The role of white matter myelin in structural-functional network coupling

Short title: White matter myelin supports functional connectivity

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Abstract

The brain is a complex network of neuronal populations interconnected by white matter tracts. The composition of these white matter connections (SC) shapes inter-regional signaling dynamics giving rise to spatial patterns of synchronous functional connectivity (FC). Several modeling approaches have proven useful for studying the mechanisms underlying the relationship between SC and FC. However, the myelination of white matter tracts — a major component of white matter connectivity — is not accounted for by conventional SC networks, and thus, has largely been excluded from models of FC. Here, we expand structure-function brain modeling by integrating a multi-feature white matter SC network. We use multi-modal MRI to compute an SC network with connections (edges) weighted by the caliber, myelination, and length of white matter tracts. We investigate the relationship of this multi-feature SC

network with both haemodynamic and electromagnetic FC. Edge myelin was strongly predictive of FC in a pattern that was heterogeneous across brain regions and timescales of neural function. Edge myelin showed strong, frequency-specific interactions with both edge caliber and length suggesting a modulatory role for white matter myelin in structure-function coupling. This was further supported by antagonistic gradients of white matter myelin and structure-function coupling along the sensory-association axis. We describe in detail the individual and joint relationships between these major white matter features and multi-frequency FC. These results illustrate the advantage of a more comprehensive characterization of white matter in structure-function models and establish how white matter myelin — known for roles in conduction velocity, plasticity, and metabolic support at the microscale — shapes brain function at the macroscale.

Introduction

Be it an ecosystem, an economy, or an encephalon, the form and function of complex systems are intricately linked(M. E. J. Newman, 2003). By applying the principals of network science(M. Newman, 2010) to the human brain(Bassett & Sporns, 2017; Fornito et al., 2016; Sporns, 2010; Suárez et al., 2020), a modular and small-world architecture is revealed which facilitates both specialized processing within regions, as well as efficient global communication. A fundamental component of this relationship is the arrangement and properties of the physical connections (edges) between regions (nodes), which constrain and shape the landscape of dynamic functional interactions(Sporns, 2011). The characterization of the mechanisms through which brain structure and function interact is a central goal in neuroscience.

Through the non-invasive lens of multi-modal magnetic resonance imaging (MRI), networks of macroscale connectivity between nodes can be estimated in the human brain *in vivo*. Functional connectivity (FC)(Salvador et al., 2005) typically quantifies the cross-correlation of blood-oxygen-level dependent (BOLD) functional MRI (fMRI) time series(Biswal et al., 1995), and structural connectivity (SC)(Hagmann et al., 2008; Honey et al., 2009) reconstructs the interconnecting white matter pathways by combining diffusion-weighted MRI with streamline tractography(Basser et al., 1994; Mori & Barker, 1999; Mori & Van Zijl, 2002). At this scale, network nodes amount to volumes of roughly 10^2-10^4 mm^3 containing as many as 10^8 neurons(Azevedo et al., 2009; Goriely, 2025), and structural edges likely represent the aggregate of both mono- and poly-synaptic white matter fiber pathways between these large gray matter regions.

While this spatial resolution may seem quite coarse, multiple modeling approaches have consistently demonstrated that SC based on diffusion MRI is predictive of BOLD-FC(Seguin et al., 2023; Suárez et al., 2020), and the link between them has implications for human behavior(Preti & Van De Ville, 2019; Seguin et al., 2020) and cognition(Litwińczuk et al., 2022; Popp et al., 2024; Shine et al., 2019). A spatially heterogeneous pattern of structural-functional network coupling has emerged(Liu et al., 2023; Preti & Van De Ville, 2019; Vázquez-Rodríguez et al., 2019; Zamani Esfahlani et al., 2022), which is closely aligned with the primary axis of brain organization: the sensory-association (S-A) axis(Huntenburg et al., 2018; Sydnor et al., 2021). This places structure-function coupling alongside other large-scale features such as cortical hierarchy(Margulies et al., 2016; Mesulam, 1998), as well as finer-grained cortical features, including laminar differentiation(Paquola et al., 2019), intracortical myelin(Glasser &

Van Essen, 2011; Huntenburg et al., 2017), neurotransmitter receptor distributions(Hansen et al., 2022) and gene expression(Burt et al., 2018).

Macroscale FC networks can also be derived from time series recorded with magnetoencephalography (MEG), which facilitates the assessment of neural function at higher frequencies (1-100+Hz) than BOLD-fMRI (0.01-0.5Hz). The fMRI signal is thought to reflect a superposition of these neurophysiological rhythms(Shafiei et al., 2022) and their cross-frequency interactions(Tewarie et al., 2016). Cross-frequency coupling plays an important role in the formation of brain networks both during rest(Florin & Baillet, 2015; Tewarie et al., 2016) and task(Brookes et al., 2016). Higher frequencies tend to reflect bottom-up sensory processing and lower frequencies top-down modulation(Baillet, 2017; Fries, 2015; Hillebrand et al., 2016; Scheeringa & Fries, 2019; Von Stein et al., 2000), which manifests as a gradient of timescales of neural function(Chaudhuri et al., 2015; Mahjoory et al., 2020; Murray et al., 2014) aligned with the S-A axis. Although these relationships — as with BOLD-fMRI — have been linked to multi-scale cortical structure(Helbling et al., 2015; Hunt et al., 2016; Mahjoory et al., 2020; Scheeringa & Fries, 2019) and conventional SC(Garcés et al., 2016), much less is known about the coupling between white matter structural and MEG-functional networks.

Thus, we come to a principal limitation of structure-function modeling: current models lack the requisite biological detail to draw strong conclusions about the underlying mechanisms(Suárez et al., 2020). One way to address this at the whole-brain level *in vivo* is by weighting the edges of structural networks using MRI-derived measures of white matter structure relevant to brain function(Assaf et al., 2008; Boshkovski et al., 2021; Caeyenberghs et al., 2016; Deligianni et al., 2016; Gast & Assaf, 2024; Lu et al., 2025; Mancini et al., 2018; Messaritaki et al., 2021; Nelson et al., 2023; M. P. van den Heuvel et al., 2010). In particular, MRI-based

estimates of white matter myelin density have been linked to both brain organization and function(Sonya Bells et al., 2017; Caeyenberghs et al., 2016; Gong et al., 2024; Messaritaki et al., 2021; Nelson et al., 2023; Petkoski et al., 2023).

The myelination of axonal fibers helps to regulate the timing of neural signaling(Huxley & Stämpfli, 1949; Lillie, 1925; Tasaki, 1939) supporting synchronization across distributed neural circuits(Nunez et al., 2015; Nunez & Srinivasan, 2014; Pajevic et al., 2014). Conversely, the plastic structure of myelin is itself shaped by neuronal activity, thus establishing a reciprocal mechanistic link between the modulation of white matter myelin and inter-regional functional coherence(Bacmeister et al., 2022; Chorghay et al., 2018; Douglas Fields, 2015; Fields et al., 2015; Mount & Monje, 2017; Zatorre et al., 2012). Although its role in conduction velocity is less clear at the macroscale(Berman et al., 2019; Mancini et al., 2021; Petkoski et al., 2023; Talidou & Lefebvre, 2025), white matter myelin is believed to support brain function through varied contributions including: gain control, circuit integration, resilience, and homeostasis(Karimian et al., 2019; Noori et al., 2020; Park & Lefebvre, 2020), as well as metabolism(Asadollahi et al., 2024; Nave, 2010; Ramos-Cabrer et al., 2025), and energetics(Harris & Attwell, 2012).

Myelination patterns in both the white matter and cortex are linked to the major S-A axis of brain organization. Along this gradient, intracortical myelin content decreases(Glasser et al., 2014; Glasser & Van Essen, 2011), and white matter tracts are myelinated progressively later(Fuster, 1995, 2008): primary sensory regions with high intracortical myelin myelinate their axons first. The strength of white matter connectivity also develops along this gradient: within-network connections are strengthened leading to an increase in modularity and differentiation of cortico-cortical connectivity at both ends; and inter-modular integration increases through the

strengthening of long-range association hub connections(Sydnor et al., 2021). This topological pattern — also supported by MRI-based metrics of white matter myelin(Boshkovski et al., 2021) — is fundamental to the brain structure-function relationship(Sporns, 2010, 2011, 2013). Thus, a coordinated blueprint of cerebral myelination gives rise to a global axis of myelin content, which is linked to the organization of both brain structure and function.

Despite these links to brain function, white matter myelin has largely been excluded from structure-function models. How does white matter myelin relate to global FC, and does this relationship vary across brain regions and functional timescales? Here, we address these questions by integrating white matter tract features including myelin into a network model of FC. Specifically, we combine a network analysis approach with multi-modal MRI to quantify three major features of white matter connectivity at the network edge level: caliber, myelin, and length. We then use these features in an edge-wise multi-linear model to predict haemodynamic and electromagnetic FC. Based on previous work(Nelson et al., 2023), we expect that myelin and BOLD-FC will be inversely related globally. We further hypothesize that the regional coupling of myelin and BOLD-FC will be stronger, heterogeneous, and aligned with the S-A axis, in line with results using spectral(Preti & Van De Ville, 2019) and communication features(Liu et al., 2023; Vázquez-Rodríguez et al., 2019; Zamani Esfahlani et al., 2022) from conventional SC. Anticipating the coupling between myelin and MEG-FC is challenging, as few or no studies have explored this. However, it is reasonable to expect stronger, heterogeneous, and frequency-specific coupling regionally, as shown for conventional SC(Liu et al., 2023).

