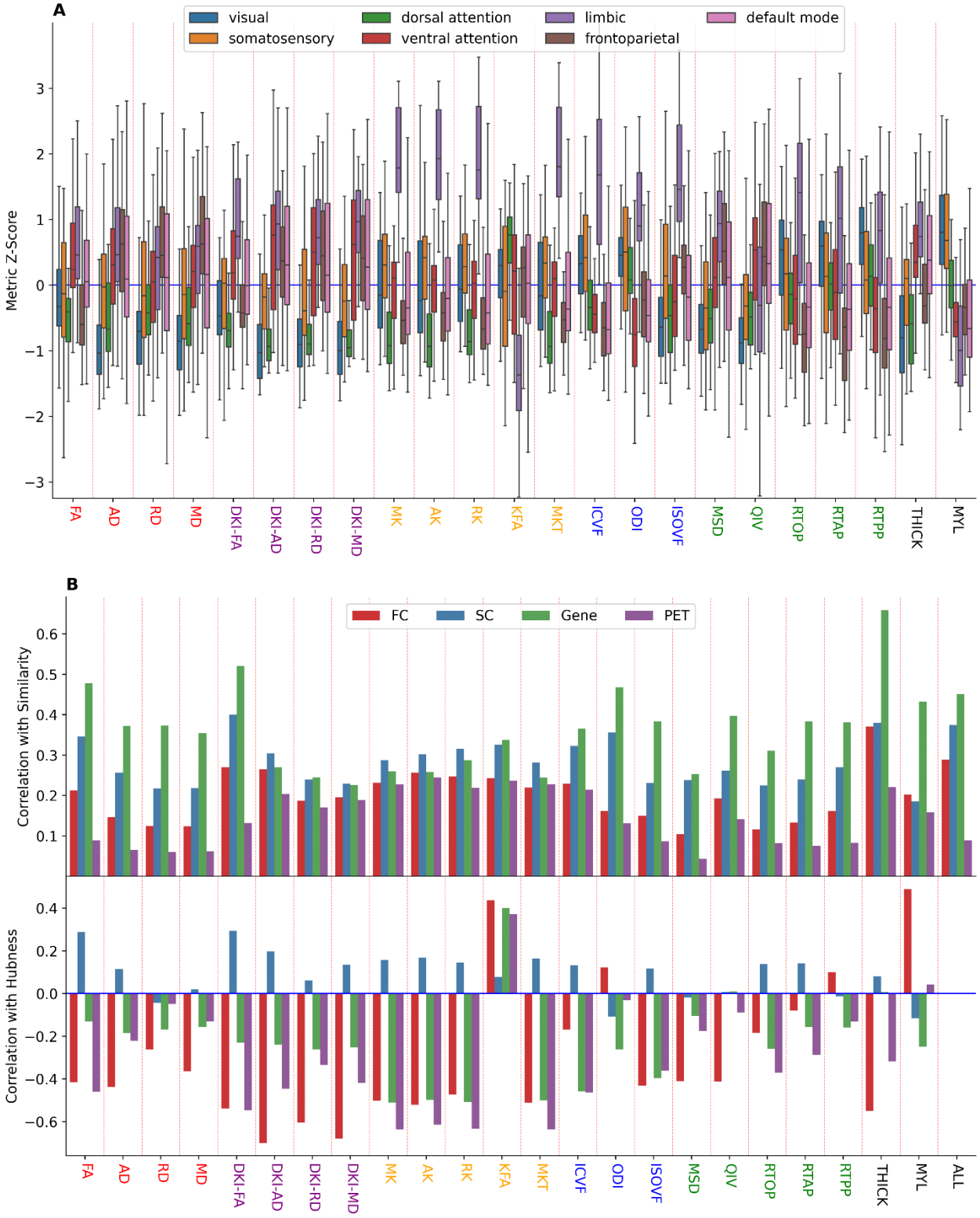
(ODI), and isotropic volume fraction (ISOVF) from NODDI; mean-squared displacement (MSD), q-space inverse variance (QIV), return-to-origin probability (RTOP), return-to-axis probability (RTAP), return-to-plane probability (RTPP) from MAP-MRI, and cortical thickness (THICK) and myelin (MYL). (B) The region-wise Pearson correlation between every pair of structural metrics is shown. The upper triangular portion displays all computed correlations, and the lower triangular portion only displays statistically significant correlations under false discover rate corrected, spin-permutation testing. (C) The t-SNE map with a distance metric of $1 - r$ and perplexity of five highlights the isotropic spectrum of microstructural metrics. Metrics signifying higher isotropy and diffusivity, such as the DTI and DKI diffusivities (AD, RD & MD), MSD and QIV from MAP-MRI, and ISOVF from NODDI are distinguished from metrics signifying deviation from isotropy, such as FA from DTI and DKI, DKI higher order metrics (AK, RK, MK, MKT & KFA), the MAP-MRI return probabilities (RTOP, RTAP & RTPP), ODI and ICVF from NODDI, and cortical myelin. Cortical thickness acts as a midpoint for this spectrum.

