1 **The Human Brain Connectome Weighted by the Myelin Content**

2 **and Total Intra-Axonal Cross-Sectional Area of White Matter**

3 **Tracts**

4

5 **Short title:**

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ABSTRACT

22 A central goal in neuroscience is the development of a comprehensive mapping between

23 structural and functional brain features which facilitates mechanistic interpretation of brain

24 function. However, the interpretability of structure-function brain models remains limited by a

25   lack of biological detail. Here, we characterize human structural brain networks weighted by

26   multiple white matter microstructural features including total intra-axonal cross-sectional area

27   and myelin content. We report edge-weight-dependent spatial distributions, variance, small-

28   worldness, rich club, hubs, as well as relationships with function, edge length and myelin.

29   Contrasting networks weighted by the total intra-axonal cross-sectional area and myelin content

30   of white matter tracts, we find opposite relationships with functional connectivity, an edge-

31   length-independent inverse relationship with each other, and the lack of a canonical rich club in

32   myelin-weighted networks. When controlling for edge length, networks weighted by either

33   fractional anisotropy, radial diffusivity or neurite density show no relationship with whole-brain

34   functional connectivity. We conclude that the co-utilization of structural networks weighted by

35   total intra-axonal cross-sectional area and myelin content could improve our understanding of the

36   mechanisms mediating the structure-function brain relationship.

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38   **AUTHOR SUMMARY**

39   For computational network models to provide mechanistic links between brain structure and

40   function, they must be informed by networks in which edge weights quantify structural features

41   relevant to brain function. Here, we characterized several weighted structural networks capturing

42   multiscale features of white matter connectivity including total intra-axonal cross-sectional area

43   and myelin density. We describe these networks in terms of edge weight distribution, variance

44   and network topology, as well as their relationships with each other, edge length and function.

45   Overall, these findings support the joint use of structural networks weighted by the total intra-

46   axonal cross-sectional area and myelin content of white matter tracts in structure-function

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47 models. This thorough characterization serves as a benchmark for future investigations of

48 weighted structural brain networks.

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51 **INTRODUCTION**

52 The quest to relate human structural and functional brain networks spans the spectrum of spatial

53 scale and repertoire of data modalities absolutely. At the macroscale, the human brain can be

54 modeled as an anatomical network of discrete neuronal populations (nodes) interconnected by

55 white matter fibers (edges) (Sporns, 2011). Coordinated spatiotemporal patterns of neuronal

56 activity unfolding upon this structural backbone are fine-tuned by white matter microstructure

57 (Hodgkin & Huxley, 1952; Huxley & Stämpfli, 1949; Moore et al., 2020; Pumphrey & Young,

58 1938) and form the basis of cognition and behavior (Biswal et al., 1995; Greicius et al., 2003;

59 Hampson et al., 2006; Liégeois et al., 2019; S. M. Smith et al., 2009; Martijn P. Van Den Heuvel

60 et al., 2009). Increasingly, MRI facilitates *in vivo* measurement of multi-scale properties of both

61 brain structure (e.g., (Alexander et al., 2019; Drakesmith et al., 2019; Jeurissen et al., 2017;

62 Mancini et al., 2020)) and function (e.g., (Finn et al., 2019; Friston, 2011; Gordon et al., 2017;

63 Liu et al., 2022)). Diffusion MRI streamline tractography and resting-state functional MRI are

64 often respectively used to estimate structural and functional connectivity (SC & FC) networks.

65 Network science provides a framework to bring these fundamentally different substrates into a

66 common space where their features can be quantified (Fornito et al., 2016; Sporns, 2010; Suárez

67 et al., 2020) and used to probe the mechanisms mediating human brain function (e.g., (Cabral et

68 al., 2017; Fornito et al., 2015)).

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70   SC network edges can be weighted by a range of MRI-derived metrics quantifying white matter

71   microstructural features relevant to brain function including: voxel-level estimates of tissue

72   diffusivity (e.g., (Caeyenberghs et al., 2016)), neurite density (H. Zhang et al., 2012), axon

73   diameter distributions (Alexander et al., 2010; Assaf et al., 2008), myelin content (Heath et al.,

74   2018; Mancini et al., 2020), and the g-ratio (ratio of inner/outer diameters of myelinated axons)

75   (Stikov et al., 2011, 2015); as well as tract/bundle-level measures of axonal cross-sectional area

76   (Daducci, Dal Palù, et al., 2015; R. E. Smith et al., 2015). Subsets of these metrics have been

77   investigated using a microstructure-weighted connectomics approach (Boshkovski et al., 2021;

78   Caeyenberghs et al., 2016; Deligianni et al., 2016; Frigo et al., 2020; Mancini et al., 2018;

79   Messaritaki et al., 2021; Schiavi et al., 2020; M. P. van den Heuvel et al., 2010; Martijn P. van

80   den Heuvel & Sporns, 2011; F. C. Yeh et al., 2016). We aim to extend this work by providing a

81   comprehensive assessment of the fundamental characteristics of a range of standard and state-of-

82   the-art weighted structural brain networks including a network weighted by myelin.

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84   The networks considered here can be grouped into two classes: those computed with tractometry

85   (S Bells et al., 2011) and those computed directly from the streamline weights in a tractogram

86   i.e., streamline-specific. We consider three examples of the latter: (1) the number of streamlines

87   (NoS); and two methods which optimize the streamline weights in a tractogram to increase

88   specificity for white matter structural features (2) spherical-deconvolution informed filtering of

89   tractograms (SIFT2) (R. E. Smith et al., 2015) and (3) convex optimization modeling for

90   microstructure informed tractography (COMMIT) (Daducci et al., 2013; Daducci, Dal Palù, et

91   al., 2015). SIFT2 and COMMIT were designed to overcome known limitations of streamline

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92   counts (Girard et al., 2014; Jones, 2010; Jones et al., 2013). While the edge weights in all three

93   networks generally capture white matter features relevant to connection strength, SIFT2 and

94   COMMIT more specifically quantify the total intra-axonal cross-sectional area of white matter

95   tracts (henceforth referred to as "edge caliber"). To date, COMMIT and SIFT2 have not been

96   compared to NoS with uniform connection density (Frigo et al., 2020; Schiavi et al., 2020; C. H.

97   Yeh et al., 2016). Thus, it remains unclear how the edge weights themselves affect network

98   topology.

99

100   In contrast, tractometry allows network edge weights to be derived from any volumetric brain

101   image that is co-registered to the tractogram. This increase in methodological flexibility comes at

102   the expense of anatomical specificity. Tractometry is unable to resolve the separate contributions

103   of individual fiber populations to the aggregate value of a voxel. Given that an estimated ~90%

104   of white matter voxels at typical diffusion MRI resolutions (~2mm) contain multiple fiber

105   populations (Jeurissen et al., 2012), the quantitative link between white matter microstructure

106   and essentially all tractometry-derived edge weights is biased by partial volume effects.

107

108   In this work, tractometry is combined with a diffusion tensor model (Basser, 1995; Basser et al.,

109   1994) to derive networks weighted by FA (fractional anisotropy) and RD (radial diffusivity),

110   which respectively quantify the degree of diffusion anisotropy (i.e., directional dependence) and

111   diffusion magnitude perpendicular to the major axis. The crossing fiber problem described above

112   is also known to limit the ability of diffusion tensor models to quantify white matter features (De

113   Santis et al., 2014; Jacques Donald Tournier et al., 2011). Additional tractometry networks

114   examined here include a network weighted by ICVF (intracellular volume fraction) computed

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115   with NODDI (Neurite Orientation Dispersion and Density Imaging) (H. Zhang et al., 2012), as

116   well as a network weighted by the longitudinal relaxation rate R_1 ($1/T_1$) derived from a

117   quantitative T_1 map. The edge weights in this network are myelin-weighted as R_1 has been

118   shown to correlate with histology-derived myelin content (Mancini et al., 2020; Mottershead et

119   al., 2003).

120

121   This characterization of weighted structural brain networks is carried out as follows: (1) within-

122   network features of edge weight distribution and variance; (2) edgewise relationships with FC,

123   edge length and myelin (R_1); and (3) topological features of small-worldness, rich club and

124   network hubs. Importantly, uniform binary connectivity is enforced across all weighted network

125   variants i.e., the underlying binary connectivity map is identical. This allows the edge weights

126   themselves to drive the characterization.

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128

129   **RESULTS**

130   In 50 healthy adults (27 men; 29.54±5.62 years; 47 right-handed), structural brain networks were

131   estimated from multi-shell diffusion MRI data with probabilistic tractography. Each subject's

132   structural network was used to compute 8 SC networks (**Table 1**) in which edges were weighted

133   by: NoS, SIFT2, COMMIT, FA, RD, ICVF, R_1 and LoS (edge length computed as the mean

134   length of streamlines). NoS, SIFT2, COMMIT and LoS correspond to streamline-specific

135   metrics, whereas networks weighted by FA, RD, ICVF and R_1 were computed using tractometry.

136   The edge weights in NoS, SIFT2 and COMMIT networks were normalized by node volume.

137   Additionally, a static FC network was derived for each subject by zero-lag Pearson cross-

138   correlation of nodewise resting-state time series. Unless otherwise stated, all results shown

139   correspond to networks parcellated with the Schaefer-400 cortical atlas (Schaefer et al., 2018)

140   and include 14 subcortical nodes.

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| Short name	Long name	Method	Data source	Interpretation
LoS	Length of Streamlines	streamline-specific	diffusion MRI	Mean length of the streamlines connecting two nodes
NoS	Number of Streamlines	streamline-specific	diffusion MRI	Number of streamlines connecting two nodes; connection strength
SIFT2	Spherical-deconvolution Informed Filtering of Tractograms	streamline-specific	diffusion MRI	Fiber density from spherical deconvolution summed across streamlines; connection strength
COMMIT	Convex Optimization Modeling for Microstructure Informed Tractography	streamline-specific	diffusion MRI	Total intra-axonal cross-sectional area summed across streamlines; connection strength
R_1	longitudinal relaxation rate	tractometry	multi-modal (diffusion + relaxometry)	$R_1=1/T_1$; index of tissue myelin content
FA	Fractional Anisotropy	tractometry	diffusion MRI	Diffusion directional dependence
RD	Radial Diffusivity	tractometry	diffusion MRI	Diffusion perpendicular to the principal axis
ICVF	Intra-Cellular Volume Fraction	tractometry	diffusion MRI	Neurite density

142   Table 1. Summary of structural network weights.

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145   ***Structural Brain Networks Vary in the Distribution of Their Edge Weights***

146   Group-level networks weighted by NoS, SIFT2 and COMMIT show spatially distributed patterns

147   of high magnitude edge weights and noticeably accentuate within-module connectivity (**Figure**

148   **1**). Modules correspond to the 7-canonical resting-state networks (Thomas Yeo et al., 2011) plus

149   the subcortex. These patterns are hallmarks of FC networks and are observed in the FC network

150   shown here. The contrast between high and low magnitude edge weights is most evident in

151   COMMIT. By comparison, the spatial variation of edge weight distribution in the tractometry

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networks is smoother with more pronounced regional concentrations. R_1 is highest in the edges

connecting the visual module to itself and to the rest of the brain; and lowest within the

subcortex and between the subcortical and limbic modules. The surface plot shows the highest

concentration of R_1 in the white matter projections of posterior cortical regions.
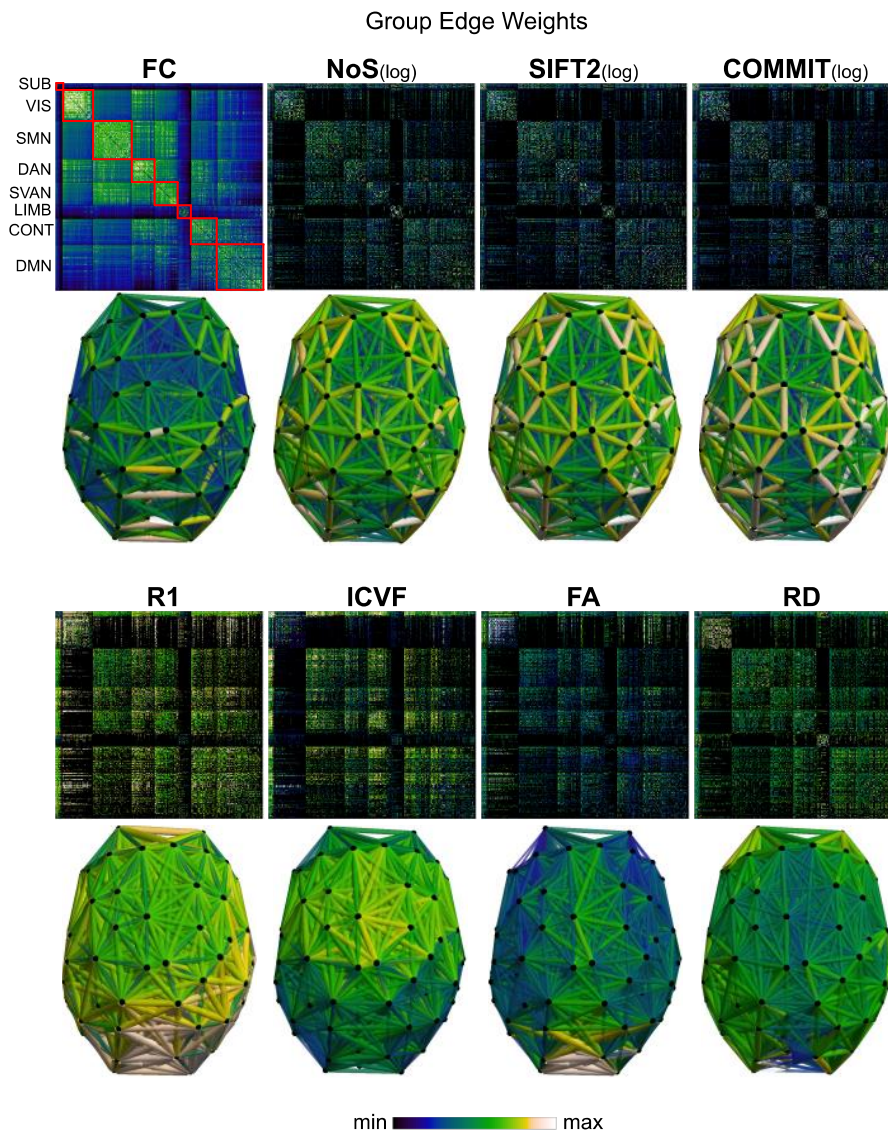
Figure 1. Edge Weight Spatial Distribution. Connectivity matrices of group-level edge weights for FC

(functional connectivity), NoS (number of streamlines), SIFT2 (spherical-deconvolution informed filtering

of tractograms), COMMIT (convex optimization modeling for microstructure informed tractography), R_1

161 *(longitudinal relaxation rate), ICVF (intra-cellular volume fraction), FA (fractional anisotropy), RD*

162 *(radial diffusivity) and LoS (mean length of streamlines). Each network is composed of 414 nodes as*

163 *defined by the Schaefer-400 cortical parcellation and 14 subcortical ROIs. Nodes are grouped into the*

164 *canonical resting state modules* (Thomas Yeo et al., 2011) *plus the subcortex: SUB (subcortex), VIS*

165 *(visual), SMN (somatomotor), DAN (dorsal attention), SVAN (salience ventral attention), LIMB (limbic),*

166 *CONT (control), and DMN (default mode). 3D cortical surfaces (shown below) of group-level edge*

167 *weights in the Schaefer-100 parcellation generated with BrainNet Viewer* (Xia et al., 2013). *Edge*

168 *diameter and color indicate weight magnitude. The edge weights in NoS, SIFT2 and COMMIT networks*

169 *were $\log_{10}$ transformed for visualization.*

170

171 Group-level edge weight distributions are summarized with respect to two important

172 organizational patterns of brain function (**Figure 2A**): within and between resting state modules

173 (Thomas Yeo et al., 2011); and along the principal functional gradient (Margulies et al., 2016).

174 NoS, SIFT2 and COMMIT mirror FC in both plots with greater edge weight magnitude within

175 module, especially within unimodal modules. R_1, ICVF, FA and RD generally mirror LoS with

176 the reverse trend: higher between module and lowest in unimodal modules. This suggests that

177 tractometry-derived networks may be influenced by edge length to a greater extent.