Results

Multi-modal MRI data acquired at 3 tesla in 30 healthy adults (14 men, 16 women; 29±6 years of age) were used to estimate the SC and in-sample FC networks. Structural connections were derived by applying streamline tractography to diffusion MRI data, then weighted by edge-level estimates of the caliber, myelin, and length of white matter tracts. Edge caliber quantifies the total cross-sectional area of the intra-axonal compartment. Edge myelin quantifies myelin density and was derived from magnetization transfer saturation images. The in-sample FC network was estimated as the zero-lag Pearson cross-correlation of node-wise time series from resting-state (task-free) BOLD-fMRI data (**$BOLD_{in}$**). Group-averaging resulted in four connectivity networks (caliber, myelin, length, and $BOLD_{in}$) from in-sample data. An additional seven out-of-sample FC networks were obtained in fully preprocessed(Shafiei et al., 2022) and group-averaged format: one from resting-state fMRI (**$BOLD_{out}$**) and six from resting-state MEG corresponding to the canonical electrophysiological frequency bands: **delta** (2-4Hz), **theta** (5-7Hz), **alpha** (8-12Hz), **beta** (15-29Hz), **$gamma_{lo}$** (30-59Hz), and **$gamma_{hi}$** (60-90Hz). These were derived from data in healthy participants (n = 33; age range 22 to 35 years) made openly available through the Human Connectome Project (HCP; S900 release(Van Essen et al., 2013)). Thus, eight unique FC networks were separately modeled as linear combinations of three weighted SC networks including interaction terms for both caliber and length with myelin (**Figure 1a**). Modeling was performed at three spatial scales: global (whole-brain), pairwise combinations of resting-state networks, and at the level of individual nodes. Network nodes were defined using the Schaefer-400(Schaefer et al., 2018) cortical atlas. The correlation between all structural features and all FC networks is shown in **Figure S11**.

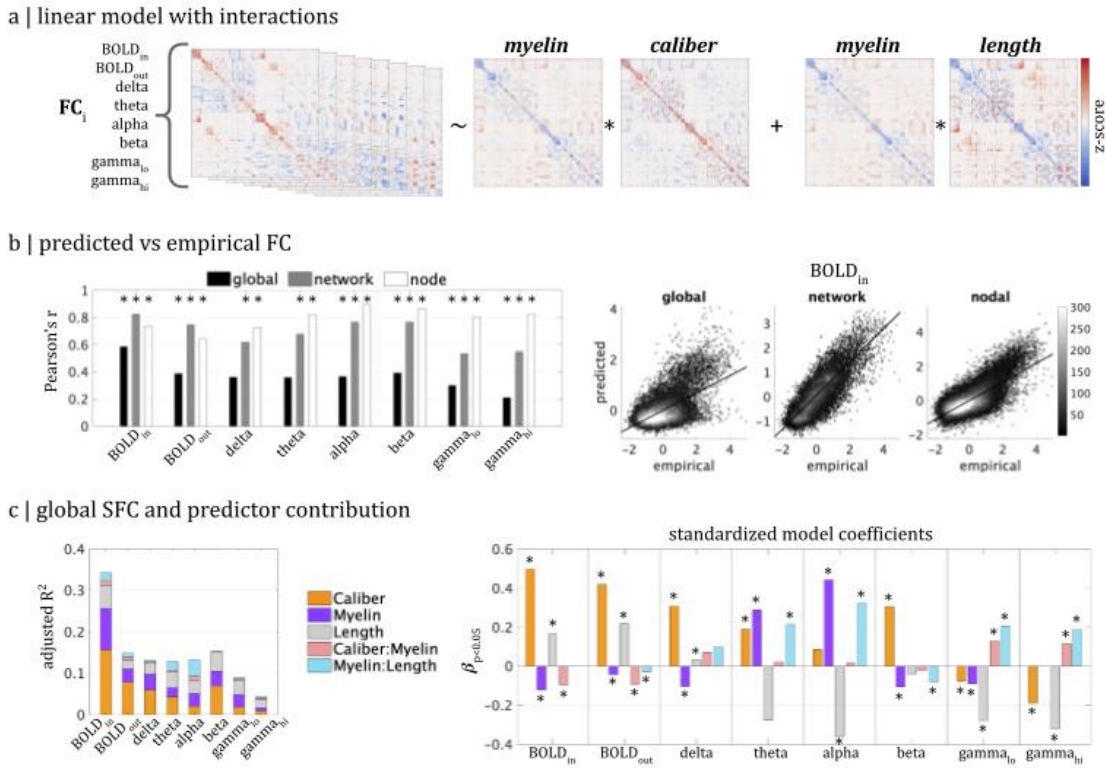

Figure 1. Relating white matter structural features to haemodynamic and electromagnetic functional connectivity. ***(a)*** *An edgewise multi-linear regression model predicting FC from SC. FC was quantified using BOLD-fMRI and multi-band MEG. SC was quantified as the caliber, myelin and length of white matter tracts from multi-modal MRI. Interaction terms with myelin were included for caliber and length. All data was z-scored before modeling.* ***(b)*** *Pearson's correlations of predicted vs empirical FC at global, network and node-level resolutions. Edges were pooled for correlations at network and node-levels. All correlations were significant ($p_{perm} < 0.05$), except global delta and theta. Scatter plots (right) are shown for $BOLD_{in}$.* ***(c)*** *Global SFC strength (left) is quantified using adjusted R^2. Colored bar segments show ratio of predictor contributions from dominance analysis. Standardized ß-coefficients (right) surviving parametric t-tests ($p < 0.05$) are shown. Asterisks additionally indicate significance from permutation testing ($p_{perm} < 0.05$) and $0 \notin 95\%$ confidence intervals.*

White matter myelin supports haemodynamic and electromagnetic connectivity

FC values predicted by the model correlated strongly with empirical FC data (**Figure 1b**). The correlation magnitude increased with model resolution for both MEG and fMRI, however the optimal resolution was modality-dependent and mirrored their temporal resolution differences: strongest at the network level for BOLD ($r > 0.75$, $p_{perm} = 0.001$) and at the node level for MEG ($r > 0.70$, $p_{perm} = 0.001$). Node-level alpha and beta models showed the highest correlations ($r >$

178 0.85, $p_{perm} = 0.001$). Delta and theta models failed to reach significance at the global level when
179 applying a spatially-constrained permutation test.

180 We assessed the global relationship between white matter edge features and FC by
181 pooling all upper triangle edges with SC ≠ 0 into a single model (**Figure 1c**). The strength of
182 structure-function coupling (SFC) was inferred from model fit (adjusted coefficient of
183 determination; R^2). The contribution of each structural feature to the prediction of FC was
184 quantified in two ways: (1) their relative importance from *dominance* analysis(Azen & Budescu,
185 2003; Budescu, 1993), and (2) the nature of their *association* from the sign and magnitude of
186 standardized ß coefficients.

187 SFC was strongest for $BOLD_{in}$ ($R^2 = 0.34$), lowest for the gamma bands ($R^2 < 0.09$), and
188 roughly equivalent for $BOLD_{out}$ and delta-beta ($R^2 \sim 0.13$-0.15). Myelin was a strong predictor
189 of FC in both BOLD and MEG data. Myelin ranked 2nd in predictor dominance behind caliber
190 for $BOLD_{in/out}$ and delta, dropped to 3rd for theta and beta as the relative importance of length
191 increased in MEG, and shared dominance with length for alpha and gamma as caliber decreased
192 in importance at higher frequencies. The ß-coefficients for all predictors showed frequency-
193 dependent sign and magnitude, and nearly all were significant ($p_{perm} < 0.05$ and parametric $p <$
194 0.05). All predictors failing to reach significance were observed for MEG-FC models including:
195 myelin for $gamma_{hi}$, caliber for alpha, and length for theta and beta. $ß_{myelin}$ was negative for
196 BOLD, delta, beta and $gamma_{lo}$, in line with the global correlation of myelin and BOLD-
197 FC(Nelson et al., 2023). $ß_{myelin}$ was positive and higher in magnitude for theta and alpha. A
198 similar sign flip was observed for caliber (ß > 0 for BOLD and most MEG bands; ß < 0 for
199 gamma) and length (ß > 0 for BOLD and ß < 0 for most MEG bands).

The interaction terms tended to be the lowest ranked predictors across models, reflecting their general role of fine tuning the larger effects of their respective lower order terms. Nonetheless, most interaction terms were significant and showed heterogeneous sign and magnitude across FC modality and frequency. Interestingly, the interaction term between myelin and length ranked 1st in predictor dominance for alpha-band MEG and showed a large magnitude positive ß-weight indicating that the role of myelin is strengthened for longer edges. We expand on these interactions with myelin in subsequent sections.

These results communicate two important points about the structure-function relationship of the brain. First, white matter myelin is an important predictor of whole-brain FC showing comparable predictive power to the much more extensively studied white matter edge features caliber and length. Second, the specific roles of white matter features including myelin in mediating brain function depend on the cellular processes contributing to the measurement technique (haemodynamic vs electromagnetic) and the timescale of the signal (frequency bands).