Fig. 2: Cortical microstructure reflects cytoarchitectural and laminar differentiation



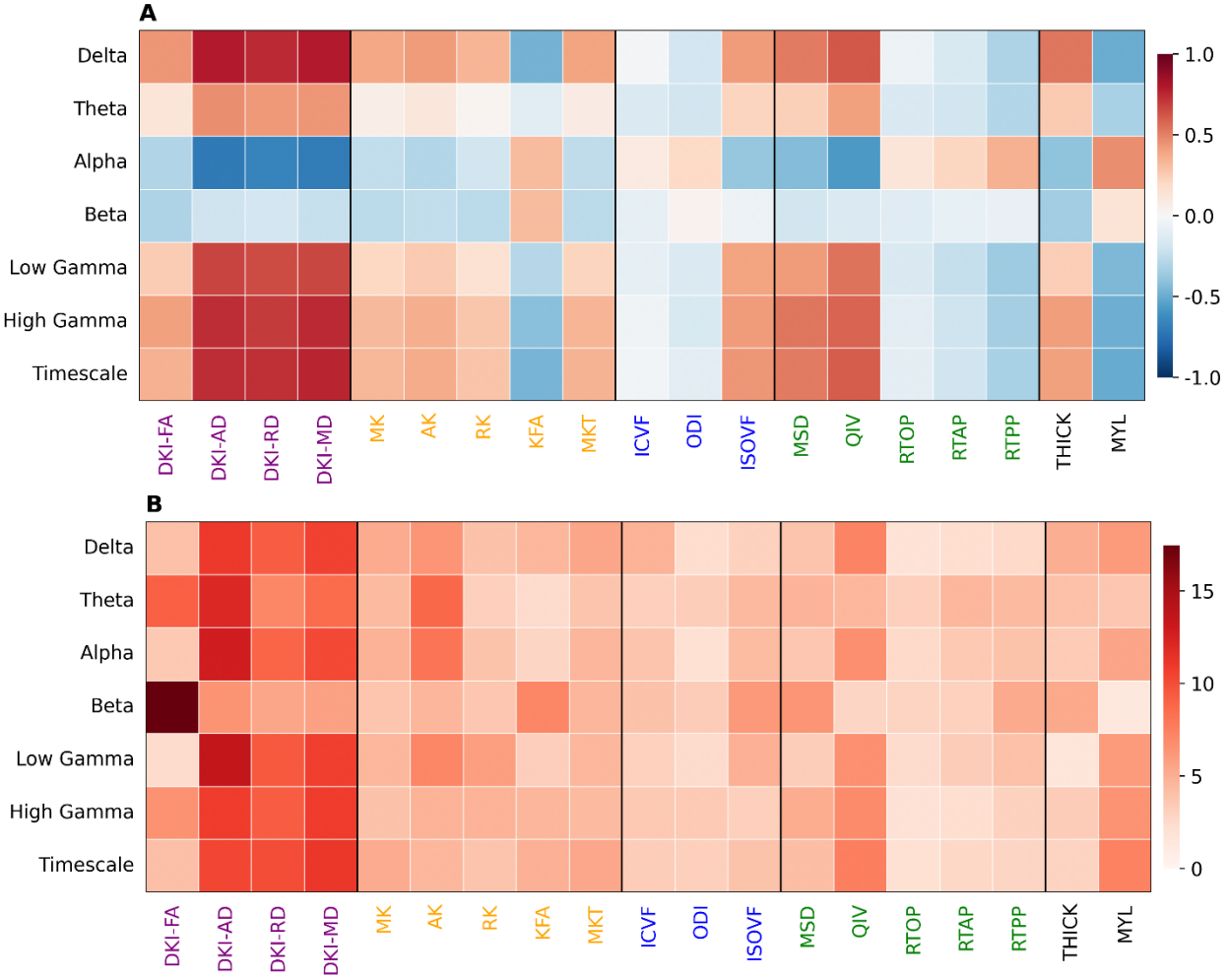
(A) The first and (B) second structural gradients (SG1 & SG2) derived from the dMRI measures along with myelin and cortical thickness. (C) The Sensorimotor-Association (SA) axis and (D) the correlation between SG2 and SA axis is statistically significant under spin permutation testing (r=0.687, p=0.004). The top tertile (60 regions with the highest rank) and bottom tertile (60 regions with the lowest rank) are taken to be the association tertile and sensorimotor tertile respectively. (E) Both SG1 (t=4.4, p=2.9e-05) and SG2 (t=11.4, p=2e-20) had statistically significant divergence between sensorimotor and association regions. (F) Cortical metrics diverged between association and sensorimotor regions: QIV (t=10.2, p=5.4e-18), DKI-RD (t=8.0, p=5.1e-12), DKI-MD (t=7.9, p=5.1e-12), DKI-AD (t=7.5, p=3.2e-11), THICK (t=7.3, p=1.3e-10), MSD (t=9.1, p=1.7e-14), KFA (t=-2.7, p=0.01), ODI (t=4.3, p=5.8e-05), RTOP (t=-4.8, p=7.9e-06), RTAP (t=-5.5, p=3.5e-07), ICVF (t=5.8, p=9.8e-08), RTPP (t=-6.3, p=1.1e-08), MYL (t=10.5, p=2.8e-17). Sensorimotor regions are shown in blue and association regions are shown in red. (G) SG1 (F=19.4, p=2.0e-14) and SG2 (F=26.5, p=6.2e-19) were stratified by the Von Economo cell types. (H) SG1 (F=21.9, p=4.7e-13), SG2 (F=27.6, p=9.3e-16) were also stratified by the Mesulam's hierarchy of laminar differentiation.

Fig. 3: Microstructural covariance networks follow functional and structural connectivity and genetic and neurotransmitter similarity