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A group edge weights

B subject edge weights
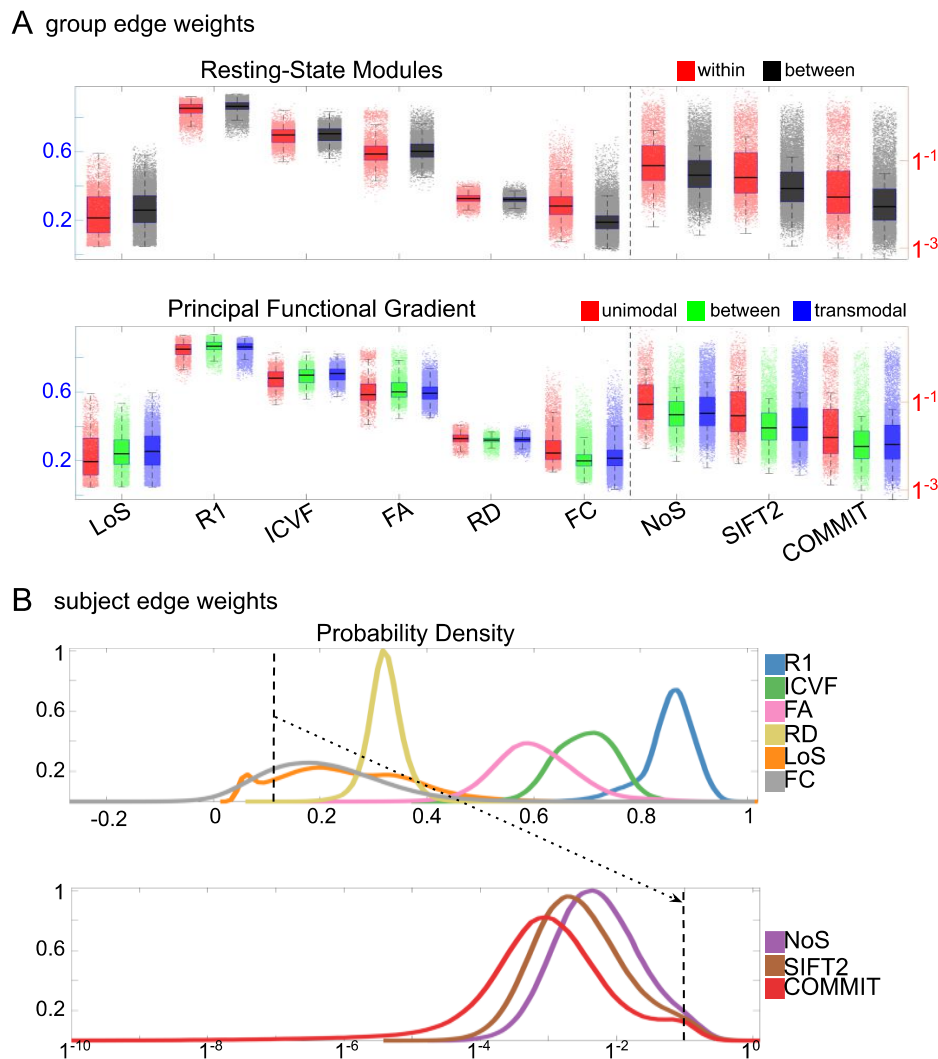
Figure 2. *Edge Weight Distribution. (A) Distribution of group-level edge weights binned by: (top) within and between module; (bottom) unimodal, transmodal and between. Unimodal is defined as the VIS and SMN modules. Transmodal is defined as the DMN, CONT, DAN and SVAN modules. (B) Probability density of pooled subject-level edge weight distributions. R_1, ICVF, FA, RD, LoS and FC are shown on a linear x-axis (top), and NoS, SIFT2 and COMMIT are shown on a logarithmic x-axis (bottom). All networks were normalized to the range [0 1] by dividing by the subject-level max for visualization.*

Subject-level edge weight distributions in R_1, ICVF, FA and RD are near-normal and network-specific (**Figure 2B**). They differ in both the magnitude (R_1 > ICVF > FA > RD) and dynamic range (FA & ICVF > R_1 & RD) of their edge weights. In contrast, NoS, SIFT2 and COMMIT distributions are highly skewed and tend to be much lower in magnitude (dashed line). This

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191 effect is greatest in COMMIT suggesting that the optimization performed by COMMIT exerts a

192 stronger scaling effect than SIFT2. These results support the conclusion that the structural

193 networks considered here quantify subsets of white matter features which are at least partially

194 non-overlapping.

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197 *Edge Weights in Streamline-Specific Networks Are More Variable*

198 Edge weight variance was quantified using the Quartile Coefficient of Dispersion (CQD) due to

199 its robustness to outliers and skewed data. The CQD is computed from the 1st and 3rd quartiles as:

200 $CQD = (Q_3 - Q_1) / (Q_3 + Q_1)$.

201

202 *Intra-subject* variance is roughly 2-fold greater in NoS, SIFT2 and COMMIT relative to LoS and

203 FC; and an order of magnitude greater than R_1, ICVF, FA and RD in all subjects (**Figure 3A**).

204 COMMIT is the highest overall. Subjects are more tightly clustered in all weighted SC networks,

205 relative to FC: *intra-subject* CQD values span roughly a 4-fold greater range in FC. This

206 suggests that individual diversity of functional connectivity is not necessarily reflected in the

207 variability of their structural networks. These patterns are repeated for *inter-subject* variance.

208 However, FC shows a small subset of highly variable edges with roughly 4-fold greater CQD
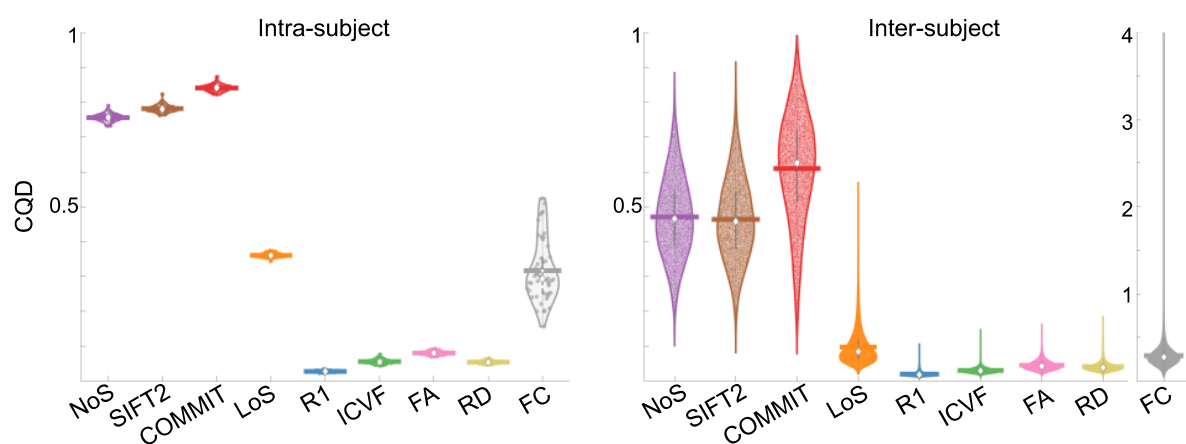
209 than the maximum values observed in COMMIT i.e., the most subject-specific connections are

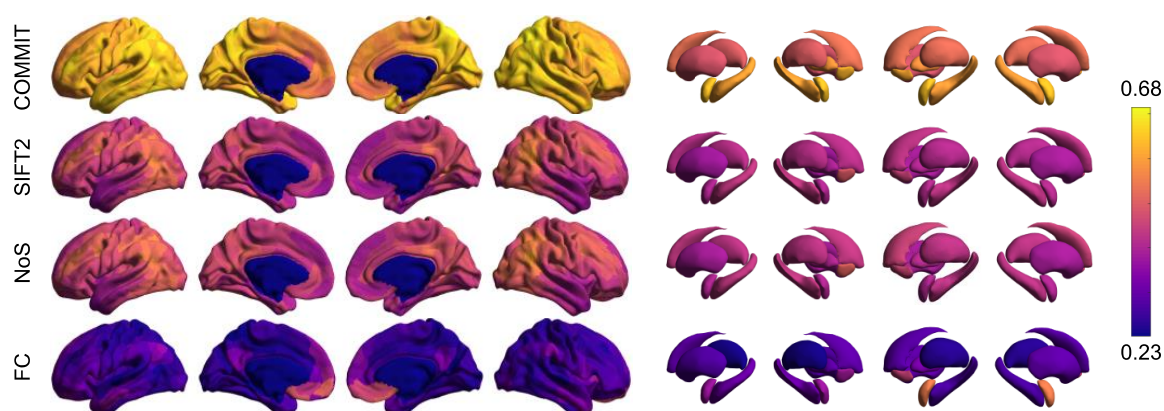210 functional. The very low edge weight variability in R1, ICVF, FA and RD is in part due to the

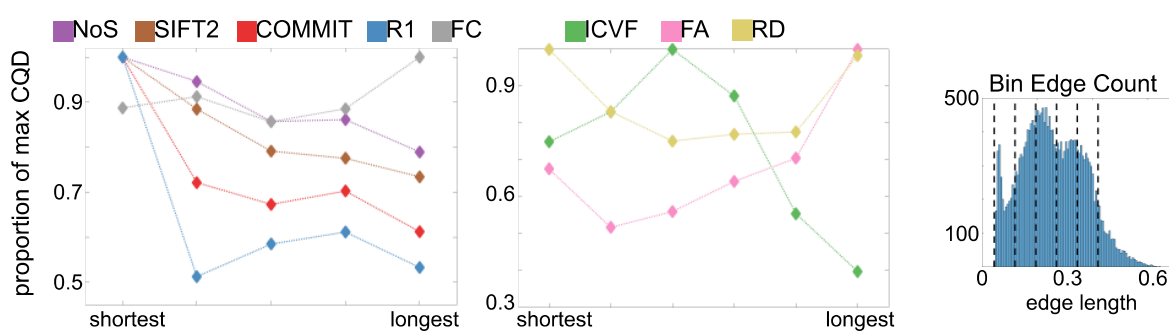211 widespread blurring effect (partial voluming) resulting from the tractometry computation.

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A subject edge weight variability

B edgewise mean inter-subject variance

C group edge weight variance across edge length bins

213

214   ***Figure 3***. *Edge Weight Variability. Variability is quantified using the coefficient of quartile dispersion*

215   *(CQD). (A) Violin distributions of **intra-subject** (left) and **inter-subject** (right) edge weight variance.*

216   *Colored data points respectively correspond to individual subjects (N=50) and edges (N=8549). (B)*

217   *Surface projections of edgewise mean inter-subject variance for cortical nodes in the Schaefer-400*

218 *parcellation (left) and 14 subcortical nodes (right). Cortical and subcortical surfaces were respectively*

219 *generated with BrainSpace* (Vos de Wael et al., 2020) *and ENIGMA toolboxes* (Larivière et al., 2021).

220 *(C) The proportion of within-network max CQD is shown across edge length bins for FC, NoS, SIFT2,*

221 *COMMIT and R_1 (left), as well as ICVF, FA and RD (middle). Edge weights are grouped into 6 bins*

222 *according to edge length, as illustrated by the histogram (right). The edges of bins 1-5 were linearly*

223 *spaced of width, w. The edges of the final bin were of width 3w.*

224

225 In general, *inter-subject* edge weight variance is more spatially distributed in SC networks

226 relative to FC (**Figure 3B**). COMMIT shows the highest mean CQD over the entire cortex and

227 subcortex. NoS, SIFT2 and COMMIT all show lateral-medial and posterior-anterior cortical

228 gradients. Mean CQD in FC shows the highest concentration in medial inferior frontal cortex and

229 to a lesser extent, the expected pattern of high variance in association cortex. The most variable

230 subcortical regions include the hippocampus, amygdala and accumbens.

231

232 Many features of brain networks (e.g., connection probability, weight magnitude) are known to

233 vary with edge length. Here, we examined the relationship between edge weight variability and

234 edge length by computing the CQD within subsets of group-level edge weights binned according

235 to their edge length (**Figure 3C**). Edge weight variance in NoS, SIFT2, COMMIT and R_1 is

236 highest in the shortest edges and decreases with edge length. ICVF roughly follows the same

237 pattern. FA and RD instead show the highest variability in the longest edges. Overall, the edge

238 weights in streamline-specific SC networks (NoS, SIFT2 and COMMIT) show greater contrast

239 both within and across subjects. SC networks show network-dependent relationships between

240 edge weight variance and edge length. Shorter edges are more variable in myelin- and

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241 connection strength-weighted networks, and longer edges are more variable in networks with

242 edge weights derived from a diffusion tensor model.

243

244 To complement the above results, a supplemental analysis was performed using intraclass

245 correlation to quantify edge weight variance within each edge weight (**Figure S9**).

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248 ***Opposing Correlations with Function in Connection-Strength- & Myelin-Weighted Networks***

249 Shifting to inter-network edge weight relationships shows that SC networks are differentially

250 related to FC (**Figure 4A**). Importantly, we also see that all brain networks (SC and FC) are

251 strongly and differentially related to edge length at the subject and group levels. Correlations

252 with edge length are negative for NoS, SIFT2, COMMIT, RD and FC; and positive for R_1,

253 ICVF, and FA. Correlation magnitude is strongest in group-level COMMIT ($\rho \approx -0.8$). To

254 account for this strong obscuring effect, we recomputed correlations using residual edge weights

255 following linear regression of edge length (**Figure 4B**). NoS, SIFT2 and COMMIT remain

256 positively associated (group-level $\rho \approx 0.35$) and R_1 remains negatively associated with FC

257 (group-level $\rho \approx -0.22$). Correlation magnitude was reduced following linear regression of edge

258 length in all cases. ICVF, FA and RD are reduced to 0 suggesting that they may not be useful in

259 modeling whole-brain FC. These results support the idea that R_1-weighted SC networks provide

260 complementary information to NoS, SIFT2 and COMMIT about the brain structure-function

261 relationship.

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A edge weight correlations

B residual edge weight correlations
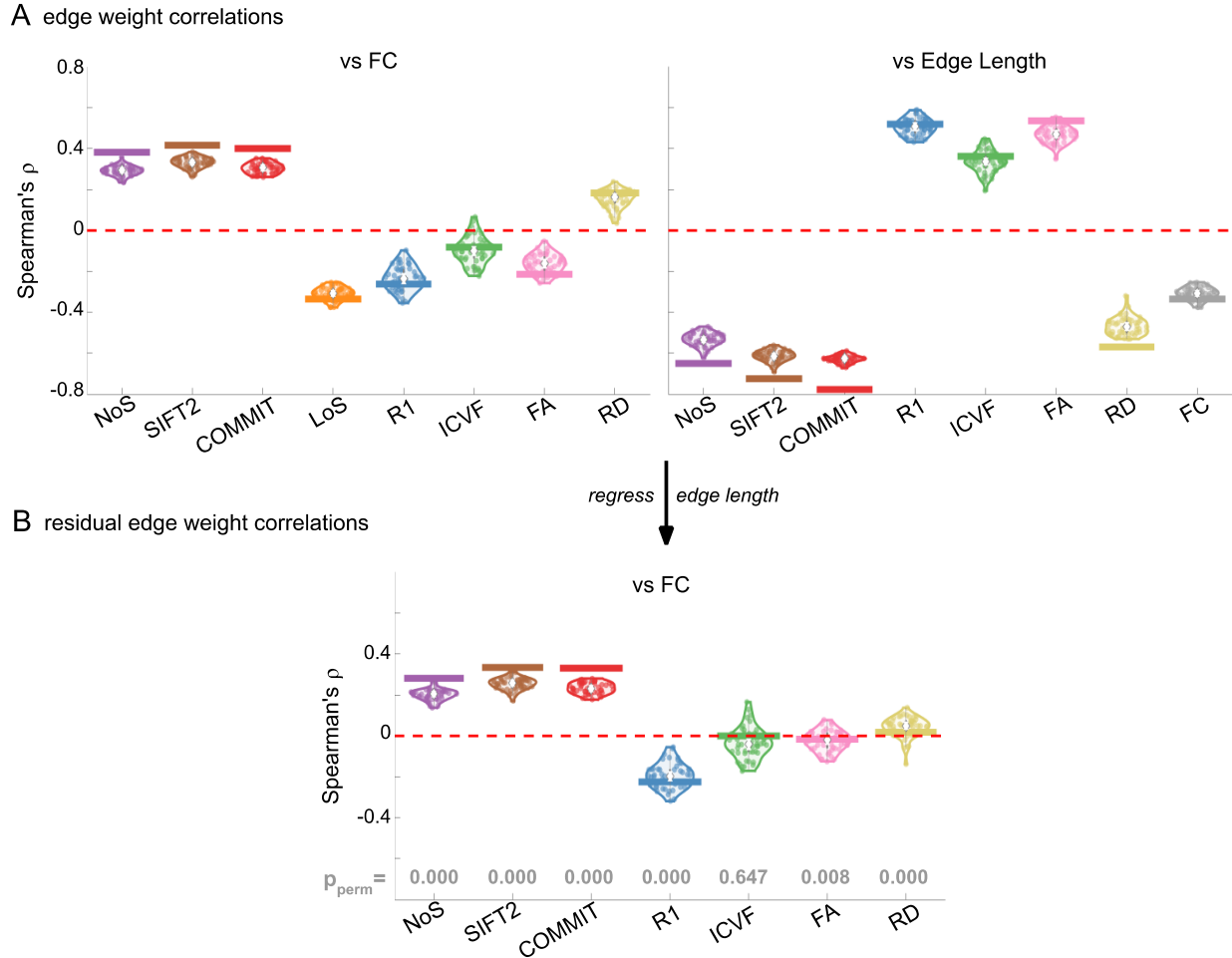
Figure 4. Edge Weight Correlations with FC and Edge Length. (A) Violin distributions of edgewise

Spearman's rank correlations of all networks with FC (left) and edge length (right). (B) Violin

distributions of edgewise Spearman's rank correlations of residual edge weights in all networks with

residual edge weights in FC. Residual edge weights were computed by linear regression of edge length.