Haemodynamic and electromagnetic connectivity show distinct, spatially varying relationships with white matter myelin

Several reports have demonstrated regional heterogeneity in SFC using conventional SC directly or analytic measures derived therefrom(Baum et al., 2020; Liu et al., 2023; Preti & Van De Ville, 2019; Vázquez-Rodríguez et al., 2019; Zamani Esfahlani et al., 2022). Given our observations above and the diversity of mechanisms by which myelin supports brain function, we next sought to describe how the coupling of edge myelin and FC varies across brain regions. We ran the same multi-linear model at two additional spatial scales: (1) within pairwise combinations of the seven canonical resting-state networks(Thomas Yeo et al., 2011), and (2) within the connections

of each individual node i to the remaining $j \neq i$ nodes. The limbic-somatomotor network pair was excluded for low degrees of freedom (d.f. < 10). We observed high correspondence between the network (**Figure 2**, **4**, **S1-S4**) and node (**Figure 3** and **S5-S7**) levels. We thus focus this description on results from the network-level models as they are more robust (μ d.f. ≈ 875 vs 85) and efficient (n = 28 models vs 400).

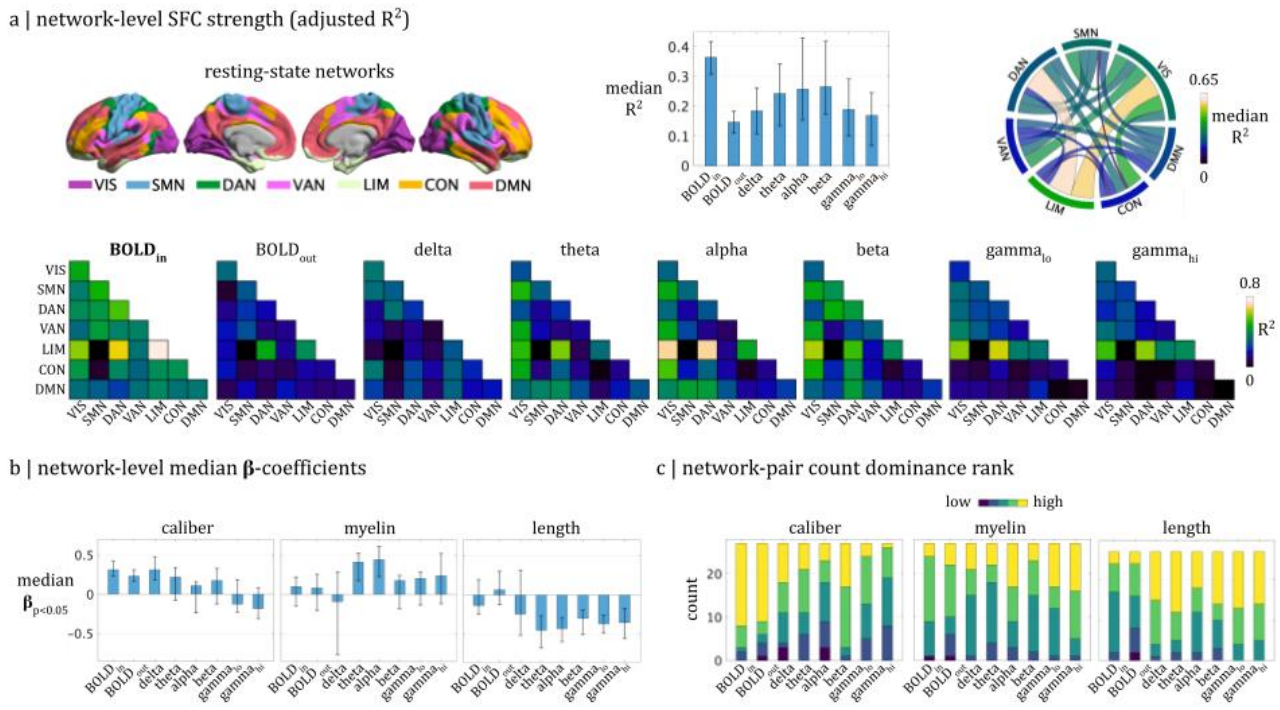

Figure 2. Relating white matter structural features to haemodynamic and electromagnetic connectivity at the level of pairwise combinations of resting-state networks. ***(a)*** *SFC strength for pairwise combinations of resting-state networks defined using the Yeo 7-network atlas (top left). Median SFC is shown across network pairs (top middle) with error bars for the 1st and 3rd quartiles, as well as across FC networks (top right). Network bars on chord plot represent within-network values. SFC for every network pair and FC network is also shown in matrix form (bottom).* ***(b)*** *Median standardized ß-coefficients with error bars for the 1st & 3rd quartiles.* ***(c)*** *The count of dominance rankings across network pairs.*

Across network pairs and FC timescales, there was considerable heterogeneity in SFC (**Figure 2a**), as well as in the standardized ß-coefficients (**Figure 2b** and **4**) and predictor dominance rankings (**Figure 2c** and **S1**) for caliber, myelin, and length. SFC was strongest for $BOLD_{in}$ followed by alpha and beta. Network pairings involving primary sensory regions (visual and somatomotor) showed stronger SFC than those involving association regions (default mode,

control, and attentional). The strongest SFC was observed for the limbic-dorsal attention, limbic-visual, and limbic-limbic network pairs. At the node-level, SFC showed significant inverse correlations with the sensory-association axis for all FC networks, except alpha (**Figure 3a**). $BOLD_{in}$ showed the most spatially distributed pattern of strong SFC, with the highest values spread across central, parietal, temporal, and occipital cortical regions (**Figure S5a**).

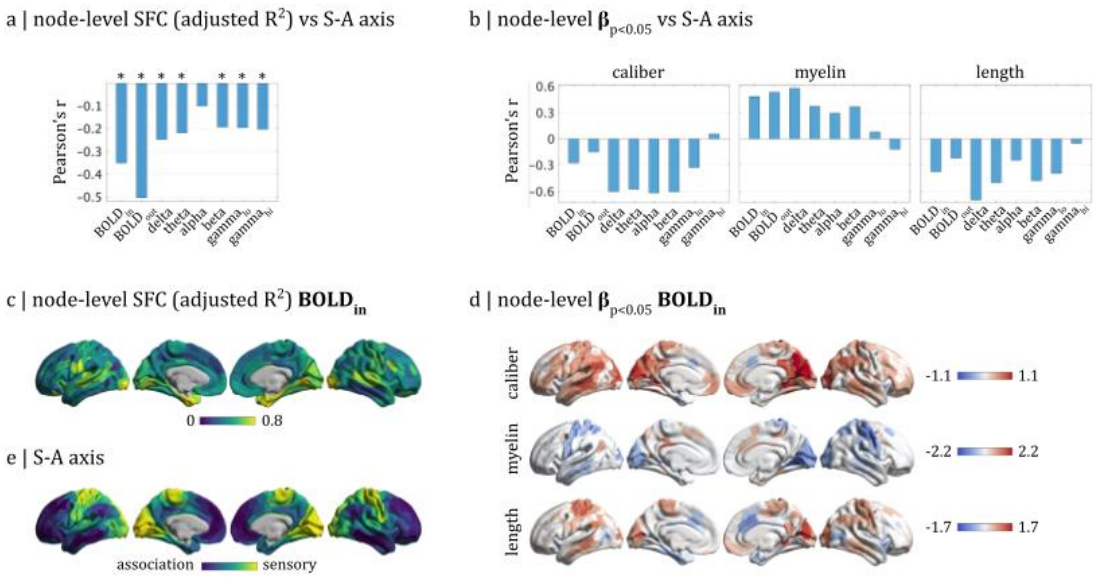

*Figure 3. Alignment of node-level **(a)** SFC and **(b)** ß-coefficients for edge caliber, myelin and length with the sensory-association (S-A) axis. Node values are shown for **(c)** SFC and **(d)** ß-coefficients from the $BOLD_{in}$ model. **(e)** The S-A axis is shown in the Schaefer-400 parcellation. All ß-values were filtered by parametric t-tests ($p < 0.05$). Asterisks indicate $p_{perm} < 0.05$.*

The standardized ß-coefficients for caliber, myelin, and length (**Figure 2b** and **4**) showed both positive and negative values across network pairs and an interesting frequency dependence. $ß_{caliber}$ showed a gradual transition from mostly positive to negative values when moving from low-to-high frequency FC (including BOLD), while $ß_{myelin}$ showed an opposite trend: balanced for BOLD and delta, and more positive for theta through gamma. $ß_{length}$ showed predominantly negative values, with exceptions for BOLD-FC and unimodal networks for most models.

Among network pairs, the spatial pattern of positive and negative $ß_{myelin}$ was on average inversely aligned with the canonical unimodal-transmodal gradient of cortical organization:

positive for network pairs involving transmodal association networks and negative for unimodal (**Figure S2a**). In contrast, $ß_{caliber}$ was on average positive within a given network and mixed between networks regardless of their position on the gradient. Interestingly, the ß-coefficients for both myelin and caliber deviated from these average trends for gamma: $ß_{myelin}$ was mostly positive including for unimodal networks, and $ß_{caliber}$ was mostly negative including within-network (**Figure 4a** and **4b**). The ß-coefficients for both interaction terms were significant across most network pairs (**Figure S3**). $ß_{myelin:caliber}$ was mostly negative for BOLD and positive for MEG. $ß_{myelin:length}$ was mostly positive and tended to be larger. These interactions are explored in more detail in the subsequent section.