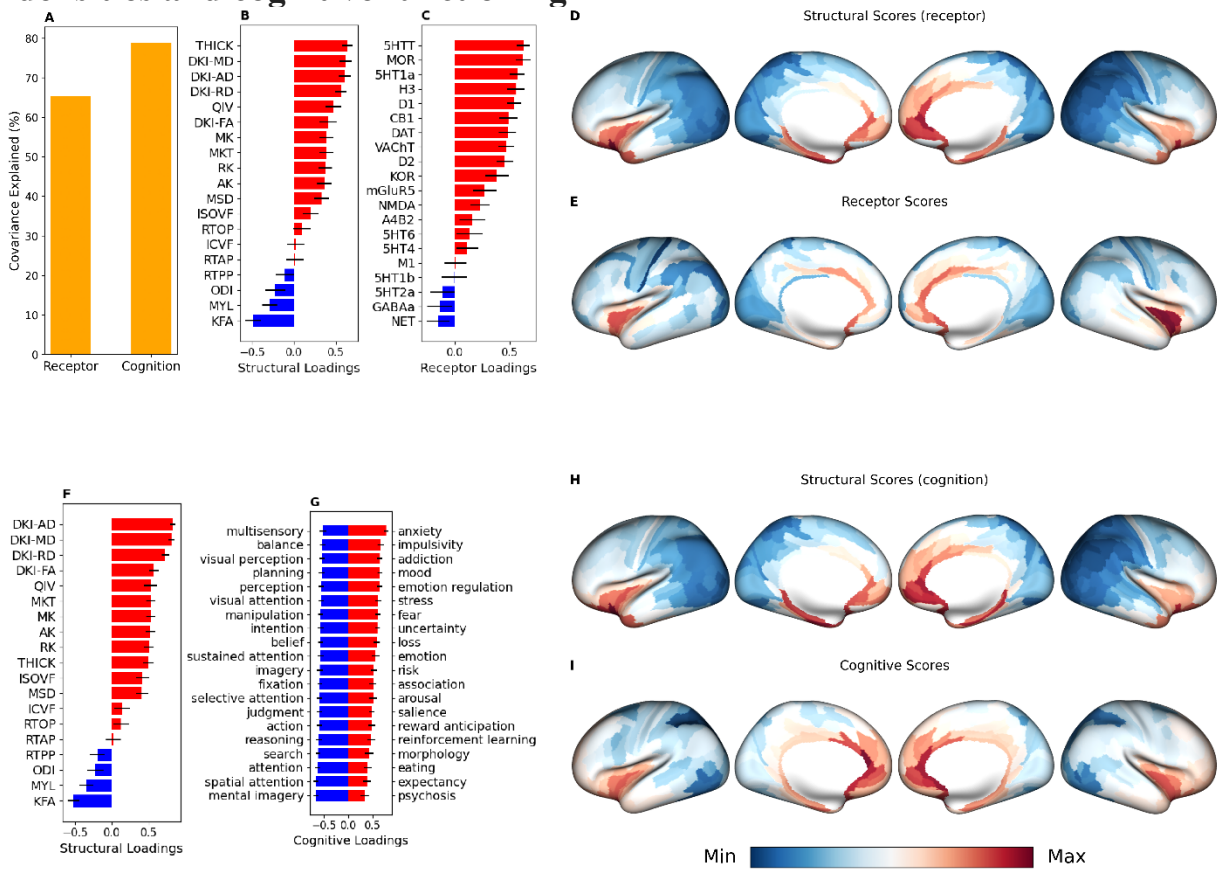
(A) Microstructural values stratified by functional networks (Yeo parcellation). Every microstructural value shows statistically significant stratification across functional networks (FDR-corrected, one-way ANOVA, $P < 0.05$). (B) Correlation between microstructural SCNs and functional, structural, gene, and receptor similarity networks (top) and correlation between microstructural metrics and functional, structural, gene, and receptor hubness (bottom). Functional hubness was significantly correlated with thickness ($r = -0.55, p = 0.032$) and myelin ($r = 0.49, p = 0.014$). Structural hubness was not significantly correlated with any metric. Receptor hubness was significantly correlated with FA ($r = -0.46, p = 0.028$), DKI-FA($r = -0.55, p = 0.011$), MK($r = -0.64, p = 0.007$), AK($r = -0.62, p = 0.007$), RK ($r = -0.63, p = 0.007$), MKT ($r = -0.64, p = 0.007$), ICVF ($r = -0.46, p = 0.048$). Gene hubness was significantly correlated with MK ($r = -0.47, p = 0.03$), AK ($r = -0.47, p = 0.03$), RK ($r = -0.44, p = 0.033$), MKT ($r = -0.46, p = 0.03$), and ISOVF ($r = -0.45, p = 0.03$).