Colored data points and bars respectively indicate subject-level and group-level correlations. P_{perm} gives

the one-sided p-value obtained from permutation testing (Figure S7).

Edge Caliber and Myelin Content are Inversely Related

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273   Here, we ask how R_1, which we refer to as the myelin-weighted network, is related to the

274   connection-strength-weighted network COMMIT. Edge-length regressed residual edge weights

275   in NoS, SIFT2 and COMMIT show a negative association with R_1 residuals for all subjects and

276   at the group level, which is strongest in COMMIT (group-level $\rho \approx$ -0.29) (**Figure 5A**). This

277   suggests an edge-length independent inverse relationship between white matter structural

278   features related to connection strength and myelin content.

279
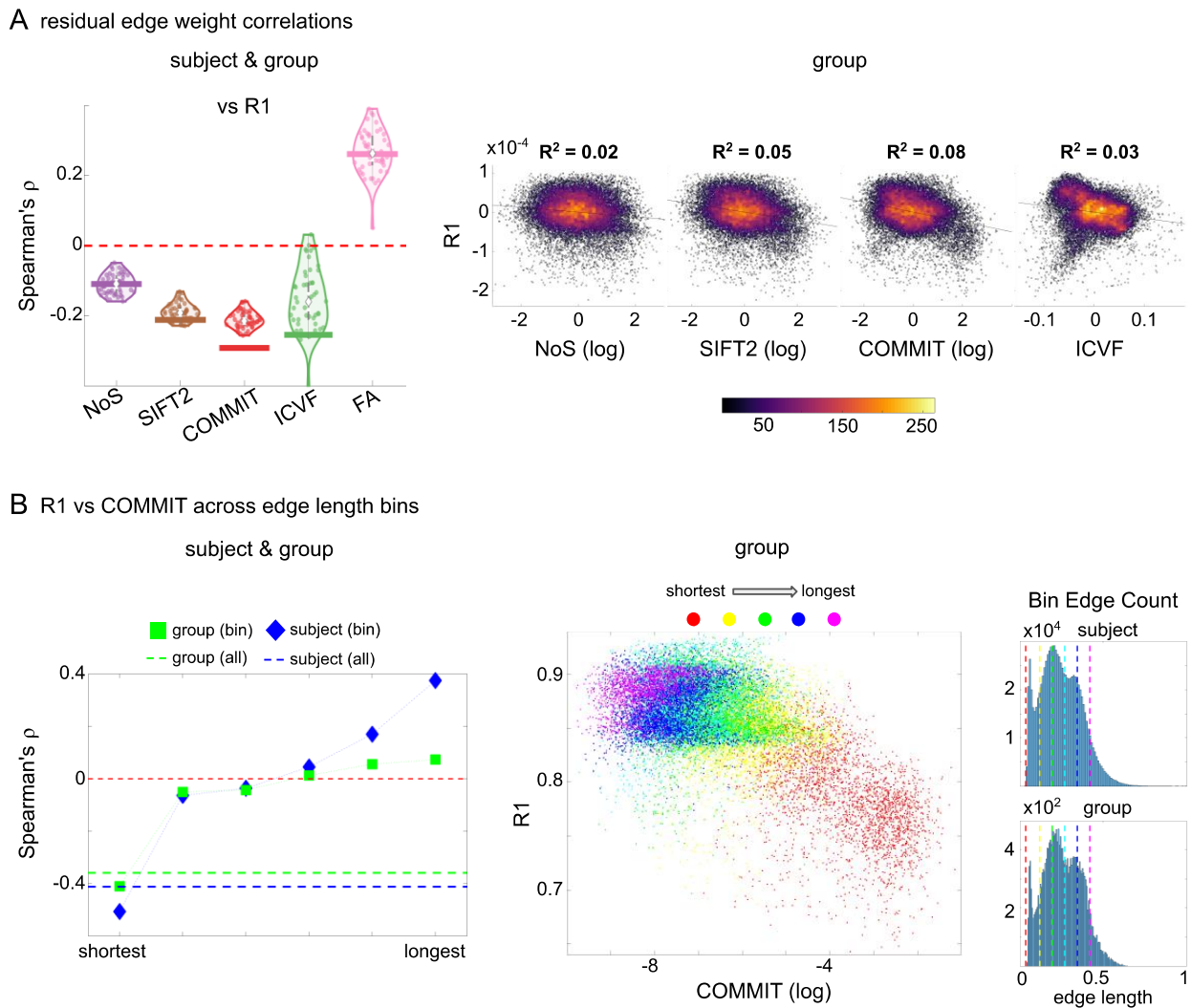
280

281   *Figure 5. The Myelin-Dependence of Structural Brain Networks. (A) Violin distributions (left) of*

282   *edgewise Spearman's rank correlations with the myelin-weighted network R_1. Residual edge weights are*

16

283 *compared following linear regression of edge length. Colored data points and bars respectively indicate*

284 *subject-level and group-level correlations. Heat scatter plots (right) of group-level residual edge weights*

285 *in R_1 as a function of NoS (left), SIFT2 (left middle), COMMIT (right middle) and ICVF (right). The best*

286 *fit linear curve is shown in black, and R^2 (coefficient of determination) is reported. Data color indicates*

287 *density. Permutation testing provided a one-sided p-value of $P_{perm} = 0.000$ for all edgewise correlations*

288 *(**Figure S8**). (B) Line plot (left) of edgewise Spearman's rank correlation of edge weights in R_1 vs*

289 *COMMIT across edge length bins. Group-level and subject-level are respectively shown in green and*

290 *blue. The square and diamond markers connected by dotted lines show binned correlation values, and the*

291 *horizontal dashed green and blue lines mark the correlation values for all edges pooled together. Scatter*

292 *plot (middle) of group-level edge weights in R_1 as a function of COMMIT with data points colored by bin*

293 *identity. Histograms (right) illustrating subject- and group-level edge length bins.*

294

295 Computing correlations of edge weights (not residuals) within edge-length bins allows the

296 inverse relationship between R_1 and COMMIT to be traced to the shortest edges of the network

297 (group $\rho \approx -0.40$, subject $\rho \approx -0.50$). As edge length increases, this relationship is reduced to 0,

298 then becomes strongly positive in the longest subject-level edges ($\rho \approx 0.39$). The scatter plot of

299 group-level R_1 vs COMMIT (middle) shows decreasing COMMIT and increasing R_1 with

300 increasing edge length. All together, these results support an inverse relationship between the

301 edge caliber and myelin content of a given white matter tract. This can be partly explained by the

302 differential dependence of these structural features on edge length: longer tracts tend to be more

303 myelinated with lower total intra-axonal cross-sectional area. However, this relationship is robust

304 to controlling for edge length supporting an intrinsic dependence between these white matter

305 features.

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307 In addition, we show that our R_1-weighted network corresponds well with a previously reported

308 (Boshkovski et al., 2021) R_1-weighted structural connectome (**Figure S13**).

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311 ***Divergent Small-Worldness, Hubness and Rich Club in Weighted Structural Networks***

312 In this final section, we apply network analysis tools (Rubinov & Sporns, 2010) based on graph

313 theory (Fornito et al., 2013; Sporns, 2018) to group-level weighted SC networks. This facilitates

314 high-level interpretation of general features of network communication such as integrative vs

315 segregative processing and the economy of network organization. Although the high material

316 and metabolic cost of brain tissue naturally tends to favor local connectivity (high clustering),

317 short overall network path length is achieved through a small number of relatively expensive

318 long-range connections (Bullmore & Sporns, 2012). These edges and the nodes they interlink

319 form a densely connected network core known as the rich club (Martijn P. van den Heuvel &

320 Sporns, 2011). While the general proclivity for high local clustering gives rise to segregated

321 functional modules, the rich-club nodes act as network communication hubs supporting inter-

322 modular integration (Collin et al., 2014; de Reus & van den Heuvel, 2014; Griffa & Van den

323 Heuvel, 2018; Kim & Min, 2020; Martijn P. van den Heuvel & Sporns, 2013). Thus, small-world

324 network topology (high clustering and low path length) (Bassett & Bullmore, 2006, 2017)

325 supports both integrative and segregative processing at a minimum of wiring cost, and the

326 underlying scaffold of hub brain regions tend to show high centrality, low path length (high
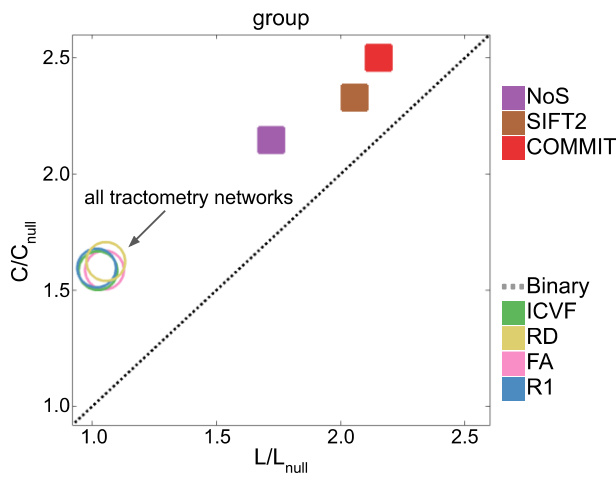
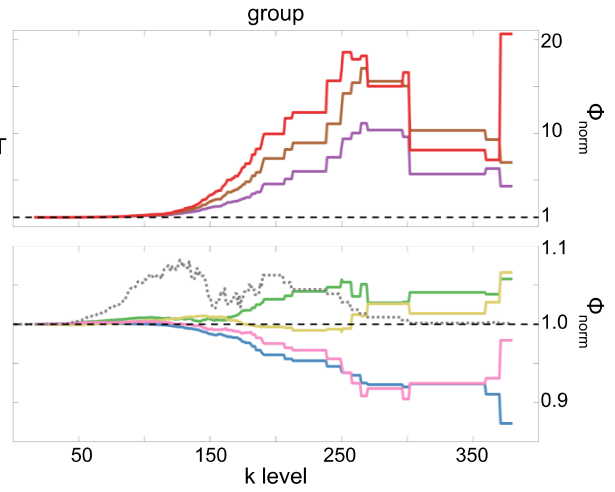327 closeness) and low clustering (M. P. van den Heuvel et al., 2010).

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329   Here, we report normalized small-worldness, normalized rich-club curves and nodal hubness

330   (**Figure 6**). Normalized small-worldness (S) is computed as the quotient of normalized measures

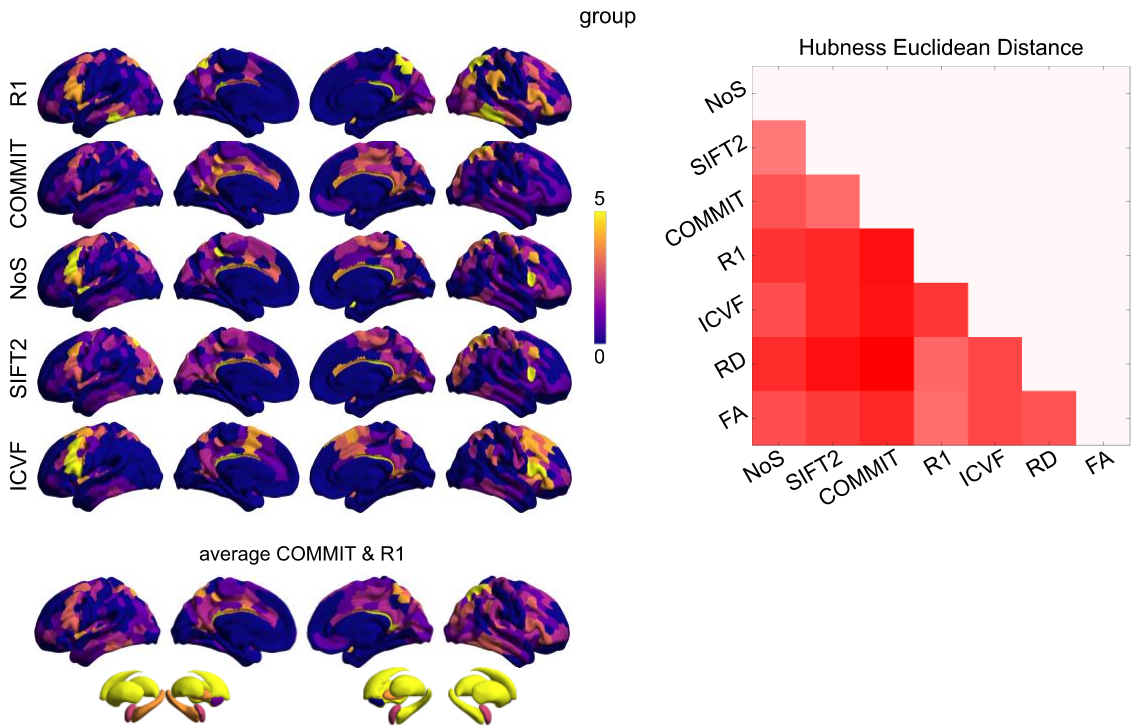331   of clustering coefficient (C/C_{null}) and path length (L/L_{null}).

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Figure 6. Group-Level Network Topology. (A) Small-worldness was estimated in all structural networks:

clustering coefficient was normalized within each node, averaged across nodes (C/C$_{null}$), then plot as a

function of normalized characteristic path length (L/L$_{null}$). Topology measures averaged across 50 degree

and strength preserving null networks were used for normalization. Networks above the identity line

(dotted black) are characterized by the small world attribute. Tractometry networks are indicated by the

arrow. (B) Normalized rich-club curves are shown for COMMIT, NoS and SIFT2 (top), as well as ICVF,

340   *RD, FA and R_1 (bottom). A single binary network (dotted gray line) is also shown (bottom) as binary*

341   *connectivity was uniform across weighted networks. The normalized rich-club coefficient (ϕ_{norm}) was*

342   *computed across the range of degree (k) and normalized against 1000 null networks (degree preserving*

343   *for binary and degree and strength preserving for weighted networks). A ϕ_{norm} value > 1 (horizontal*

344   *dashed black lines) over a range of k indicates the presence of a rich club. (C) Nodewise hubness scores*

345   *are projected onto Schaefer-400 cortical and 14-ROI subcortical surfaces. Scores (0-5) were computed*

346   *for each node as +1 point for all nodes in top 20% strength, betweenness, closeness and eigenvector*

347   *centrality, as well as bottom 20% clustering coefficient. The matrix (right) shows the Euclidean distance*

348   *between all pairs of nodal hubness vectors.*

349

350   All group-level weighted SC networks show the normalized small-world property (S > 1) of

351   higher clustering and lower path length than would be expected by chance (**Figure 6A**). Small-

352   worldness is highest in COMMIT (S ≈ 2.5) and lowest in R_1, ICVF, FA and RD (S ≈ 1.6). In

353   contrast, all weighted SC networks did not show a canonical rich club (**Figure 6B**). Relative to

354   the tractometry and binary SC networks, the normalized rich-club coefficient (ϕ_{norm}) was much

355   higher in magnitude in NoS, SIFT2 and COMMIT. A rich club was detected in these networks

356   across a large range of degree (k) levels (150 < k < 300). ϕ_{norm} was maximal at k ≈ 265 in

357   COMMIT. A rich club was also detected across a similar range of k levels in ICVF and across k

358   in the range [250 300] for RD, albeit with much lower magnitude ϕ_{norm}. However, no clear rich

359   club was observed in R_1 or FA. In fact, the rich-club curves for these networks are roughly

360   symmetric about the $\phi_{norm} = 1$ line relative to COMMIT. A densely connected core was of course

361   recovered in all weighted SC networks (uniform binary connectivity), but these results suggest

362   that its interconnecting edges were consistently weaker than would be expected by chance in R_1

363   and FA. By comparison, a rich club was observed in the binary SC network across the very large

364   range of k [50 300]. This supports two important concepts: (1) SC network edge weights can

365   provide an additional layer of information useful for refining the topology of binary SC; and (2)

366   different methods for computing SC network edge weights yield diverse network topology.