At the node-level, $ß_{caliber}$ and $ß_{length}$ were inversely correlated and $ß_{myelin}$ positively correlated with the S-A axis across FC networks (**Figure 3b**). These trends were weakest or absent in the highest frequency gamma. $ß_{myelin}$ tended to be larger in magnitude than $ß_{caliber}$ (**Figure S5c**).

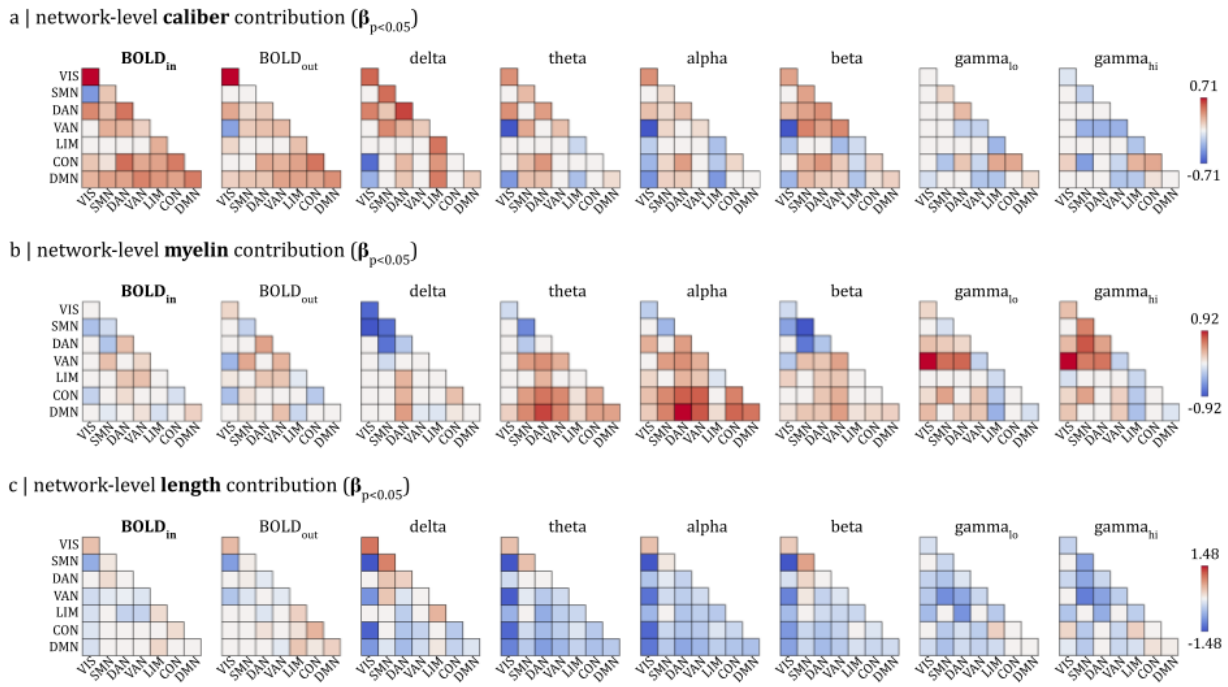

*Figure 4. Standardized ß-coefficients for edge **(a)** caliber, **(b)** myelin and **(c)** length at the pairwise network level. Only significant values are shown (t-test $p < 0.05$).*

We also observed a frequency-dependence for the network-level predictor dominance rankings of caliber, myelin, and length (**Figure 2c** and **S1**). Caliber tended to rank 1st and myelin 2nd for BOLD. As FC frequency increased, length became more dominant and caliber became less dominant, such that myelin and length shared dominance for most network pairs in alpha and gamma. Beta resembled BOLD but with greater influence of length. Myelin showed strong interactions, especially with length for alpha and theta (**Figure S4b** and S**4c**). At the node-level, caliber tended to dominate in frontal and temporal regions and myelin in central, parietal and occipital regions for BOLD (**Figure S6a** and **S6b**).

With these results, we have revealed distinct spatial patterns of structure-function coupling for each frequency band. Furthermore, we have demonstrated how these relationships can be decomposed to examine the influence of individual predictors (white matter features).

Despite the heterogeneity of spatial patterns, there is generally a shared alignment with the sensory-association axis across predictors and most frequencies of FC.

Antagonistic gradients of structure-function coupling and white matter myelin

Next, we dove deeper into the strong interactions with myelin reported above by asking how the relationships of caliber and length with FC may be different for high vs low myelin edges. We partitioned network edges into 5 equal-sized bins (n ≈ 3667) according to the magnitude of their myelin weight (**Figure 5a**). Within these bins, we computed Pearson's correlations of the z-scored SC and FC edge weights, as well as a version of the previously described multi-linear model excluding the myelin-interaction terms.

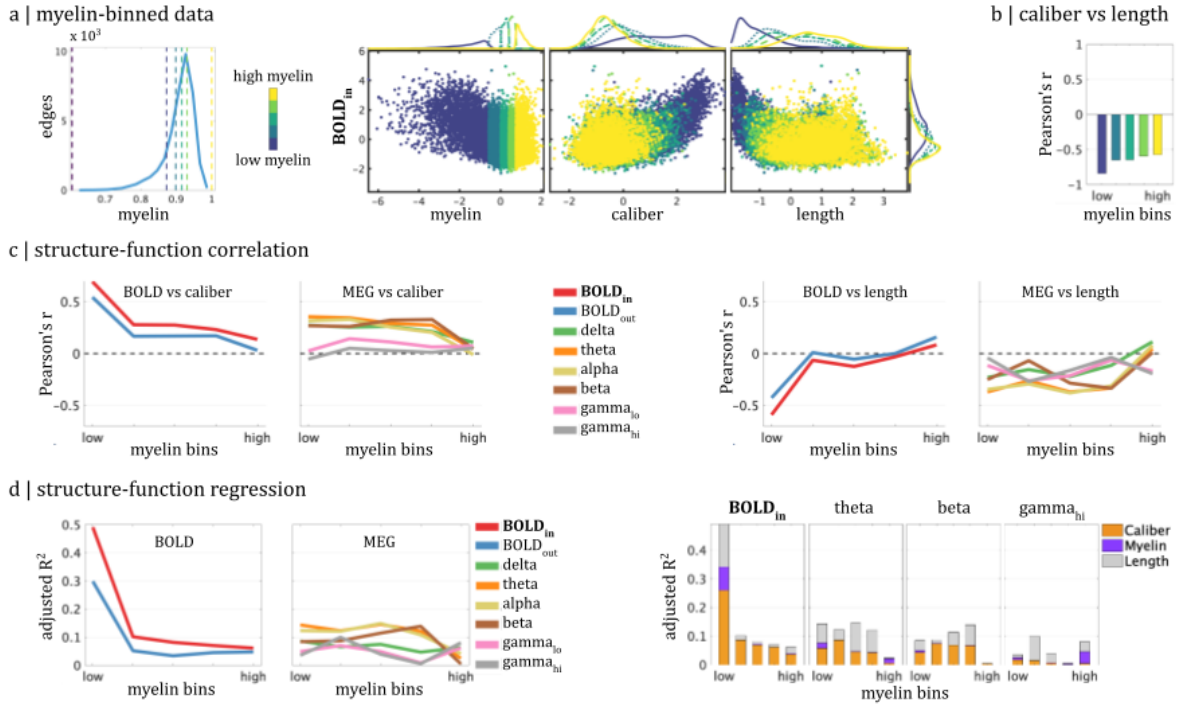

Figure 5. The coupling of white matter structure and FC weakens along the gradient of white matter myelin. ***(a)*** *Network edges were partitioned into 5 equal-sized bins by edge myelin magnitude. Each bin contained 20% or ≈ 3667 network edges.* ***(b)*** *The Pearson correlation of caliber and length across myelin bins.* ***(c)*** *The Pearson correlation of caliber (left) and length (right) with both BOLD-FC and MEG-FC is shown across myelin bins.* ***(d)*** *SFC (adjusted R^2) across myelin bins is shown for all FC networks (left) and for a subset including predictor dominance ratios (right).*

While the relationship between caliber and length remained relatively constant with increasing myelin magnitude (**Figure 5b**), both length and caliber uncoupled from BOLD-FC and low-intermediate frequency MEG-FC (delta, theta, alpha, beta) (**Figure 5c**). This trend is in line with a potential role for white matter myelin in mediating the relationship between FC and white matter edge macrostructure. For BOLD-FC, this uncoupling effect was gradual for caliber, whereas the correlation of length and BOLD-FC was already near 0 in the 2nd myelin bin. For low-to-intermediate frequency MEG, uncoupling of either length or caliber did not occur until the final bin with the highest myelin magnitude. The gamma bands remained relatively uncoupled from caliber independent of myelin and showed distinct patterns of coupling with length.