Fig. 4: Cortical microstructure molds neural oscillatory dynamics captured by MEG



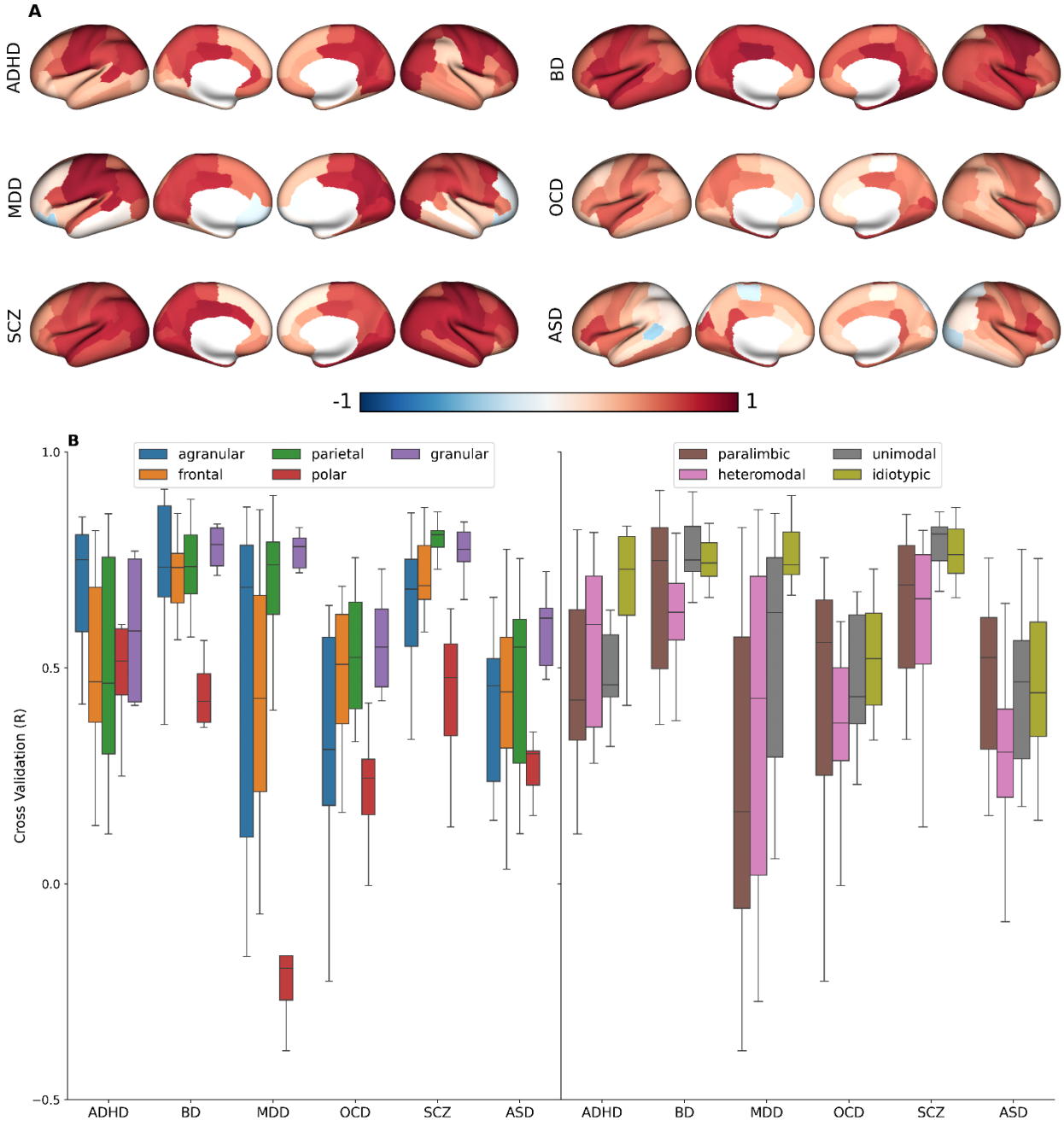
(A) Pearson Correlation coefficients between MEG power distributions for the delta (2-4 Hz), theta (5-7 Hz), alpha (8-12 Hz), beta (15-29 Hz), low gamma (30-59 Hz) and high gamma (60-90 Hz) frequency bands and intrinsic timescale and structural metrics. (B) Dominance analysis shows the relative contribution of each variable to a linear model. The DKI diffusivities and DKI-FA, specifically for the beta frequency band, played the largest roles in MEG Power and timescale prediction. Each prediction was statistically significant: delta ($r = 0.92, p = 0.0002$), theta ($r = 0.81, p = 0.003$), alpha ($r = 0.90, p = 0.0003$), beta ($r = 0.79, p = 0.007$), low gamma ($r = 0.87, p = 0.0002$), high gamma ($r = 0.88, p = 0.0002$).