367

368   Weighted SC networks show network-dependent spatial topology of hubness scores (**Figure**

369   **6C**). The COMMIT and R1 averaged surface shows prominent hubs distributed throughout the

370   brain including the fronto-parietal network. Nearly all of the subcortex showed a hubness score

371   of 4 or greater in all networks. The Euclidean distance between hubness score vectors (right) was

372   lower for COMMIT and SIFT2 than for either network with NoS. Of the streamline-specific

373   networks, NoS was more similar to both R1 and IVCF. Overall, these results illustrate the

374   considerable impact that edge weighting can have on network topology.

375

376

377   **DISCUSSION**

378   Structure-function brain models provide a flexible framework for investigating the mechanistic

379   relationship between human brain structure and function *in vivo*, yet the interpretability of these

380   models is currently limited by a lack of biological detail. Here, we assemble a thorough

381   characterization of structural brain networks weighted by a range of quantitative MRI metrics

382   capturing the macro- and microscopic features of white matter tracts. Notable trends included:

383   (1) greater edge weight contrast and skewed (heavy-tailed) distributions in the streamline-

384   specific networks NoS, SIFT2 and COMMIT; (2) whole-brain correlations with FC in networks

385   weighted by connection strength (positive) and myelin (negative) which were robust to

22

386 controlling for edge length; (3) whole-brain inverse relationships with myelin for networks

387 weighted by connection strength and neurite density independent of edge length; and (4) the

388 absence of a rich club in R_1 and FA networks. All weighted SC networks showed a strong spatial

389 dependence and small-world architecture. Collectively, these results support the overall

390 conclusion that SC networks weighted by edge caliber (e.g., SIFT2 and COMMIT) and myelin

391 (e.g., R_1) can be used to quantify non-overlapping subsets of white matter structural features

392 related to FC supporting their joint utilization in modeling function.

393

394

395 *Interpretable Measures of Connection Strength Provided by COMMIT and SIFT2*

396 A principal goal of this work is to identify what, if any, advantage over NoS is provided by the

397 global optimization methods SIFT2 and COMMIT. NoS has previously been used to inform the

398 strength of interregional coupling in computational models of function (e.g., (Honey et al.,

399 2009)). However, important limitations restrict model interpretation. Besides suffering from a

400 range of biases related to the position, size, shape and length of white matter tracts (Girard et al.,

401 2014), NoS varies as a function of tracking parameters limiting its specificity for white matter

402 structural features (Jones, 2010; Jones et al., 2013).

403

404 SIFT2 and COMMIT reportedly restore the quantitative link between connectome edge weights

405 and white matter structural features related to connection strength. COMMIT and SIFT2 solve

406 for the effective cross-sectional area (i.e., signal fraction) of each streamline using different

407 approaches. COMMIT uses the global diffusion signal to optimize these values, whereas SIFT2

408 seeks to fit the streamline density throughout the white matter to the fiber densities estimated

409   using spherical deconvolution. Thus, while both methods rely on the simplifying assumption that

410   streamline features are invariant along their length, SIFT2 additionally requires that the estimates

411   of fiber density derived from the fiber orientation distribution (FOD) are biologically accurate.

412

413   These networks also differ in the computation of their edge weights: SIFT2 is computed as the

414   simple sum of streamline weights, whereas COMMIT is computed as the length-weighted-sum

415   of streamline weights. Indeed, our analysis methods do not permit us to make strong claims as to

416   the relationship between these methodological differences and our observed results, however we

417   do show that both SIFT2 and COMMIT display comparable but not identical fundamental

418   characteristics to NoS. This supports the use of SIFT2 or COMMIT in place of NoS as a measure

419   of connection strength, which brings with it improved biological interpretability.

420

421

422   *Myelin Complements Connection Strength in Predicting FC*

423   Despite the differences between COMMIT, SIFT2 and NoS; our results indicate that their edge

424   weights show roughly equivalent positive correlations with FC over the whole brain. R_1 was

425   negatively correlated with FC. Significant evidence indicates a link between cerebral myelin and

426   FC including: a relationship between intracortical myelin and FC (Huntenburg et al., 2017;

427   Wang et al., 2019); the prediction of cognition (Sonya Bells et al., 2017; Caeyenberghs et al.,

428   2016) and FC-derived components (Messaritaki et al., 2021) using myelin-sensitive metrics; and

429   a relationship between damaged myelin sheaths and greater conduction delays in multiple

430   sclerosis (Sorrentino et al., 2022). At the cellular-level, myelin contributes to conduction velocity

431   (Huxley & Stämpfli, 1949), metabolic support (Nave & Werner, 2014) and plasticity (Gibson et

24

432   al., 2018), all of which could be argued to support brain function. Myelin plasticity in particular

433   can be described in terms of "activity-dependence", whereby an increase in the functional

434   activity of a given circuit stimulates cellular signaling cascades promoting greater myelination

435   (Douglas Fields, 2015; Mount & Monje, 2017). Coupled with our results, this complex mix of

436   functional roles supports the idea that structure-function models will be improved by integrating

437   measures of myelin and connection strength.

438

439

440   ***An Opposing Relationship with Edge Length for Edge Caliber and Myelin Content***

441   When controlling for edge length, we found an inverse relationship between R_1 and COMMIT

442   over the whole brain in all subjects and at the group level. This suggests that the aggregate g-

443   ratio (ratio of inner/outer diameters of myelinated axons) of a white matter tract may increase

444   with edge caliber. At the cellular-level, the diameter of an axon and the thickness of its myelin

445   sheath show nearly a linear relationship over a broad range of smaller diameter axons which

446   becomes increasingly nonlinear as axon diameter increases (Berthold et al., 1983; Hildebrand &

447   Hahn, 1978). In general, increasing axon diameter tends to outpace increasing myelin thickness

448   i.e., g-ratio tends to increase with increasing axon caliber (Hildebrand & Hahn, 1978). Our

449   findings suggest that this cellular-level principle may extend to the systems level: increases in

450   edge caliber tend to outpace changes in the myelin content resulting in a concomitant increase in

451   the g-ratio of white matter tracts.

452

453   We localized the inverse relationship between R_1 and COMMIT to the shortest edges suggesting

454   that the g-ratio was the highest in the shortest connections. This result is supported by a previous

25

455   imaging study showing the highest g-ratio in "local" connections (Mancini et al., 2018). In

456   general, we found that R_1 increased and COMMIT decreased with increasing edge length, which

457   aligns with previously reported results of higher R_1 and fewer streamlines for the white matter

458   connections between transmodal regions (Boshkovski et al., 2021). Both of these trends fit well

459   with theories of brain wiring economy in which the energetic cost of maintaining biological

460   material increases with connection length (Bullmore & Sporns, 2012). This natural pressure acts

461   to reduce the total axonal volume of longer white matter bundles. Increasing the myelin content

462   of longer tracts comes at a cost as well, but this may be at least partially offset as increasing

463   myelin content reduces the total membrane surface area along which expensive electrochemical

464   gradients must be maintained (Bullmore & Sporns, 2012). Although, a cost-benefit analysis of

465   the energetics of myelination concluded that the energetic cost of myelin maintenance outweighs

466   any savings on action potentials (Harris & Attwell, 2012). This suggests that higher myelination

467   of longer edges may be better explained as a mechanism to provide trophic support (Nave &

468   Werner, 2014) to vital inter-regional connections (Martijn P. Van Den Heuvel et al., 2012) or to

469   reduce conduction delays.

470

471

472   ***Edge Weight Variance Decreases with Edge Length in Most Weighted Structural Networks?***

473   White matter features related to myelin content, connection strength and neurite density tend to

474   become more consistent across tracts as tract length increases. Greater variability in the weights

475   of the shortest connections could result from a higher proportion of false positive streamlines

476   influencing these edge weights. For SIFT2 and COMMIT, streamline weight computation

477   becomes increasingly unstable with decreasing length as fewer voxels contribute to the fit.

26

478   However, this result could also be explained more generally by contrasting the roles of shorter

479   and longer connections in the brain. Shorter white matter tracts connect brain regions near each

480   other in space e.g., within the same module. Just as we might expect the characteristics of

481   smaller roads and streets (e.g., width, building materials, markings, signs, sidewalks, etc.) to vary

482   by neighborhood and city, we might also expect the morphology of shorter white matter

483   connections to change as the functional specialization of any given region or module changes.

484   On the other hand, longer tracts (i.e., the freeways of the brain) may overlap more in both their

485   functional role and morphological features relative to shorter connections, hence lower edge

486   weight variability. Breaking with the above pattern, FA and RD showed the highest edge weight

487   variance in the longest connections. Given that structural measures derived using a voxel-wise

488   diffusion tensor model are particularly sensitive to the white matter "architectural paradigm"

489   (Jones et al., 2013), these results suggest that white matter features related to fiber orientation

490   and geometry actually diverge with increasing tract length. Note that we are unable to say

491   decisively whether the edge weight variance measured in these structural and functional brain

492   networks corresponds to true signal or noise. The inclusion of scan-rescan data (e.g., as in

493   (Amico & Goñi, 2018)) could support stronger conclusions as to the source of this variability.

494

495

496   ***The Absence of a Rich Club in Structural Networks Weighted by R_1 and FA***

497   Group-level R_1 and FA did not show a normalized weighted rich club for any degree k. Higher

498   myelination in the white matter tracts connecting rich club nodes has previously been reported

499   (Collin et al., 2014); however, methodological differences limit comparability. A rich club has

500   previously been reported in FA-weighted networks using similar methods to ours (Martijn P. van

501 den Heuvel & Sporns, 2011). The source of this disagreement could potentially be attributed to

502 differences in our tractography algorithm, parcellation or null network computation.

503

504 In weighted rich-club detection, the identification of a densely connected core is independent of

505 edge weight (depends only on node degree), but the designation of this subnetwork as a rich club

506 requires that it contains a higher-than-chance proportion of the strongest edges from the full

507 network. Indeed, this is the case over a broad range of degree k for COMMIT. Over the same

508 range of k, the normalized rich-club curves for R_1 and FA are inverted about the threshold value

509 of 1 with respect to COMMIT. This implies that the subnetwork found at a given k in this range

510 contains edges which tend to show higher COMMIT and lower R_1 edge weights than expected

511 by chance. We previously showed edgewise inverse correlations between R_1 and COMMIT

512 which were robust to controlling for edge length. We also showed that R_1 and FA are positively

513 correlated under these same conditions. In this light, it is not surprising that the edges connecting

514 rich-club nodes tend to show opposite trends in R_1- and FA-weighting with respect to COMMIT.

515 Nonetheless, it is possible that the lack of a rich club in our myelin-weighted network is an

516 artifact of tractometry. Future work will attempt to replicate this result using myelin-weighted

517 networks computed with a different methodology (Schiavi et al., 2022).

518

519

520 ***Replication Across Parcellation Resolution and in a Second Dataset***

521 In this report, we have chosen to feature data in the Schaefer-400 cortical parcellation plus 14

522 subcortical nodes. However, there is little consensus on the best brain atlas, and the optimal

523 choice likely depends on the specifics of your data and the question being investigated. In a

524   supplementary analysis, we replicated our results across 100-900 node Schaefer cortical atlases.

525   We found that residual edgewise correlations with FC (**Figure S1**) and R_1 (**Figure S2**), as well

526   as normalized rich club and normalized small worldness (**Figure S3**) were robust to parcellation

527   resolution. In contrast, the spatial topography of high-hubness brain regions appears qualitatively

528   dependent on parcellation granularity, although further analyses would be necessary to draw

529   stronger conclusions (**Figure S4**).

530

531   An independent multimodal dataset was also used to replicate the main SC results including the

532   residual edgewise correlations with R_1 and the relationship between R_1 and COMMIT across

533   edge length bins (**Figure S5**), as well as all network topology results (**Figure S6**).

534

535

536   *Limitations*

537   Streamline tractography is known to suffer from several important biases including both false

538   positive and negative streamlines, which can influence downstream analyses (Maier-Hein et al.,

539   2017; Schilling et al., 2019; Sotiropoulos & Zalesky, 2019; Zalesky et al., 2016). Through

540   probabilistic tractography, we opted to minimize false negatives while maximizing false

541   positives. This allowed us to implement careful streamline- and edge-filtering strategies in post-

542   processing to address this known bias. Still, without a ground truth, we cannot quantify the

543   extent to which we were successful in mitigating this issue, nor can we guarantee that we did not

544   erroneously filter true positive streamlines or edges. All processing and filtering methods were

545   consistent and network density was uniform across weighted structural networks. Thus, any

546   major tractography bias should be as homogeneous as possible across networks.

29

547

Tractometry-derived brain networks suffer from widespread partial volume effects due to

crossing and kissing fibers in a majority of white matter voxels. The net effect of this bias is well

understood and is apparent in our results and previous work (De Santis et al., 2014; Schiavi et

al., 2022). Nonetheless, this method was included here as our goal was to characterize widely

used structural connectivity methods. New techniques for reducing this bias are currently being

developed which allow for the estimation of tract-specific microstructural features (e.g.,

(Barakovic, Girard, et al., 2021; Barakovic, Tax, et al., 2021; De Santis et al., 2016; Leppert et

al., 2021, 2023; Schiavi et al., 2022)).

556

We were unable to assess repeatability in this work as we did not have scan-rescan data.

However, reproducibility has already been assessed for NODDI (Chung et al., 2016; Lehmann et

al., 2021), MP2RAGE-derived T1 maps (Marques et al., 2010), diffusion-tractography-based

structural connectivity (Bonilha et al., 2015), as well as COMMIT and SIFT2 tractogram

filtering (Koch et al., 2022). The reproducibility of the tractometry features (R_1, FA, RD, ICVF)

will mainly depend on these previous steps and the accuracy of the spatial alignment of the

multi-modal data.

564

In this work, we have attempted to thoroughly examine the fundamental properties of a wide

range of standard and state-of-the-art metrics for quantifying white matter brain structure.

However, the scope of possible methods and their respective variants is too broad to treat

thoroughly in a single body of work. In particular, track-weighted imaging (Calamante, 2017;

Calamante et al., 2010, 2012) and fixel-based analysis (Dhollander et al., 2021; Raffelt et al.,

30

570 2015, 2017) provide state-of-the-art solutions to the challenge of quantifying white matter

571 structural features in the presence of crossing fibers.

572

573

574 *Conclusion*

575 We presented a thorough characterization of weighted SC networks. Overall, our findings

576 support the joint use of SC networks weighted by connection strength and myelin in predicting

577 FC. In particular, using the COMMIT or SIFT2 algorithms to quantify connection strength

578 shows promise to improve model interpretability relative to NoS. Beyond R_1, there is a wide

579 array of myelin sensitive metrics that could be used to compute useful myelin-weighted

580 networks. The integration of this microstructure-weighted connectivity approach into structure-

581 function models will advance the mechanistic interpretation of both the function and dysfunction

582 of the living human brain.

583

584

585 **MATERIALS and METHODS**

586 These data are available for download (https://portal.conp.ca/dataset?id=projects/mica-mics). See

587 Royer et al. (Royer et al., 2022), Cruces et al. (Cruces et al., 2022) for full details of data

588 acquisition and processing. All data processing and analysis code is openly available at

589 https://github.com/TardifLab/Weighted-SC-Networks.