For BOLD, SFC was much stronger when myelin was lowest ($BOLD_{in}$ $R^2 = 0.49$; $BOLD_{out}$ $R^2 = 0.30$) and decreased dramatically with increasing myelin magnitude (**Figure 5d**). The predictor contributions show that this reduction in SFC is driven by a large reduction in the impact of caliber and a complete elimination of length. For theta, alpha, and beta bands, caliber and length continue to drive consistent SFC until a drop off in the final high myelin bin. Delta and gamma deviate from this trend by showing weak relationships with structure in all myelin bins. These results provide evidence for a progressive dissociation of white matter structural and functional connectivity with increasing white matter myelin content. The modality-specificity of this effect highlights the multi-layered relationship between brain structure and function.

A multi-feature structural model predicts robust general FC patterns but weak subject-specificity

Our final goal was to assess the generalizability of the full linear model with interaction terms to unseen subject-level data from $BOLD_{in}$ (n = 10; 5 subjects, 2 scans, inter-scan interval < 3 weeks). In a leave-one-out analysis by test subject (S_x), group-level SC and FC networks were computed excluding data from both scans, and multi-linear modeling was performed at the pairwise network level. The resultant group-level ß-coefficients were then combined with the unseen subject-level SC data to compute predicted FC, which was correlated with the corresponding empirical FC for both time points using Pearson's correlation ($r_{true} = FC_{predicted}(S_x)$ vs $FC_{empirical}(S_x)$). We assessed the significance of r_{true} using a 2-level approach. (1) The ability of the model to produce a general FC pattern was assessed by correlating the predicted FC for S_x with permuted versions of their empirical FC (n = 1000; $r_{perm} = FC_{predicted}(S_x)$ vs $FC_{empirical\text{-}shuffled}(S_x)$). Shuffling was performed within network pairs to preserve spatial relationships. (2) The ability of the model to produce subject-specific FC patterns was assessed by correlating the predicted FC for S_x with the empirical FC for every other subject $y \neq x$ ($r_{spec} = FC_{predicted}(S_x)$ vs $FC_{empirical}(S_y)$). For both tests, correlations were performed over all pooled edges (**Figure 6a** and **6b**) and within network pairs (**Figure 6c**). Significance was assessed using one-sided p-values and z-statistics.

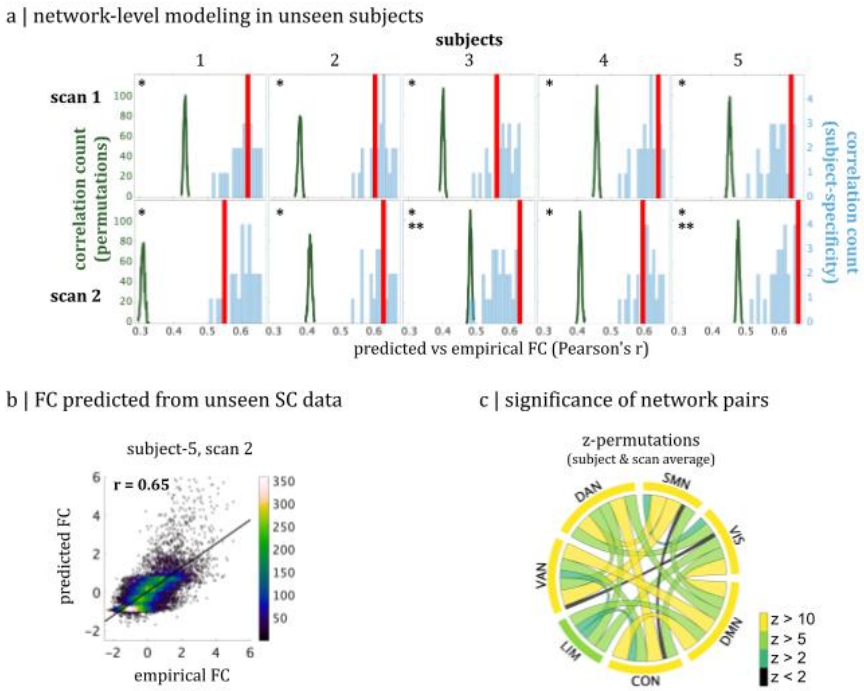

Figure 6. Generalizability and subject-specificity of the full regression model at the network level. ***(a)*** *True correlations of empirical and predicted FC (r_{true}; red bar) are overlaid on the distributions of test correlations for generalizability (r_{perm}; forest green) and subject-specificity (r_{spec}; light blue). Single (*) and double asterisks (**) indicate p_{perm} and $p_{spec} < 0.05$, respectively.* ***(b)*** *Empirical vs predicted FC for the highest true correlation ($r_{true} = 0.65$).* ***(c)*** *Generalizability significance for each network pair was computed as $z_{perm} = (r_{true} - mean_r_{perm}) / std_r_{perm}$. No network pair showed significant subject-specificity.*

For every subject and scan, r_{true} was significantly higher than r_{perm} ($p_{perm} = 0.001$), indicating that the pattern of predicted FC was more similar to empirical FC than random sequences of FC edges controlling for spatial relationships. In contrast, r_{true} was only significantly higher than r_{spec} for 2 of 10 tests ($p_{spec} = 0.001, 0.041$). When averaging across subjects and scans, r_{true} was significantly higher than r_{perm} ($z > 2$) for nearly every network pair and was an extreme outlier ($z > 10$) for 12 of 29 pairs which included all except the limbic network. No network pairs showed significantly higher r_{true} than r_{spec} (all $z < 1$). Thus, the predicted FC from our multi-linear structural model of function showed strong general patterns of FC but weak subject-specificity.

Sensitivity analyses

Finally, we test the extent to which our results may be sensitive to our specific dataset or processing choices. Our main results showed good consistency when replicated using an independent multi-modal MRI dataset(Royer et al., 2022) to define the structural features and the $BOLD_{in}$ network (**Figure S10**). Edge myelin was quantified using a different metric in these data ($R_1 = 1/T_1$; longitudinal relaxation rate). We also observed consistency using the lower-resolution Schaefer-200 parcellation (**Figure S8**). All processing steps were identical, except a more conservative threshold was used for consistency-based filtering. In our work, the COMMIT framework was used to derive an estimate of edge caliber, which can be interpreted as quantifying the strength of white matter connectivity. However, the number of streamlines output from streamline tractography is more often used to quantify SC in structure-function models. To support comparability to previous literature, we additionally show that our results are consistent when using the number of streamlines as an estimate of caliber (**Figure S9)**.

Discussion

The white matter tracts connecting gray matter neuronal populations play a central role in supporting the synchronous neural activity necessary for healthy brain function(Sonya Bells et al., 2017; Filley & Fields, 2016). Yet, we still know very little about the mechanisms mediating this relationship, in part, due to a lack of requisite biological detail in structure-function brain models(Suárez et al., 2020). Here, we provide the most thorough account to date of the relationship between multi-feature white matter structural connectivity and multi-modal functional connectivity. We find that white matter myelin is strongly predictive of FC with coupling patterns that vary regionally and across timescales of neural function.

381 Mounting evidence supports a role for white matter myelin in mediating macroscale brain
382 function, which complements the established relationship between intracortical myelin and
383 BOLD-FC(Huntenburg et al., 2017). White matter myelin has been used to predict latent
384 components of MEG-FC(Messaritaki et al., 2021). Changes in white matter myelination have
385 been linked causally with disruptions in network connectivity in mouse models(Asleh et al.,
386 2020; Saskia Hübner et al., 2017) and with working memory impairment using computational
387 modeling(Ibañez et al., 2023). Using MRI-based white matter myelin markers, changes in both
388 network myelination(Metzler-Baddeley et al., 2017) and myelin-weighted network
389 topology(Caeyenberghs et al., 2016) have been detected following working memory training.
390 Connectivity networks weighted by white matter myelin have also been shown to differ
391 markedly in topology and correlation with FC from conventional SC networks supporting their
392 complimentary relationships with function(Boshkovski et al., 2021; Nelson et al., 2023). We
393 extend this work by describing in detail how white matter myelin shapes the relationship
394 between structural and functional human brain networks.
395

396 ***White matter myelin as a modulator of structure-function coupling***

397 Structure-function coupling strength was inversely related to the sensory-association axis, in line
398 with previous studies which did not include white matter myelin(Baum et al., 2020; Liu et al.,
399 2023; Osmanlıoğlu et al., 2019; Preti & Van De Ville, 2019; Vázquez-Rodríguez et al., 2019;
400 Wang et al., 2019; Zamani Esfahlani et al., 2022). The oft-observed uncoupling of white matter
401 SC from FC along this gradient is thought to be related to a progressive untethering of the cortex
402 from underlying molecular gradients throughout evolution, which has occurred to the greatest
403 extent in association cortex in humans(Buckner & Krienen, 2013). This — along with a similar

404 pattern in development(Hill et al., 2010) — has been linked to cortical features including
405 myelin(Glasser et al., 2014; Glasser & Van Essen, 2011), cell morphology(Elston, 2003; Glasser
406 & Van Essen, 2011), and transcriptomic alignment(Burt et al., 2018), as well as the genetic
407 heritability of FC(Giles L. Colclough et al., 2017). But what is the role of white matter itself in
408 the uncoupling of SC and FC?