Fig. 5: Microstructure reflects neurotransmitter receptor & transporter densities and cognitive functioning



(A) PLS correlation between receptor/transporter densities and microstructural metrics revealed a statistically significant principal gradient (p=0.002) that explained 65.4% of the covariance. Equivalent PLS correlation analysis between cognitive task activation maps and microstructural metrics revealed a principal gradient (p=0.001) that explained 78.9% of the covariance. (B) Structural and (C) receptor/transporter loadings showed universally positive weightings, except for KFA, myelin, ODI and GABAa and NET. (D) Structural and (E) receptor/transporter scores had strong correspondence with each other (r=0.678, p=0.0002) and showed the most positive weighting in paralimbic cortex and the most negative weighting in idiotypic and unimodal cortex. (F) Structural loadings from PLS analysis with cognitive maps mirrored those from PLS analysis with receptor/transporter densities and the two corresponding structural scores (D & H) were almost identical (r=0.995, p < 0.0001). (G) The twenty most positive cognitive loadings were associated with emotional and reward processing, while the twenty most negative loadings were associated with sensory processing/integration, attention, judgement, and planning. (I) The cognitive scores were well correlated with the structural scores (r=0.83, p=0.0004) and even the receptor/transporter scores (r=0.62, 0.0004). Both the receptor ($r = -0.62, p = 0.0036$) and structural ($r = -0.76, p = 0.0012$) scores (D & E) showed statistically significant correspondence with the first principal component of gene expression. Similarly, the cognitive ($r = -0.69, p = 0.006$) and the structural ($r = -0.72, p = 0.01$) scores (H & I) also showed statistically significant association with the first principal component of gene expression.

Fig. 6: Cross-validation of microstructural modeling in neuropsychiatric disorders



(A) The Pearson correlation coefficients from distance-dependent cross validation (CV) analysis on case-control cortical thickness effect sizes for various neurological disorders: attention deficit hyperactivity disorder (ADHD), bipolar disorder (BD), major depressive disorder (MDD), obsessive compulsive disorder (OCD), schizophrenia (SCZ), and autism spectrum disorder (ASD). Distance-dependent CV was performed for each region in the Desikan-Killiany parcellation by setting the test set to the closest 17 regions and the training set to the furthest 51 regions to avoid spatial autocorrelation effects. We fit a multiple linear regression model on the

training set with the microstructural metrics as inputs and the effect sizes as outputs and report the Pearson correlation coefficient we achieve on the test dataset. (B) The CV Pearson correlation coefficients stratified by the von Economo cell types (left) and Mesulam's hierarchy (right). CV predictions for BD ($F=11.4$, $p<0.001$), MDD ($F=14.7$, $p<0.001$), OCD ($F=6.6$, $p<0.003$), SCZ ($F=8.9$, $p<0.001$) were stratified by the von Economo cell types and CV predictions for BD ($F=5.1$, $p<0.004$), MDD ($F=7.7$, $p<0.001$), and SCZ ($F=5.8$, $p<0.004$) were stratified by Mesulam's hierarchy.