590

591

592 *Data Acquisition & Preprocessing*

593   Multimodal MRI data was collected in 50 healthy volunteers at 3 Tesla on a Siemens Magnetom

594   Prisma-Fit scanner equipped with a 64-channel head coil as follows:

595   • T_1-weighted (T_1w) anatomical: 3D magnetization-prepared rapid gradient-echo sequence

596   (MP-RAGE; 0.8mm isotropic; TR = 2300ms; TE = 3.14ms; TI = 900ms; iPAT =

597   2; partial Fourier = 6/8)

598   • Multi-shell diffusion-weighted imaging (DWI): 2D pulsed gradient spin-echo echo-planar

599   imaging sequence consisting of three shells with b-values 300, 700, and 2000s/mm^2 and

600   diffusion directions 10, 40, and 90, respectively (1.6mm isotropic; TR = 3500ms, TE =

601   64.40ms; multi-band factor = 3). b0 images were also acquired with reverse phase

602   encoding direction to facilitate distortion correction of DWI data.

603   • 7 minutes of resting-state functional MRI: multi-band accelerated 2D-BOLD gradient

604   echo echo-planar sequence (3mm isotropic; TR = 600ms, TE = 30ms; mb factor = 6; flip

605   angle = 52°). Two spin-echo images with AP and PA phase encoding were additionally

606   acquired (3mm isotropic; TR = 4029ms; TE = 48ms; flip angle=90°).

607   • Quantitative T_1 relaxometry data was acquired with a 3D-MP2RAGE sequence (Marques

608   et al., 2010) (0.8mm isotropic; TR = 5000ms, TE = 2.9ms, TI_1 = 940ms, $T1_2$ = 2830ms;

609   iPAT = 3; partial Fourier = 6/8). This was used to compute a T_1 map which was sampled

610   to estimate the edge weights in R_1 (1/T1) networks (myelin-weighted).

611

612   The multi-modal processing pipeline *micapipe* (Cruces et al., 2022)

613   (https://micapipe.readthedocs.io/) was used to preprocess diffusion, anatomical, and functional

614   images. T_1w images were deobliqued, reoriented to standard neuroscience orientation (LPI),

615   corrected for intensity non-uniformity (Tustison et al., 2010), intensity normalized and skull

616 stripped. Subcortical segmentations were performed with FSL FIRST (Jenkinson et al., 2012;

617 Patenaude et al., 2011) and tissue types were classified using FSL FAST (Y. Zhang et al., 2001).

618 A five-tissue-type image segmentation was generated for anatomically constrained tractography

619 (R. E. Smith et al., 2012). Cortical surface segmentations were generated with FreeSurfer 6.0

620 (Dale et al., 1999; Fischl, Sereno, & Dale, 1999; Fischl, Sereno, Tootell, et al., 1999).

621

622 Diffusion preprocessing was performed in native DWI space using tools from MRtrix3 (J.

623 Donald Tournier et al., 2012, 2019) and proceeded in the following sequence: (1) image

624 denoising (Cordero-Grande et al., 2019; Veraart, Fieremans, et al., 2016; Veraart, Novikov, et

625 al., 2016); (2) two b=0s/mm^2 volumes with reverse phase encoding were used to correct for

626 susceptibility distortion, head motion, and eddy currents via FSL's eddy and TOPUP tools

627 (Andersson et al., 2003; Andersson & Sotiropoulos, 2016; S. M. Smith et al., 2004); and (3) B1+

628 bias-field correction (Tustison et al., 2010). This pre-processed data was used to estimate multi-

629 shell and multi-tissue response functions for constrained spherical-deconvolution (Christiaens et

630 al., 2015; Dhollander et al., 2016, 2019; Jeurissen et al., 2014) followed by intensity

631 normalization. Non-linear registration was performed with ANTs (Avants et al., 2008) to co-

632 register anatomical images to DWI space.

633

634 Resting-state fMRI pre-processing entailed discarding the first five TRs, reorientation (LPI),

635 motion correction by registering all volumes to the mean, and distortion correction using main

636 phase and reverse phase field maps. Nuisance signal was removed using an ICA-FIX (Salimi-

637 Khorshidi et al., 2014) classifier and by spike regression using motion outlier outputs from FSL

638 (Jenkinson et al., 2012). Volumetric timeseries were averaged for boundary-based registration

33

639 (Greve & Fischl, 2009) to native Freesurfer space and mapped to individual surfaces using

640 trilinear interpolation. Spatial smoothing (Gaussian, FWHM = 10mm) was applied to native-

641 surface and template-mapped cortical timeseries.

642

643

644 ***Tractography and Microstructural Metrics***

645 To estimate structural connectomes, anatomically constrained tractography (R. E. Smith et al.,

646 2012) was performed on the normalized white matter FOD image using the probabilistic

647 algorithm iFOD2 (J.-D. Tournier et al., 2010). Tractograms of 5 million streamlines were

648 generated by seeding the gray-white matter interface using the following parameters:

649 maxlength=400, minlength=10, angle=22.5, step=0.5, cutoff=0.06, backtrack, crop_at_gmwmi

650 (gray-matter-white-matter interface). These tractograms were filtered in a two-stage process. (1)

651 a temporary whole-brain connectome weighted by NoS was computed then decomposed into its

652 composite streamlines to derive a new tractogram in which any streamline which failed to

653 connect two gray matter ROIs in the temporary connectome was excluded. This "streamline-

654 filtering" step typically resulted in approximately a 5% decrease in the size of the tractogram

655 (~250k streamlines removed) and was undertaken to ensure that these erroneous streamlines did

656 not affect the COMMIT model. Streamline-filtered tractograms were used to compute NoS and

657 were used as inputs to both the SIFT2 and COMMIT models. COMMIT was run using a Stick-

658 Zeppelin-Ball forward model and default settings (see https://github.com/daducci/COMMIT). (2)

659 Any streamline with a COMMIT weight $< 1e^{-12}$ (machine precision 0) was interpreted as a false

660 positive and filtered from the tractogram. This streamline-level COMMIT-filtering step typically

661 resulted in greater than a 90% decrease in the size of the tractogram with most containing

34

662   between ~300-600k streamlines. COMMIT-filtered tractograms were used not only in the

663   computation of COMMIT, but all tractometry networks as well. This additional filtering step was

664   performed on COMMIT streamline weights only (not SIFT2) to reduce the impact of false

665   positive streamlines in tractometry networks as much as possible.

666

667   In a supplemental analysis, the COMMIT streamline weights were additionally used in the

668   computation of edge weights in tractometry-derived networks by performing a COMMIT-

669   weighted average of a given tractometry metric (e.g., FA) over streamlines for each node pair

670   (**Figure S10-S12**).

671

672

673   ***Construction of Weighted Structural Networks***

674   The streamline-specific SC networks were computed in the following manner: (1) NoS as the

675   summed streamline count; (2) LoS as the mean streamline length; (3) SIFT2 as the sum of SIFT2

676   streamline weights; and (4) COMMIT as the length-weighted sum of COMMIT streamline

677   weights as in (Schiavi et al., 2020). Explicitly, edgewise entries in COMMIT-weighted networks

678   were computed as:

679
$$\alpha_{ij} = \frac{\sum_{k=1}^{N_{ij}}(x_{ij}^k * l_k)}{\bar{L}_{ij}},$$

680   where α_{ij} is the edge weight between nodes i and j; $\bar{L}_{ij}$ is the mean streamline length; N_{ij} is the

681   number of streamlines; x_{ij}^k is the COMMIT weight of streamline k; and l_k is its length. Edge

682   weights in NoS, SIFT2 and COMMIT were normalized by node volume.

683

684   SC networks weighted by FA, RD, ICVF (H. Zhang et al., 2012) and R_1 were derived using

685   multi-modal tractometry (S Bells et al., 2011). Streamline weights were computed by: (1) co-

686   registering the tractogram and desired image; and (2) sampling the voxel-level aggregate value

687   along the length of each streamline. Edge weights were computed as the median along each

688   streamline and the mean across streamlines by node pair. Voxel-wise measures of FA and RD

689   were computed with a diffusion tensor model (Basser et al., 1994) and ICVF by applying the

690   NODDI multi-compartment model (H. Zhang et al., 2012) to preprocessed DWI data (Daducci,

691   Canales-Rodríguez, et al., 2015).

692

693   The 400-node Schaefer (Schaefer et al., 2018) cortical parcellation is used in all results.

694   Subcortical ROIs corresponded to 7 bilateral regions (14 nodes) including the amygdala,

695   thalamus, caudate, accumbens, putamen, hippocampus, and pallidum. A single static, zero-lag

696   FC network was derived by product-moment pairwise Pearson cross-correlation of node-

697   averaged time series. FC network edge weights were Fisher Z-transformed.

698

699

700   ***Connectome post-processing***

701   COMMIT-weighted networks were used to filter all other weighted structural networks at the

702   edge level. This was chosen as COMMIT-weighted networks had the lowest connection density

703   to start, and all non-zero COMMIT edges were also non-zero in all other SC networks. All SC

704   networks were thresholded at the edge level within subject by: (1) setting edges = 0 in all

705   weighted SC networks if that edge had a COMMIT weight $< 1e^{-12}$; and (2) applying a 50%

706   uniform threshold mask to facilitate group-consensus averaging. This minimized differences in

36

707   binary structural network density across subjects and enforced a uniform binary connectivity

708   map across weighted SC networks at the group level and within subject. Group-level networks

709   were computed as the subject-wise mean at each edge excluding zero-valued edges.

710

711

712   ***Network Analysis***

713   Network analysis was performed using tools (Rubinov & Sporns, 2010) based on graph theory

714   (Fornito et al., 2013; Sporns, 2018). Measures of clustering coefficient and path length were

715   normalized against 50 degree and strength preserving null networks. Clustering coefficient was

716   normalized within node then averaged across nodes to obtain a scalar value per network. The

717   following weight (W_{ij}) to length (L_{ij}) transform was used in path length computation: $L_{ij} = -$

718    $\log(W_{ij})$. Weighted rich-club curves were normalized against 1000 degree and strength

719   preserving null networks. The edges in all degree and strength preserving null networks were

720   rewired $1e^6$ times total, and the strength sequence was approximated using simulated annealing.

721   Rich-club curves were normalized in binary networks against 1000 degree preserving null

722   networks in which each edge was rewired 100 times. All edge rewiring followed the Maslov &

723   Sneppen rewiring model (Maslov & Sneppen, 2002). Similar to (M. P. van den Heuvel et al.,

724   2010), hubness scores (0-5) were computed as 1 point for all nodes showing top 20% strength,

725   betweenness, closeness or eigenvector centrality; and lowest 20% clustering coefficient.

726

727

728   ***Permutation Testing***

729   Statistical significance for the edgewise correlation of residual edge weights in NoS, SIFT2,

730   COMMIT and R_1 with FC (**Figure S7**); as well as all connection-strength-weighted networks

731   with R_1 (**Figure S8**) was quantified using permutation testing as described in supplementary

732   material. One-sided p-values are reported in the main text figures as p_{perm}.

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1068

Figure 1

Group Edge Weights

FC

SUB
VIS
SMN
DAN
SVAN
LIMB
CONT
DMN

NoS(log)

SIFT2(log)

COMMIT(log)

R1

ICVF

FA

RD

min ▮▮▮▮▮▮ max

Figure 2

A group edge weights

Resting-State Modules

Legend: ■ within (red) ■ between (black)

Principal Functional Gradient

Legend: ■ unimodal (red) ■ between (green) ■ transmodal (blue)

X-axis labels: LoS, R1, ICVF, FA, RD, FC, NoS, SIFT2, COMMIT

B subject edge weights

Probability Density

Legend: R1, ICVF, FA, RD, LoS, FC

Legend: NoS, SIFT2, COMMIT

Figure 3

A subject edge weight variability
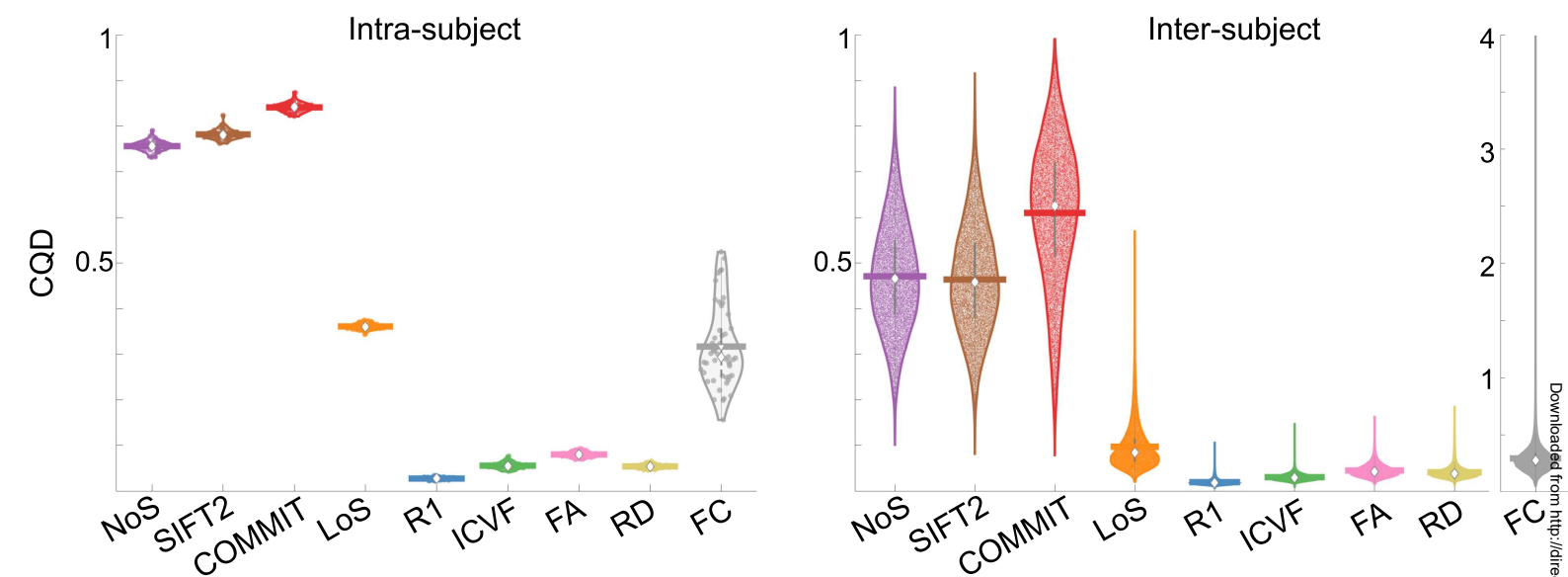
Intra-subject