409 Myelin showed the opposite relationship with BOLD and MEG FC across the sensory-
410 association axis relative to caliber and length. We observed consistently strong interactions with
411 white matter myelin for both caliber and length. When stratifying by myelin content, BOLD
412 structure-function coupling was much stronger when myelin was lowest. Both length and caliber
413 uncoupled from BOLD-FC with increasing myelin, while remaining relatively strongly
414 correlated with each other. These results suggest a role for white matter myelin as a *moderator* of
415 structure-function coupling. When myelin is low, the neural synchrony quantified by FC may be
416 more heavily influenced (i.e., constrained) by other physical properties of white matter
417 connections, such as their length and caliber. Increasing myelination may gradually compensate
418 for variability in these other features, such that a sufficient threshold of myelin has the net effect
419 of equalizing functional synchrony across a diverse range of tract profiles: i.e., a flattening of the
420 structure-function gradient. In other words, white matter myelin may confer functional flexibility
421 or resilience(Noori et al., 2020; Park & Lefebvre, 2020), whether it be to normal or pathological
422 variability in white matter structural properties. Future work may explore this further, e.g., in
423 aging(Slater et al., 2019; Yeatman et al., 2014). Thus, we provide evidence for a modulatory role
424 for white matter myelin in the progressive decoupling of function from its underlying white
425 matter macrostructural constraints, which may contribute to the greater flexibility of brain
426 function characteristic of association networks.

427 Previous work has established that the fMRI signal is best described by a spatially
428 varying superposition of multiple MEG frequency bands(Shafiei et al., 2022; Tewarie et al.,
429 2016). The modulatory effect of myelin on structure-function coupling was consistent in the out-
430 of-sample BOLD data but was heterogeneous across MEG frequency bands: mostly absent from
431 the gamma bands, and mostly present for low-intermediate frequency bands, although only for
432 edges with the highest myelin content. Taken together, these results suggest that FC for low-to-
433 intermediate frequency MEG may be more strongly constrained by white matter macrostructure,
434 as decoupling is only observed at a higher myelin threshold. Furthermore, FC for high-frequency
435 MEG may be fundamentally decoupled from white matter caliber, which is additionally
436 supported by the relative unimportance of caliber in the prediction of gamma-FC. This is
437 consistent with a more local and transient nature, which is more strongly dependent on cortical –
438 – as opposed to white matter —structural features(Buzśaki & Wang, 2012). Thus, the stronger
439 modulatory effect observed for BOLD-FC may reflect the filtered integration of heterogeneous
440 modulation of structure-function coupling by white matter myelin across multiple
441 neurophysiological rhythms of brain function.
442 In sum, we provide robust evidence that white matter myelin has a frequency-dependent
443 modulatory effect on structure-function coupling, which may contribute to the gradual
444 uncoupling of white matter structure and FC along the sensory-association gradient.
445

446 ***Differential roles for white matter myelin in supporting BOLD-FC across the***
447 ***unimodal-transmodal gradient***

448 The FC of a given node pair derived from BOLD-fMRI is an indirect measure of synchronized
449 neural activity, which will intuitively depend on signal transmission speed and distance. Myelin

450 was a stronger predictor of BOLD-FC than length both globally and for most network pairs. On
451 face value, this would suggest that white matter myelin would be a useful proxy for *in vivo*
452 conduction delays; however, previous work has provided evidence to the contrary(Mancini et al.,
453 2021).

454 Myelin generally showed a balanced relationship with BOLD-FC: mostly negative in
455 unimodal and positive in heteromodal networks. This implies that the strength of neural coupling
456 measured with BOLD-fMRI is associated with lower tract myelination in unimodal and higher
457 myelination in heteromodal networks, which agrees with previous work(Boshkovski et al., 2021;
458 Sydnor et al., 2021). Whereas the hub regions(Martijn P. van den Heuvel & Sporns, 2013)
459 driving the inter-modular integration characteristic of heteromodal networks tend to be
460 connected by long-range white matter tracts, the more segregated processing attributed to
461 unimodal networks tends to be supported by dense local circuits with shorter connections(Betzel
462 & Bassett, 2018; Sepulcre et al., 2010; Sydnor et al., 2021). In this light, our results could
463 indicate that BOLD-FC in heteromodal networks is more reliant on high myelination of white
464 matter connections for temporal coordination between distant brain regions.

465 Alternatively, higher myelination may help reduce the energetic costs of topologically
466 central long-range connections(Bullmore & Sporns, 2012; Harris & Attwell, 2012). A related but
467 separate consideration is adequate trophic support, especially when viewing the insulating effect
468 of myelin from the perspective of metabolic isolation(Nave, 2010). Indeed, mounting evidence
469 suggests that oligodendrocytes directly support axonal energy metabolism independent of their
470 role in modulating conduction velocity(Asadollahi et al., 2024; Fünfschilling et al., 2012; Y. Lee
471 et al., 2012; Narine & Colognato, 2022; Nave et al., 2023; Nave & Werner, 2014; Ramos-Cabrer
472 et al., 2025; Saab et al., 2016). Thus — alongside temporal coordination — both energetics and

473 trophic support may contribute to the observed differential association between myelination and
474 BOLD-FC across the S-A axis.
475

476 ***Connecting white matter and neural synchrony***

477 Our approach provides the unique opportunity to speculate on the interplay between
478 white matter structure and neural synchrony across functional timescales. MEG captures
479 oscillatory neural activity at higher frequencies than BOLD-fMRI and should thus be more
480 sensitive to increasing conduction delays in longer white matter tracts. Indeed, we observed that
481 length increased in importance shifting from BOLD to MEG to become the dominant predictor
482 overall across MEG frequency bands. Myelin also increased in importance and showed
483 predominantly positive associations in the highest frequency FC. This could be argued to bolster
484 the support of conduction velocity, or perhaps to reflect increasing energy demands at higher
485 frequencies(Lord et al., 2013; Saab et al., 2016; Trevisiol et al., 2017). In line with past
486 work(Hagmann et al., 2008; Koch et al., 2002), caliber dominated the prediction of BOLD-FC
487 showing almost exclusively positive associations. However, as the frequency of brain function
488 increased, caliber decreased in predictive power and shifted to predominantly negative
489 associations with gamma-FC. Taken together, these observations support an intuitive shift in
490 priorities across functional timescales: from higher bandwidth at lower frequencies to greater
491 temporal precision and/or metabolic demands at higher frequencies.

492 Myelin and length shared dominance in predicting alpha and gamma across network
493 pairs. The association of myelin and FC was inverted between these frequency bands as well:
494 mostly positive in unimodal and negative in heteromodal for $gamma_{hi,}$ and the inverse for alpha.
495 Gamma is associated with local, bottom-up sensory processing and alpha with top-down

496 modulation over longer distances(Baillet, 2017; Fries, 2015; Scheeringa & Fries, 2019). Thus,
497 for intermediate-frequency alpha, the dual-dependence of strong FC on both myelin and length
498 may reflect the role of supporting synchronization over longer distances — as in low-frequency
499 BOLD-FC — alongside a greater reliance on high temporal fidelity. Whereas for high-frequency
500 gamma, the strong dependence of synchrony on physical proximity is evident in the dominance
501 of length, and the significant contribution of myelin reinforces its importance for both timing and
502 metabolic support.

503 In sum, our results support a frequency-dependent relationship between white matter
504 structure and neural synchrony. In the lowest-frequency BOLD-FC, a global emphasis on
505 bandwidth is suggested by a strong reliance on caliber, and high myelination could be argued to
506 promote temporal coordination and metabolic support for topologically central long-range
507 connections. As the frequency of FC increases, the global reliance on bandwidth is gradually
508 reduced and eventually overcome by a greater dependence on temporal precision, which is
509 supported by the increasing dominance of length and myelin.

510

511 ***Advantages of a multi-feature, network-level structure-function model***

512 In line with past work(Liu et al., 2023; Zamani Esfahlani et al., 2022), structure-function
513 coupling strength and the correlation of empirical with predicted FC increased when moving
514 from a single global model to smaller regional models. We found the strongest structure-function
515 coupling in limbic network pairs, however the limbic network is typically among the lowest
516 ranked. Previous studies have defined network-level coupling by aggregating over node-level
517 models(Liu et al., 2023; Vázquez-Rodríguez et al., 2019; Zamani Esfahlani et al., 2022), but
518 each node-level model contains edges from multiple network pairs. In contrast, our network-

level model focused specifically on edges between pairwise combinations of resting-state networks, which reduced the overall number of models by an order of magnitude and increased the number of data points in each model. Thus, our network-centric approach was more robust, efficient and yielded a more nuanced perspective of structure-function coupling. A complementary but uniquely informative example can be seen in the somatomotor network. Past work has reported strong average structure-function coupling here(Liu et al., 2023; Zamani Esfahlani et al., 2022), and our results generally support this, however with a caveat. The somatomotor network showed no coupling with the limbic and very low coupling strength with control and default mode networks. Therefore, relative to the ventral attention network, which is typically ranked among the weakest in structure-function coupling, the somatomotor network had lower total coupling strength across all network pairs.