Inter-subject

CQD

NoS SIFT2 COMMIT LoS R1 ICVF FA RD FC

NoS SIFT2 COMMIT LoS R1 ICVF FA RD FC

B edgewise mean inter-subject variance

COMMIT

SIFT2

NoS

FC

0.60

0.25

C group edge weight variance across edge length bins

NoS SIFT2 COMMIT R1 FC ICVF FA RD

proportion of max CQD

shortest   longest

shortest   longest

Bin Edge Count
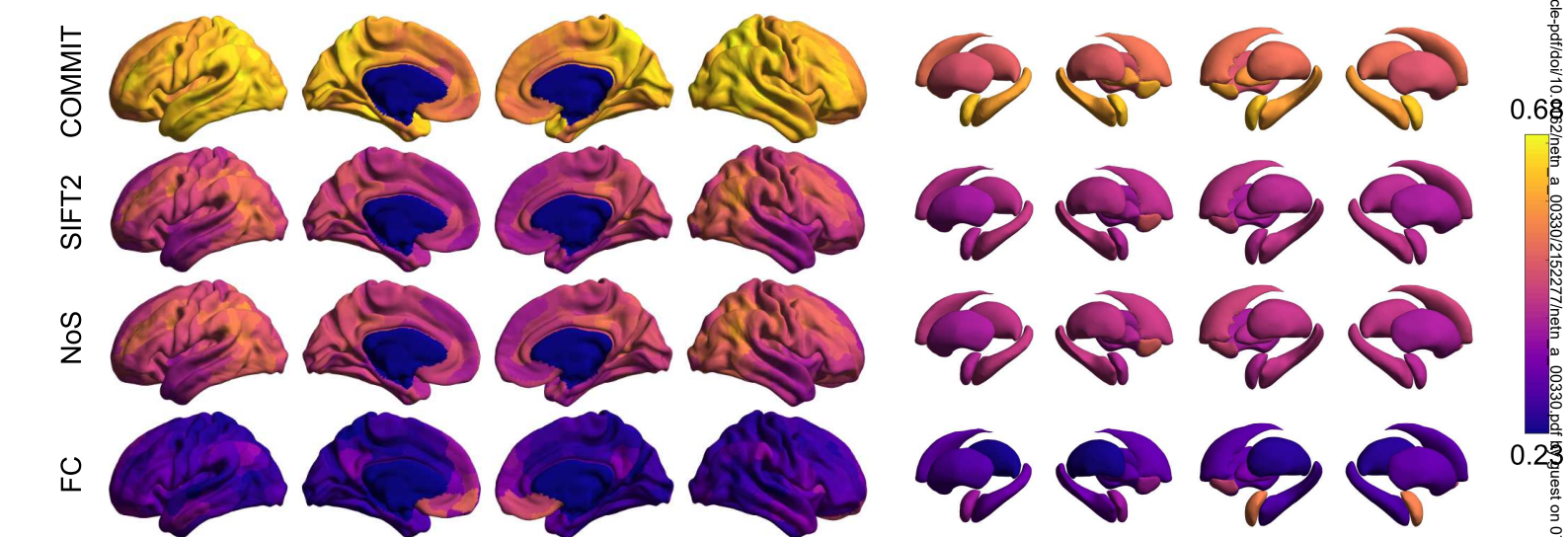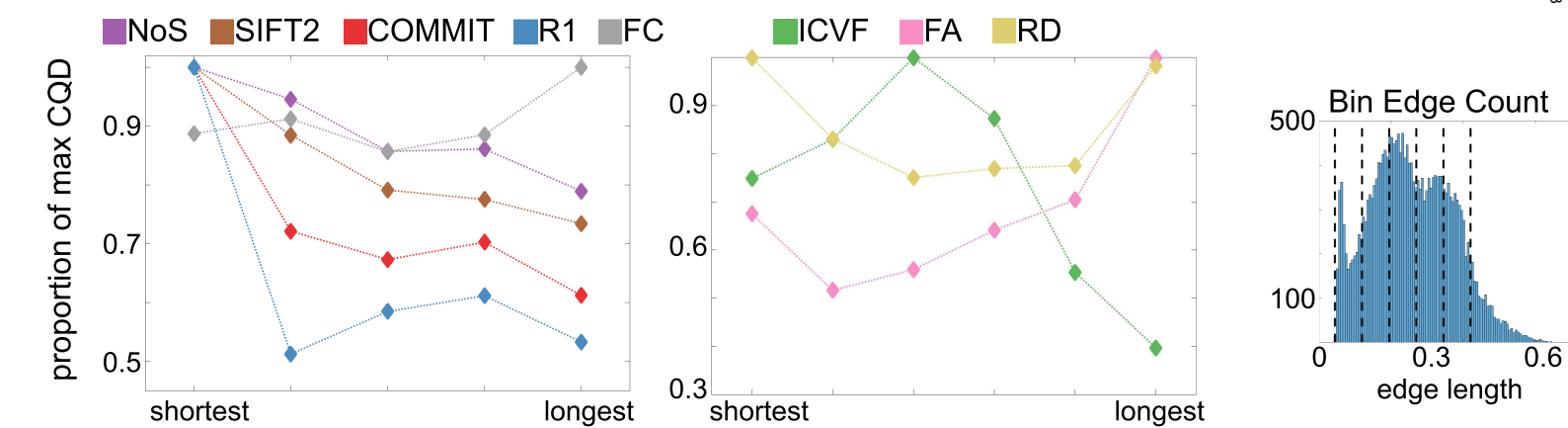
edge length

Figure 4

A edge weight correlations

vs Edge Length

vs FC

B residual edge weight correlations

vs FC
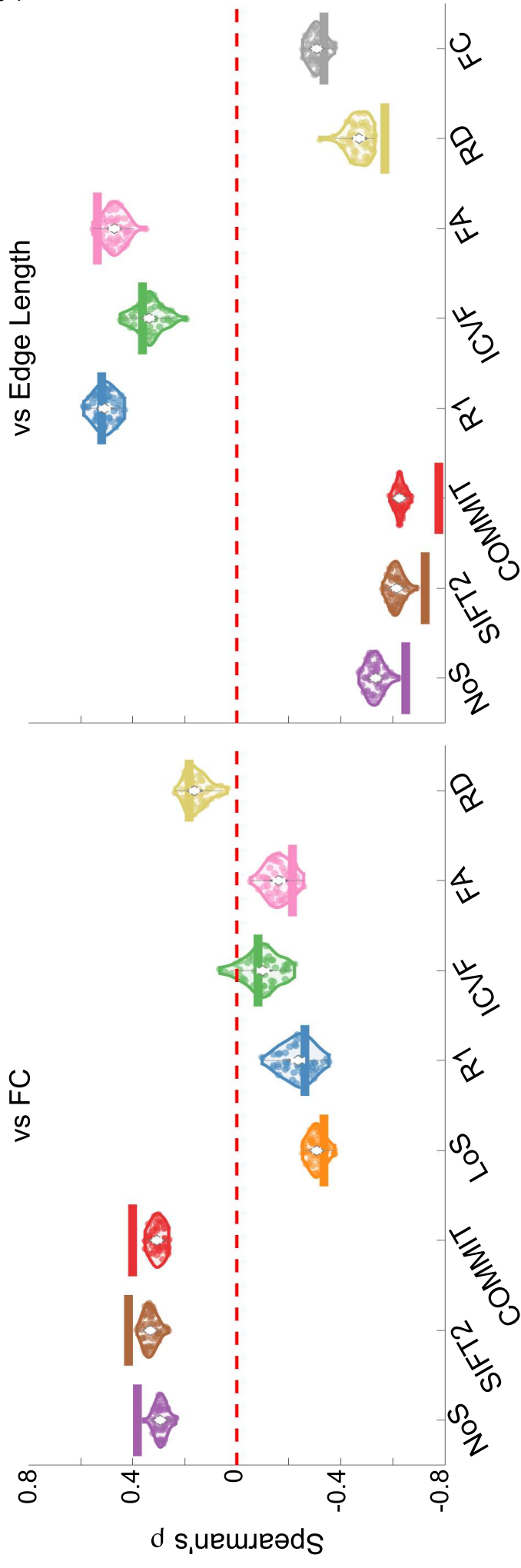
regress edge length

Figure 5
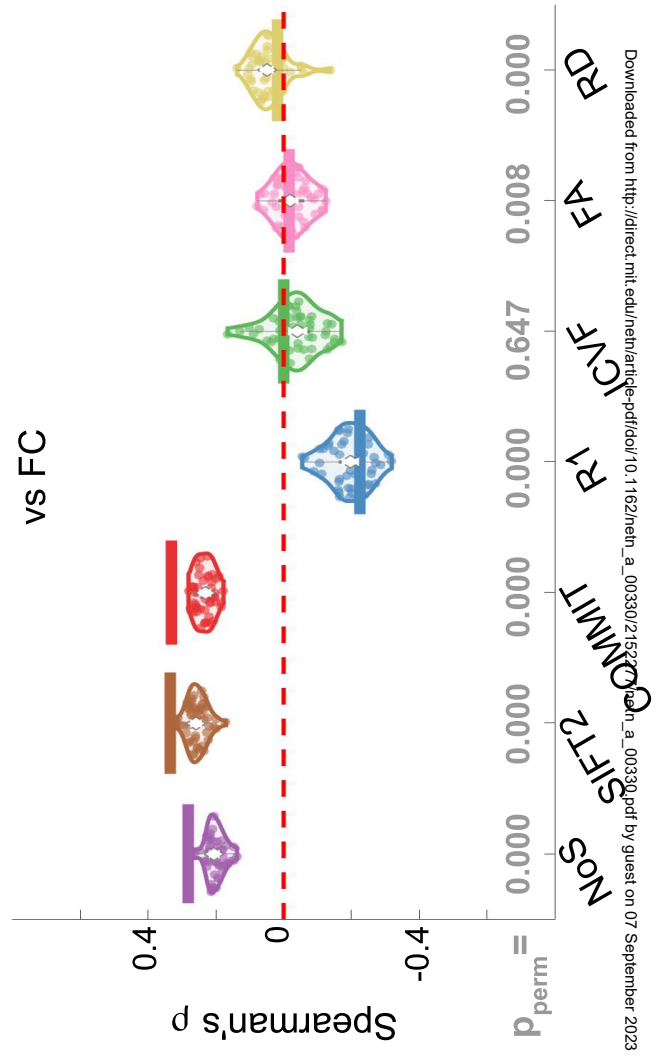
A residual edge weight correlations
subject & group
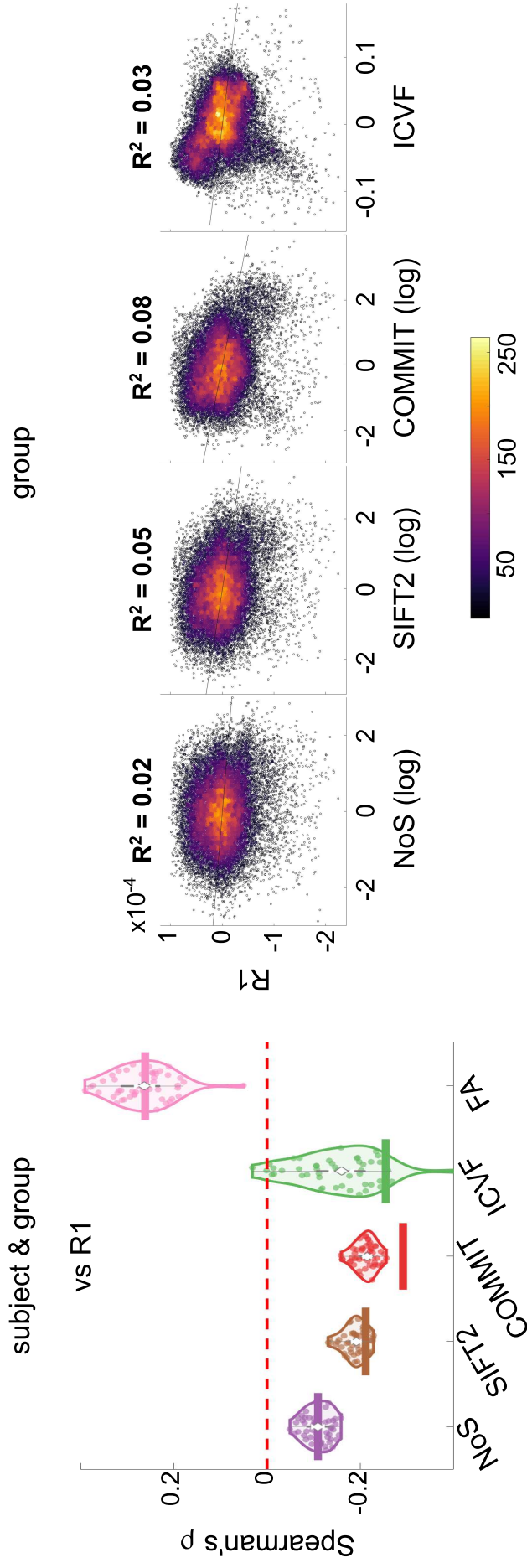
B R1 vs COMMIT across edge length bins
subject & group
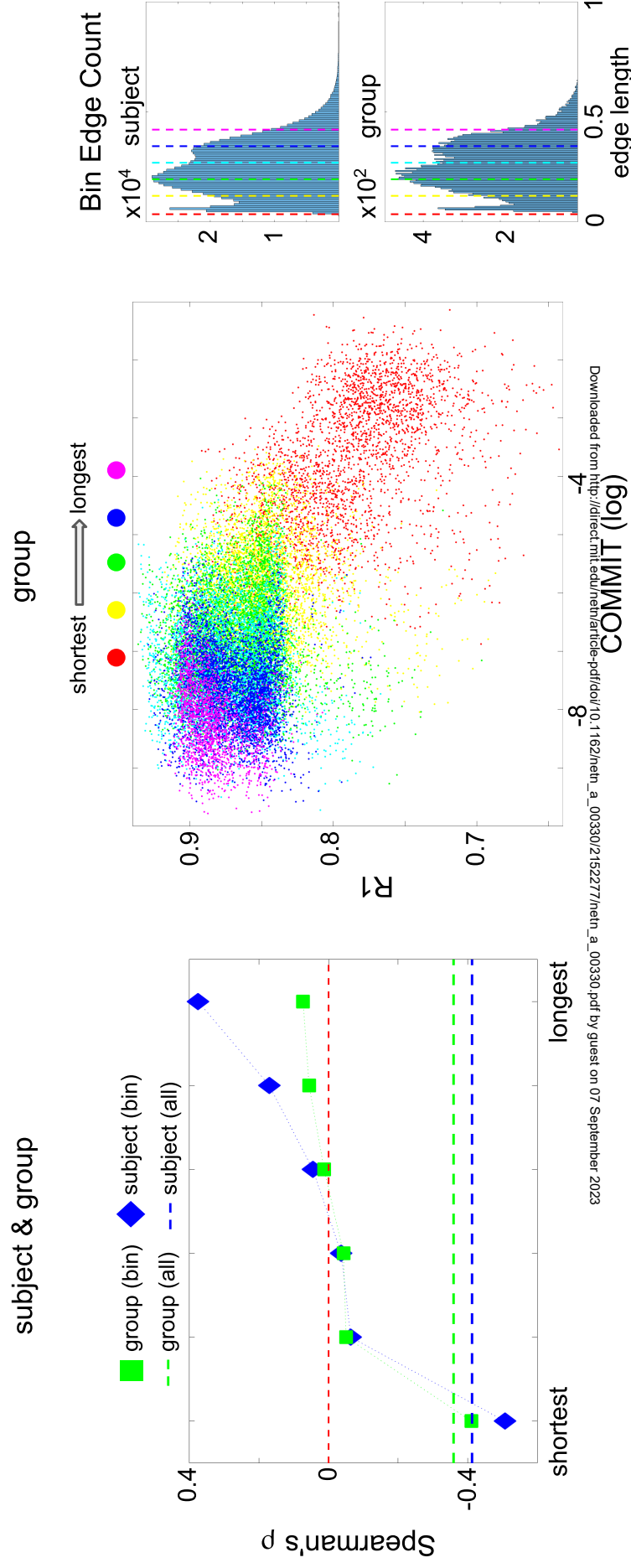
Figure 6

A normalized small-worldness

group

NoS
SIFT2
COMMIT

Binary
ICVF
RD
FA
R1

all tractometry networks

B normalized rich club

group

Φ_{norm}

Φ_{norm}

k level

C normalized hubness

group

R1
COMMIT
NoS
SIFT2
ICVF

average COMMIT & R1

Hubness Euclidean Distance

NoS
SIFT2
COMMIT
R1
ICVF
RD
FA

NoS SIFT2 COMMIT R1 ICVF RD FA

Supplemental Figure 1

A group & subject residual edge weight correlations with FC

B group residual edge weights

Supplemental Figure 2

A group residual edge weight correlations with R1

B group residual edge weights

Schaefer-100

Schaefer-200
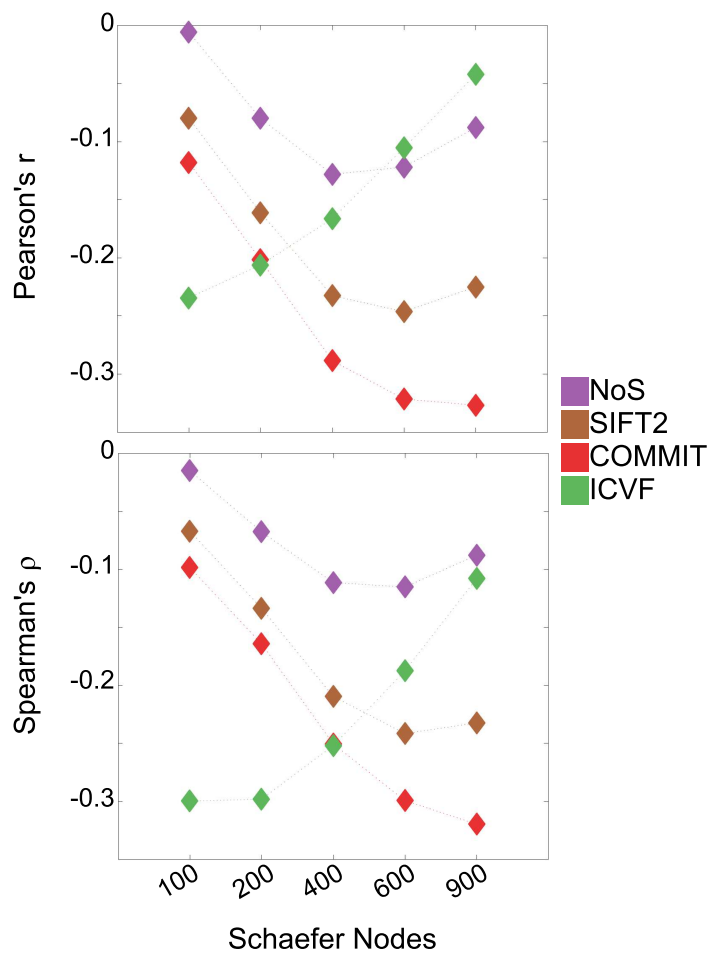
Schaefer-400

Schaefer-600
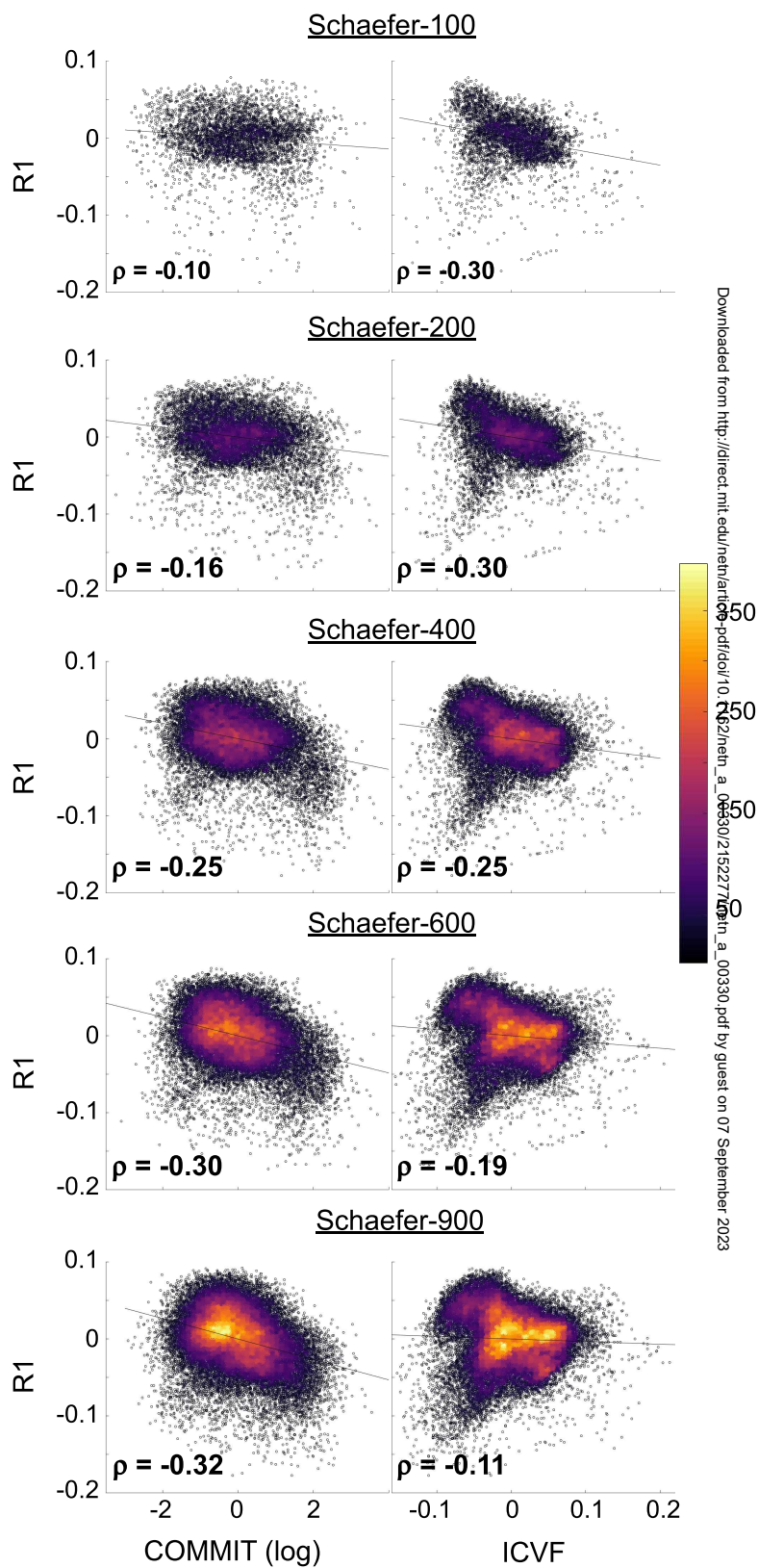
Schaefer-900

C edge weight correlations across edge length bins

R1 vs COMMIT (Schaefer-200)

Supplemental Figure 4
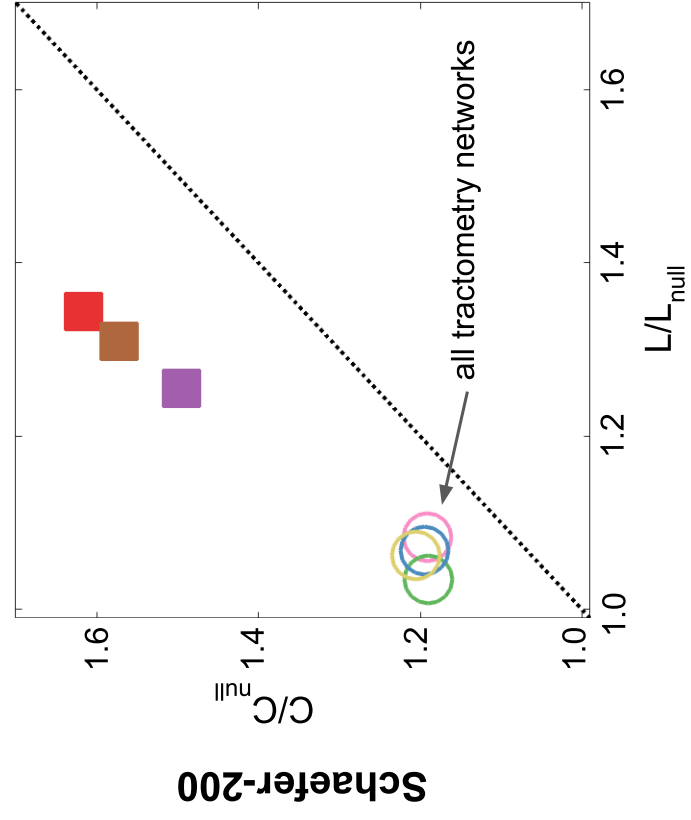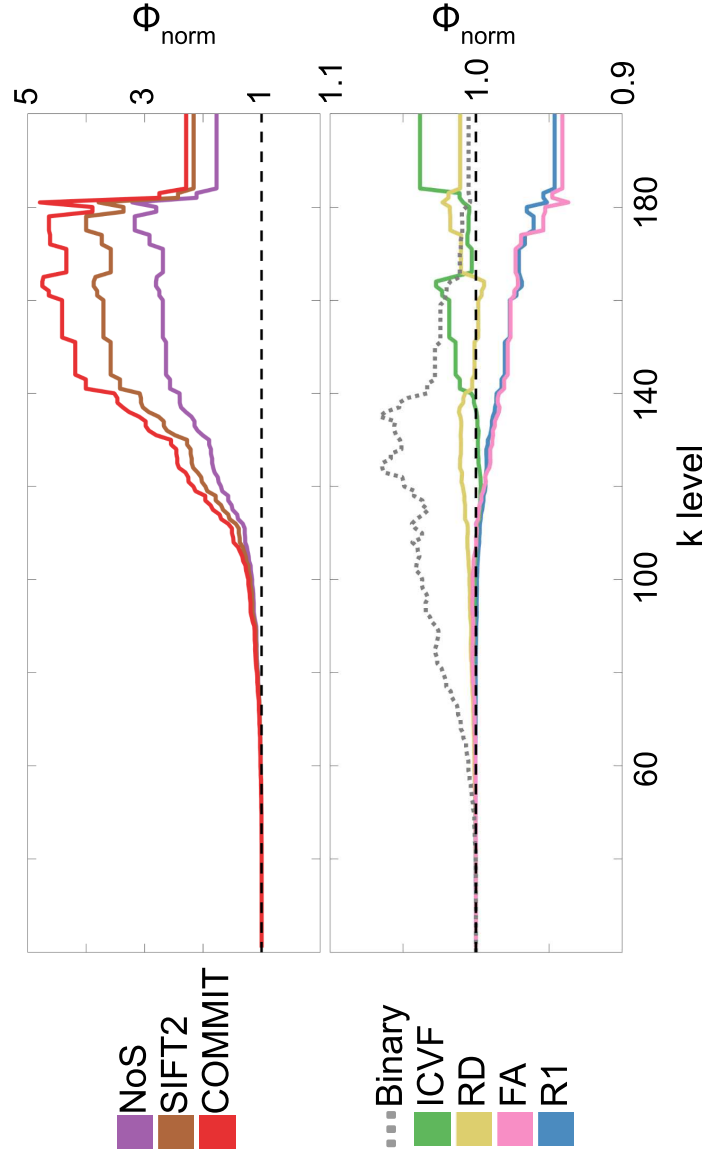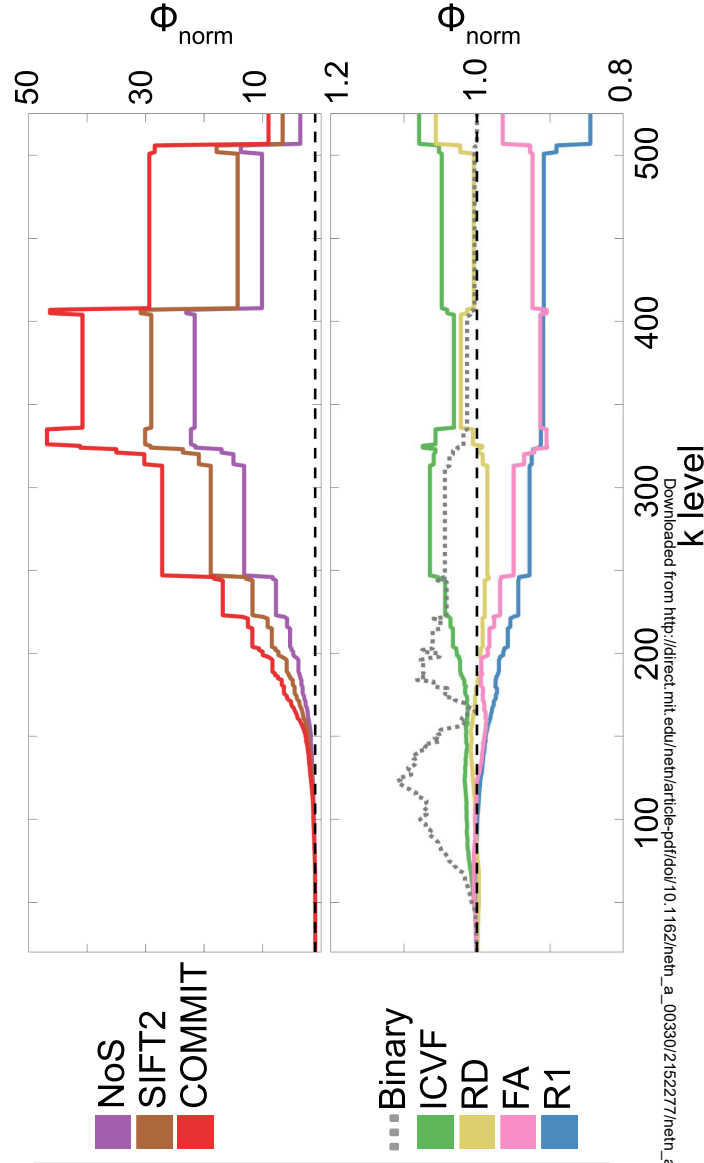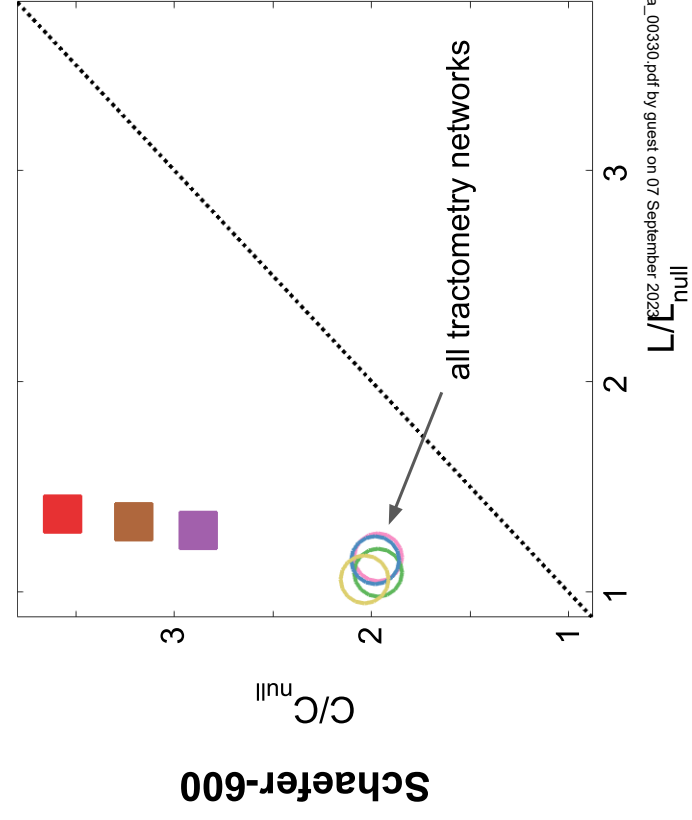
Group Normalized Hubness