Our analysis also deviated from past work by including multiple white matter structural features and their interactions. Structure-function coupling in BOLD was strongest for network pairs including the visual and dorsal attention networks. The finding in the visual network is corroborated by multiple investigations(Liu et al., 2023; Vázquez-Rodríguez et al., 2019; Zamani Esfahlani et al., 2022), however, the dorsal attention network does not typically rank highly in terms of structure-function coupling strength among resting-state networks(Vázquez-Rodríguez et al., 2019). While most network pairs with the dorsal attention network showed edge caliber as the dominant predictor, large magnitude ß-coefficients were observed for both myelin and length for the network pair with the strongest coupling overall: dorsal attention and limbic. This suggests that the strong structure-function coupling observed with the dorsal attention network in our study may result from our multi-feature approach which included myelin. Another example can be provided using our beta-FC results. While BOLD-FC is best characterized by a mixture of

MEG frequency bands, the beta band is thought to be a primary driver of their correspondence(Shafiei et al., 2022). We observed a similar balanced association between myelin and both BOLD and beta FC which showed roughly the same distribution across resting-state networks. In contrast, caliber, length, and both interaction terms showed noticeable differences, suggesting that the strong correspondence between FC in BOLD and beta may be related to overlap in their relationships with white matter myelin. Future work could further explore this possibility using EEG, which is more widely available and also related to SC(Babaeeghazvini et al., 2021).

In sum, the pairwise network-level of analysis yielded a nuanced perspective of regional structure-function coupling while maximizing model robustness and efficiency, and our multi-feature account of white matter structure facilitated deeper interpretation of the relationship between brain structure and function.

Limitations

The principal limitation of this work was the exclusion of some parts of the network from our analysis. (1) Network edges with SC = 0 were excluded, which constitutes more than 80% of the FC network. This is unavoidable when modeling edgewise relationships with structural edge weights directly, as structural brain networks are inherently sparse. This could be addressed in future work using communication modelling(Seguin et al., 2020, 2023). (2) The subcortex and cerebellum were excluded, as these are associated with increased artifact and a lack of standardization for their inclusion in whole brain analyses. (3) Cortical features were excluded in order to focus our analysis on the white matter. Future extensions of this work could integrate these other network components.

Another limitation was the use of streamline-tractography and tractometry to compute SC networks. This imparts well known biases(Maier-Hein et al., 2017; Nelson et al., 2023; Schilling et al., 2019). We attempted to mitigate this to the fullest extent possible through careful filtering at both the streamline and connectome levels. We also used a group-consensus approach. This improves the stability of the analysis and focuses on population-level trends at the expense of subject-specificity, e.g., through personalized parcellations(Kong et al., 2021).

Throughout, we have interpreted the sign and magnitude of standardized ß-coefficients in terms of the relationship between predictors (white matter features) and the dependent variable (FC). We recognize that this must be done cautiously, as the ß-coefficients from a given model are sensitive to the predictors included and their collinearity, which is unavoidable in our context. To account for this, all variables were normalized and centered prior to modeling, and dominance analysis was used to quantify relative predictor contributions independent of collinearity.

Conclusion

This work constitutes the most complete description of the relationship between white matter structural features — including myelin — and functional connectivity across time scales and brain regions. We detail the complex interplay between white matter structure and neural synchrony and describe how it evolves across the neurophysiological rhythms of the brain. Crucially, we provide robust evidence of a frequency-dependent modulatory role for white matter myelin on structure-function coupling along the sensory-association gradient. In all, our contributions highlight the necessity of a multi-feature account of white matter which includes myelin for investigations of the structure-function relationship of the brain.

Materials and Methods

Data acquisition

This study was approved by the Research Ethics Board of McGill University, and all participants provided written informed consent. Multi-modal MRI data were collected in a cohort of healthy volunteers (n = 30; 14 men; 29±6 years of age) on a 3 tesla Siemens Magnetom Prisma-Fit scanner equipped with a 64-channel head coil. All sequences used the Siemens *Prescan Normalize* option to generate maps with minimal receive B1-field bias. The protocol was as follows:

- T_1-weighted (T_1w) anatomical: 3D magnetization-prepared rapid gradient-echo sequence (MP-RAGE; 1.0 mm isotropic; TE/TI/TR = 2.98/900/2300 ms; FA = 9°; iPAT = 2).
- T_1 relaxometry: sparse 3D-MP2RAGE(Marques et al., 2010; Mussard et al., 2020) sequence (1.0 mm isotropic; TE/TI_1/TI_2/TR = 2.66/940/2830/5000 ms; FA_1/FA_2 = 4°/5°; TF = 175; undersampling factor = 4.6.
- Resting-state fMRI: multiband accelerated 2D-BOLD gradient echo echo-planar sequence (2.6 mm isotropic; TE/TR = 30/746 ms; MB factor = 6; FA = 50°). Two spin-echo images with AP and PA phase encoding were additionally acquired for distortion correction (2.6 mm isotropic; TE/TR = 60.6/6160 ms; FA = 90°).
- Magnetization transfer-weighted 3D gradient-echo sequence (1.0 mm isotropic; TE/TR = 2.76/27 ms; FA = 6°; iPAT = 2; partial Fourier = 6/8; MT pulse parameters: 12-ms Gaussian pulse, 2kHz off-resonance, $B1_{rms}$ = 3.26μT.

- Multi-shell diffusion-weighted imaging (DWI): 2D pulsed gradient spin-echo echo-planar imaging sequence composed of three shells with b-values 300, 1000 and 2000 s/mm^2 and diffusion directions 10, 30, and 64, respectively (2.6 mm isotropic; TE/TR = 57/3000 ms; iPAT = 3; partial Fourier = 6/8). Two b = 0 images with AP and PA phase encoding were additionally acquired to facilitate distortion correction.

Data processing

A custom version of the multi-modal processing pipeline *micapipe* (v0.1.5)(Cruces et al., 2022) was used in the processing of all diffusion, anatomical, and functional images. This pipeline makes use of multiple software packages including: *AFNI*(Cox, 1996; Cox & Hyde, 1997), *FSL*(Jenkinson et al., 2012; S. M. Smith et al., 2004; Woolrich et al., 2009), *ANTs*(B. Avants et al., 2009; Brian B. Avants et al., 2014), *FreeSurfer*(Dale et al., 1999; Fischl, 2012; Fischl et al., 2002, 2004; Fischl, Sereno, & Dale, 1999; Fischl, Sereno, Tootell, et al., 1999), and *MRtrix3*(J. D. Tournier et al., 2012, 2019).

T_1w anatomical MRI (MPRAGE). T_1w images were deobliqued, reoriented to standard neuroscience orientation (LPI), N4 bias field corrected(Tustison et al., 2010), intensity normalized, and skull stripped(Hoopes et al., 2022). Model-based segmentation of subcortical structures was performed with FSL FIRST(Patenaude et al., 2011) and tissue types were classified using FSL FAST(Zhang et al., 2001). A five-tissue-type image segmentation was generated for anatomically constrained tractography(R. E. Smith et al., 2012). Cortical surface segmentations were generated with the *FreeSurfer* (v7.2) *recon-all* pipeline with manual edits to remove dura mater.

631 **Resting-state fMRI**. After dropping the first 5 TRs from the main scan, all fMRI images
632 (including field maps) were reoriented to standard neuroscience orientation (LPI) and motion
633 corrected within-scan by registering all volumes to their respective temporal mean. Framewise
634 displacement was computed for all main scan volumes, and a threshold (3rd quartile + 1.5 *
635 Interquartile Range) was used to identify volumes with large motion artifacts. The main-phase
636 and reverse-phase field maps were used to correct the main fMRI scan for geometric distortions
637 due to magnetic field inhomogeneity(Andersson et al., 2003; Graham et al., 2017). All
638 subsequent processing involves only the main fMRI scan. Brain extraction(S. M. Smith, 2002)
639 was performed, followed by registrations to native FreeSurfer space with *bbregister*(Greve &
640 Fischl, 2009) and with the T_1w image using a multi-stage method (rigid, affine, SyN)
641 implemented in ANTs(B. B. Avants et al., 2008).
642 The fMRI data was denoised by applying a high-pass filter at a cutoff frequency of 0.01 Hz
643 followed by Independent Component Analysis with FSL MELODIC(C.F. Beckmann & Smith,
644 2004; Christian F. Beckmann et al., 2005). All independent components (n = 3,825) were
645 manually labeled by 2 independent raters, and components labeled as "noise" by both raters were
646 removed (n = 2761). The denoised data was then used to calculate tissue-specific signals for gray
647 matter, white matter, and cerebrospinal fluid tissue classes, before being mapped to native
648 surface space and smoothed (Gaussian, FWHM = 6 mm). Linear regression was applied to the
649 surface-based time series to remove nuisance signal resulting from motion, cerebrospinal fluid or
650 white matter tissue.
651 **Multi-shell DWI**. The DWI data including field maps (b = 0 s/mm^2 volumes with reverse
652 phase encoding) were denoised(Cordero-Grande et al., 2019; Veraart, Fieremans, et al., 2016;
653 Veraart, Novikov, et al., 2016), then corrected for Gibbs ringing(H. Lee et al., 2021). The field

maps were then used to correct for susceptibility distortion, head motion, and eddy currents via FSL's TOPUP(Andersson et al., 2003) and eddy(Andersson & Sotiropoulos, 2016). This was followed by $B1^+$ bias-field correction(Tustison et al., 2010). The corrected DWI image was upsampled to match the T1w resolution (1 mm isotropic), and brain extraction was performed(S. M. Smith, 2002). These preprocessed data were used to estimate multi-shell and multi-tissue response functions (Christiaens et al., 2015; Dhollander et al., 2016, 2019), which informed the estimation of fiber orientation distributions (FOD) via spherical deconvolution(Jeurissen et al., 2014). All FODs were intensity normalized(Dhollander et al., 2021). A multi-stage (rigid, affine, SyN) registration(B. B. Avants et al., 2008) was computed with the T_1w image to allow co-registration of anatomical images to DWI space.

T_1 relaxometry and magnetization transfer saturation (MTsat) maps. A dictionary matching approach incorporating the B_1^+ map was applied to generate S_0 and T_1 maps from the MP2RAGE inversion 1, inversion 2 and UNI images. This produced ΔB_1^+ corrected S_0 & T_1 maps. An affine transformation (ANTs) was used to register the MP2RAGE denoised UNI image, the S_0 and T_1 maps, and the MT-weighted image to the T_1w image. MTsat maps were computed using (Helms et al., 2008):

$$MTsat = \left(\frac{S0 \cdot \alpha \cdot \Delta B_1^+}{S_{MT_w}} - 1\right) \cdot \frac{TR}{T1} - \frac{(\alpha \cdot \Delta B_1^+)^2}{2} \quad (1)$$

where α is the excitation flip angle in the MT-weighted sequence, S_{MTw} is the MT-weighted signal, and TR is the repetition time of the MT-weighted sequence. A gain factor of 2.5 was applied to the S_0 maps to match the receiver gain of the MT-weighted gradient echo sequence for computing MTsat. ΔB_1^+ was corrected using a model-based approach (Rowley et al., 2021).

Structural connectivity network reconstruction

Tractography and filtering. Anatomically constrained(R. E. Smith et al., 2012) tractography was run on the normalized white matter FOD with the probabilistic algorithm iFOD2(J.-D. Tournier et al., 2010) and a dynamic seeding strategy(R. E. Smith et al., 2015) to generate tractograms of 3 million streamlines. All tractograms were filtered in a multi-stage process (see (Lu et al., 2025) for more detail):

1. Any erroneous streamlines that failed to connect two gray matter ROIs were manually removed to ensure they did not bias the model in step 2.
2. COMMIT v2.1(Daducci et al., 2013, 2015) (convex optimization modeling for microstructure informed tractography) was run on the stage-1 filtered tractograms. The model was optimized to the DWI image using a Stick-Zeppelin-Ball forward model with diffusivities $Đ_{\parallel} = 1.7e^{-3}$, $Đ_{\perp} = 0.51e^{-3}$ and $Đ_{iso} = 1.7e^{-3}, 3.0e^{-3}$ mm^2/s (gray matter and CSF). Estimates of the signal fraction or intra-cellular volume fraction (ICVF) of each streamline were extracted from the COMMIT model. Streamlines < $1e^{-12}$ were filtered as they did not contribute to the global DWI signal. A volumetric ICVF map was also obtained from COMMIT. This was used to calibrate the MT_{sat} map yielding a myelin volume fraction (MVF) map as:

$$MVF = \alpha_{calib} \times MT_{sat} \quad (2)$$

   where α_{calib} is the global calibration factor as described in (Lu et al., 2025).
3. The stage-2 filtered tractograms were optimized to the MVF map with a myelin-based COMMIT extension(Schiavi et al., 2022) yielding a signal fraction for each streamline which corresponded to a myelin cross-sectional area. Streamlines < $1e^{-12}$ were filtered as they did not contribute to the global MVF signal.

4. To get the final signal fraction (ICVF) for the surviving streamlines, a modified version of step 2 was repeated on the stage-3 filtered tractograms. Instead of optimizing COMMIT to the DWI signal itself, a scaled version was computed (1-MVF), which was then normalized by the b = 0 images. This was done to account for the potential bias of myelination to the ICVF estimates from COMMIT. A very small number of streamlines $< 1e^{-12}$ were filtered in this stage as well.

These filtered tractograms were used for all structural connectomes i.e., connection density was uniform across structural edge weights.

Weighted structural connectomes. The edge *caliber* connectome was computed by summing the final COMMIT weights (signal fractions) of all remaining streamlines connecting each node pair normalized by total node volume for each pair. The edge *myelin* connectome was computed by applying tractometry(S Bells et al., 2011) to the MTsat image: the median MTsat value was computed along each streamline, followed by the average across streamlines for each node pair. The edge *length* connectome was computed as the mean length of streamlines for each node pair. The Schaefer-400(Schaefer et al., 2018) cortical atlas was used to define network nodes in all primary analyses.

Functional connectivity network reconstruction

Functional connectivity was computed as the zero-lag Pearson cross-correlation of fMRI time series. These values were Fisher z-transformed and averaged across subjects yielding a single in-sample-fMRI functional connectome in the Schaefer-400 parcellation.

HCP data. Fully-processed(Shafiei et al., 2022) fMRI and MEG functional connectivity matrices were obtained at the group-level in the Schaefer-400 parcellation. These connectomes

were derived from resting-state data acquired in healthy young adults (n = 33; age range 22 to 35 years) as part of the Human Connectome Project (HCP; S900 release(Van Essen et al., 2013)). The MEG data corresponded to 6 minutes of scanning (sampling rate = 2,034.5 Hz; anti-aliasing low-pass filter = 400 Hz), and the fMRI data were comprised of 4 scans of 15 minutes across 2 sessions (TR = 720 ms; 3 Tesla; 2 mm isotropic). Static functional connectivity was computed as (1) the Pearson cross-correlation of fMRI time series and (2) the amplitude envelope correlation(Bruns et al., 2000) of MEG time series data. An orthogonalization process was then applied to correct for spatial leakage in the MEG functional connectomes(G. L. Colclough et al., 2015). Group-averaging yielded one fMRI and six MEG functional connectomes corresponding to the canonical electrophysiological frequency bands: delta (δ: 2-4 Hz), theta (θ: 5-7 Hz), alpha (α: 8-12 Hz), beta (β: 15-29 Hz), low gamma (γ_{lo}: 30-59 Hz), and high gamma (γ_{hi}: 60-90Hz). See (Shafiei et al., 2022) for full processing details.

Multi-linear modeling

We quantified the role of white matter features in predicting synchronized brain function using multiple linear regression. The dependent variable (response variable) was functional connectivity (FC) from one of the following modalities: in-sample-fMRI ($BOLD_{in}$), HCP-fMRI ($BOLD_{out}$) or HCP-MEG in the 6 canonical frequency bands (n = 8 unique dependent variables). The predictors were structural connectivity (SC) weights quantifying the *caliber*, *myelin* and *length* of each edge. Interaction terms were included for both caliber and length with myelin. Only edges with SC $\neq 0$ were included. The *adjusted* R^2 (coefficient of determination) was interpreted as the magnitude of structure-function coupling. The contribution of each predictor was quantified with dominance analysis(Azen & Budescu, 2003; Budescu, 1993), which

745 measures relative predictor importance as the incremental change in R^2 from the addition (or
746 absence) of a given predictor to all possible subset models. Dominance analysis was adapted to
747 handle interaction terms for this work. Variables with an absolute skewness > 1.5 were log-
748 transformed, and all variables were z-scored. Modeling was restricted to group-level data.
749 Parametric t-tests were used exclude any ß-coefficients with $p > 0.05$.

750 **Global model**. The whole-brain linear regression model was computed as:

751 $$FC_k = 1 \quad + \quad caliber * myelin \quad + \quad length * myelin \tag{3}$$

752 where the predictors *caliber*, *myelin* and *length* are the vectorized lower triangle elements of the
753 corresponding weighted structural connectome, and the dependent variable FC_k is the
754 corresponding vectorized lower triangle elements of the kth FC dataset.

755 **Network model**. Nodes (cortical parcels) were grouped by affiliation to the 7-canonical
756 resting state sub-networks(Thomas Yeo et al., 2011), and linear regression was performed within
757 pairwise combinations of sub-networks as:

758 $$FC_k^{ij} = 1 \quad + \quad caliber^{ij} * myelin^{ij} \quad + \quad length^{ij} * myelin^{ij} \tag{4}$$

759 where the FC and SC data corresponded to the weights of network edges linking the nodes of
760 subnetworks i and j. Within-subnetwork modeling is quantified by the case where $i = j$.

761 **Node model**. Linear regression was performed separately for each node as:

762 $$FC_k^{i} = 1 \quad + \quad caliber^{i} * myelin^{i} \quad + \quad length^{i} * myelin^{i} \tag{5}$$

763 where the FC and SC data corresponded to the weights of network edges linking node i to all
764 other $j \neq i$ nodes.

765

766 ***Null models***

To account for the lack of strictness of parametric t-tests applied to our data, we additionally assessed the significance of our results using edgewise permutation testing with 1000 repetitions. When testing the model outputs, the FC edge weights were shuffled to ensure the relationships between the structural predictors were preserved. For the global model, a spatial constraint was added to the permutation test by shuffling FC edge weights within 10 equally sized bins defined by Euclidean distance. One-sided p-values were computed in which the empirical value was included in the null distribution to avoid $p_{perm} = 0$.

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