Schaefer-200

Schaefer-400

Schaefer-600

Supplemental Figure 5

A residual edge weight correlations

subject & group

vs R1
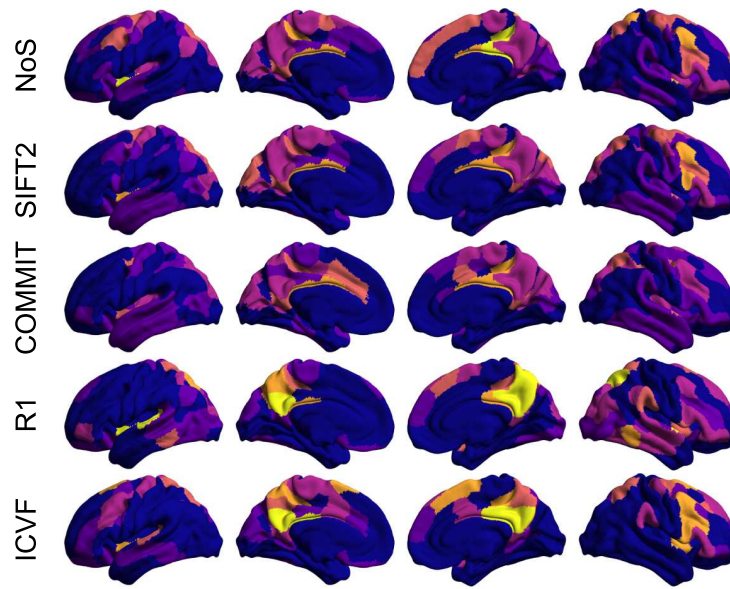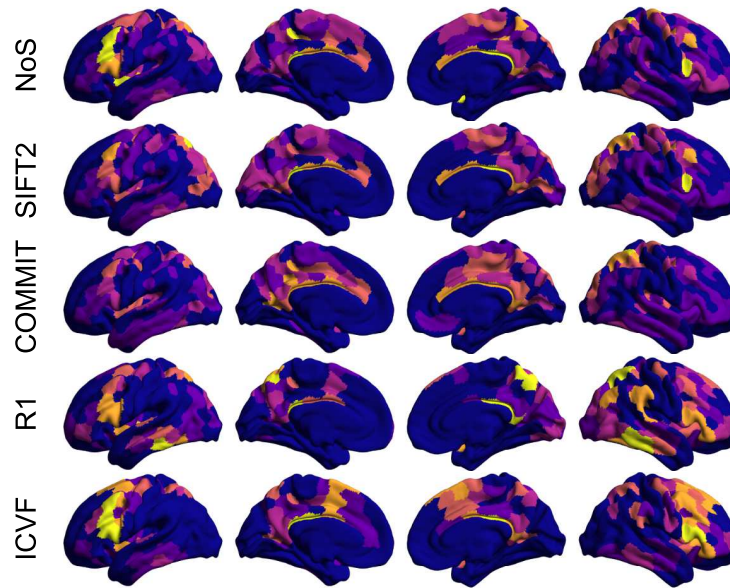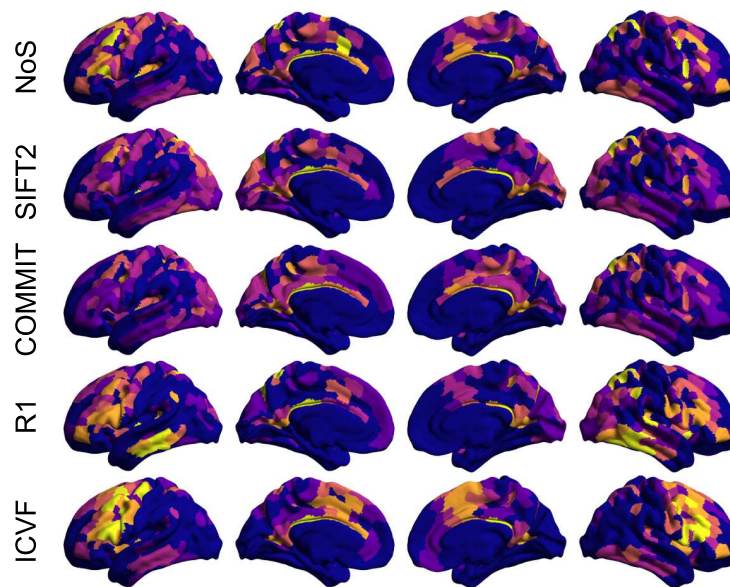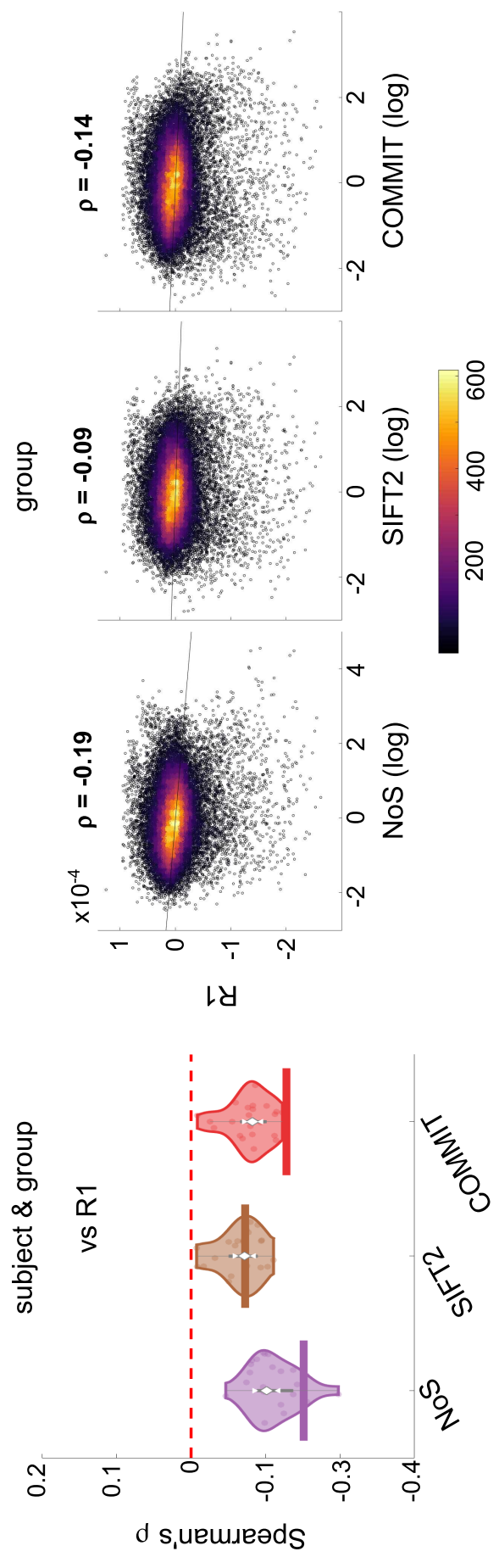
B edge weight correlations across edge length bins

R1 vs COMMIT

Bin Edge Count
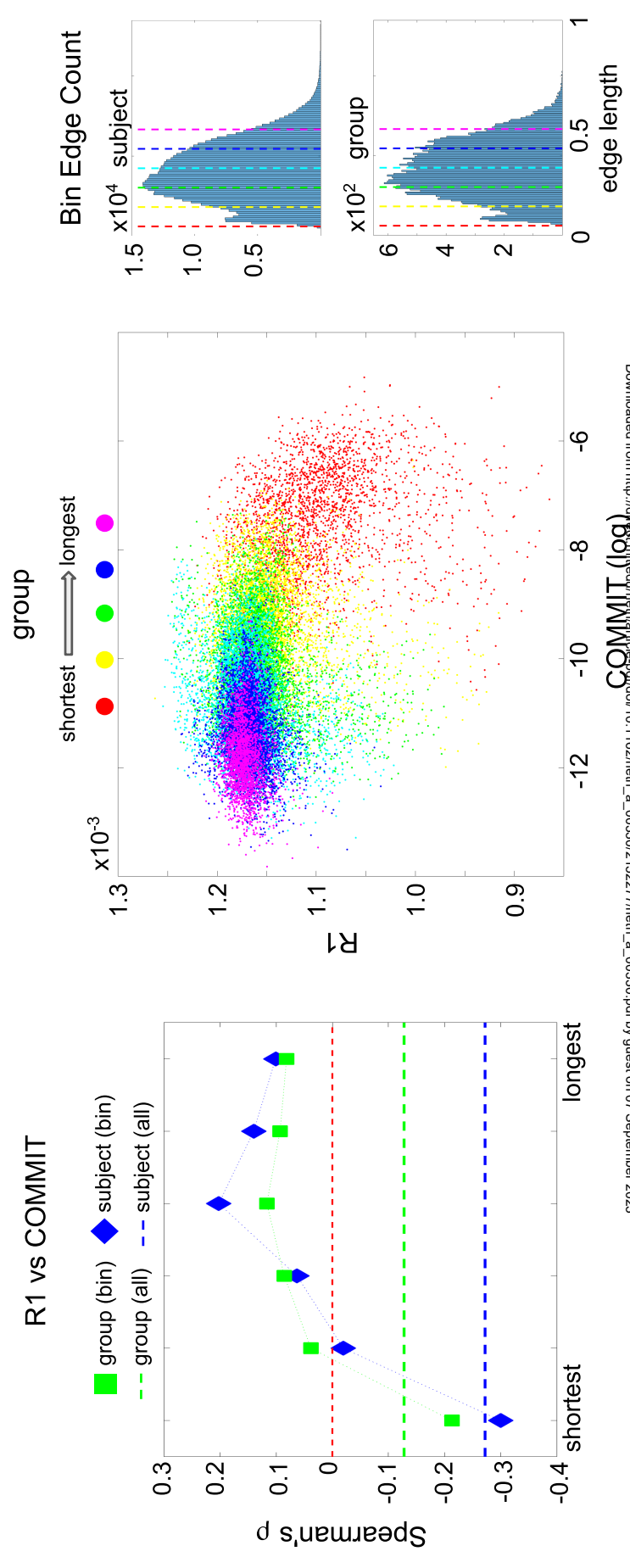
A   normalized small-worldness
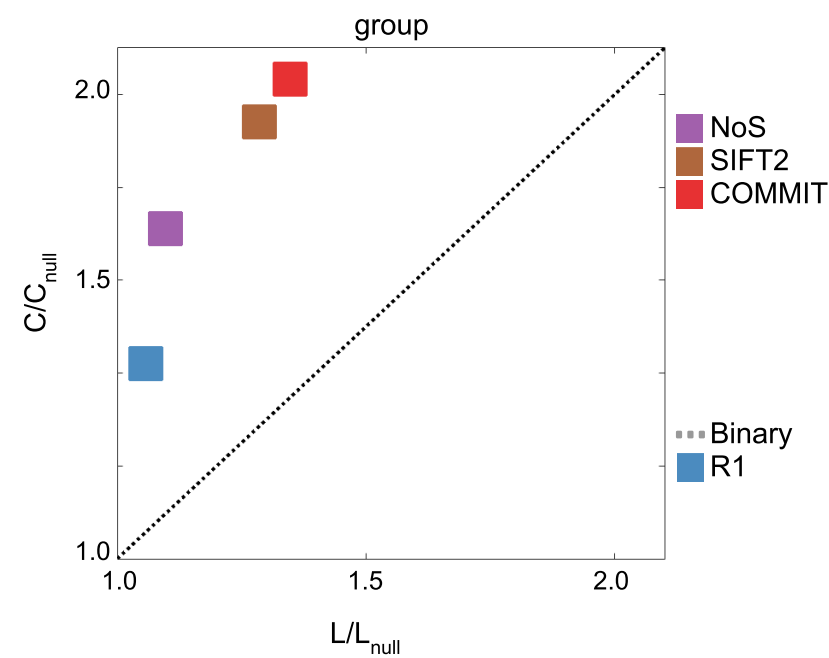
B   normalized rich club

C   normalized hubness

Group Permutation Testing
Spearman's ρ with **FC**
(edge-length regressed residuals)
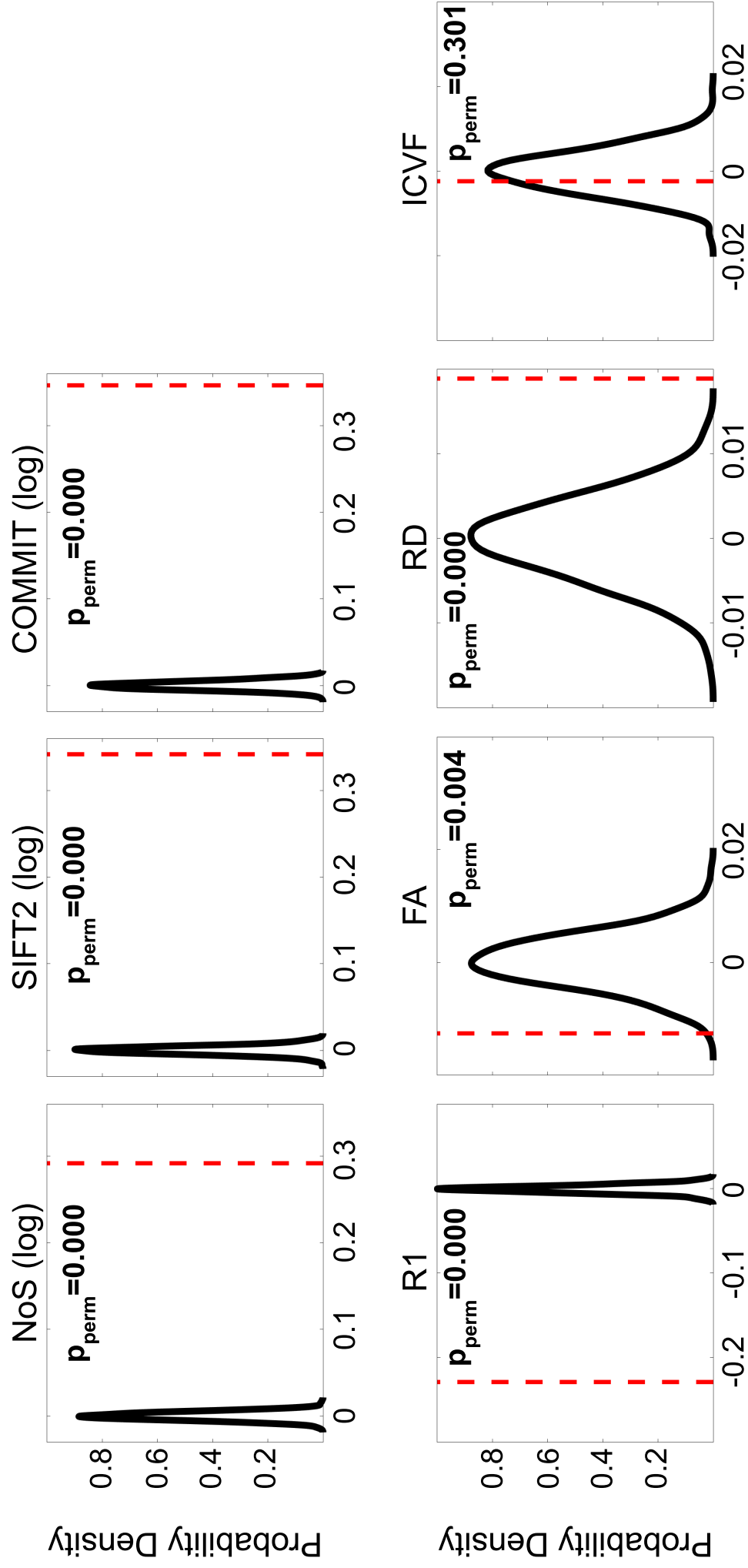
Group Permutation Testing
Spearman's ρ with **R1**
(edge-length regressed residuals)

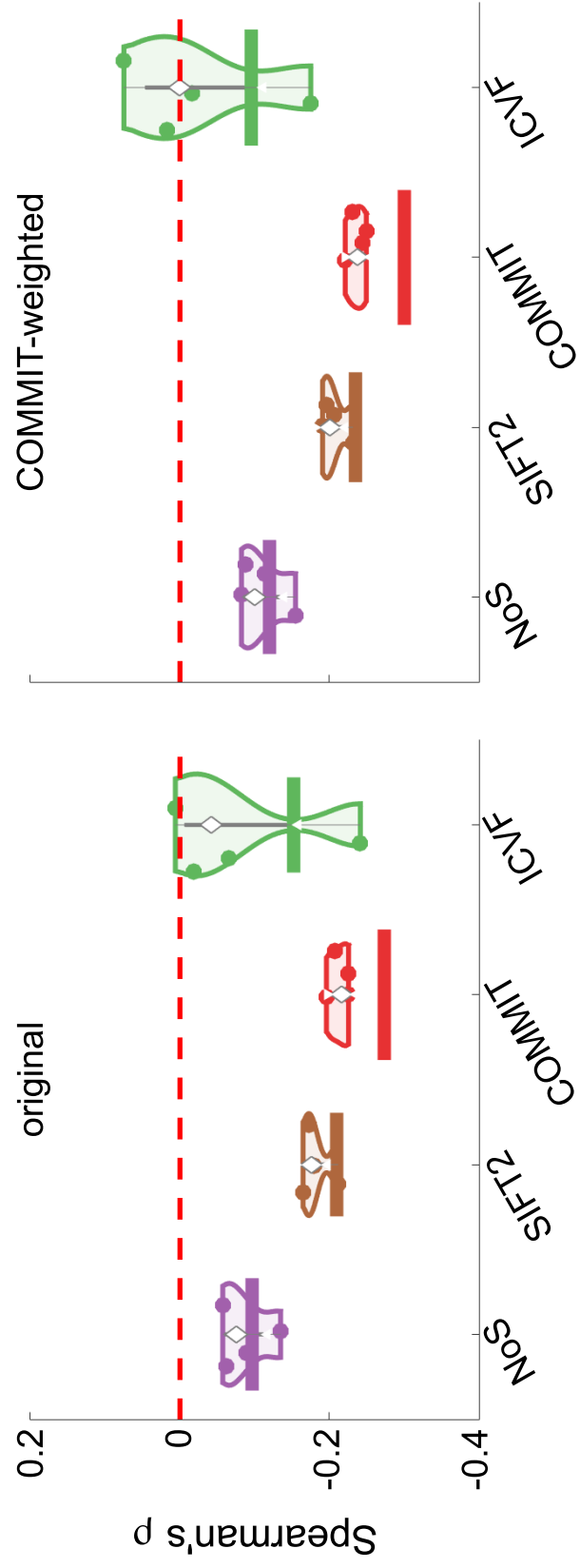**All p$_{perm}$ = 0.000**
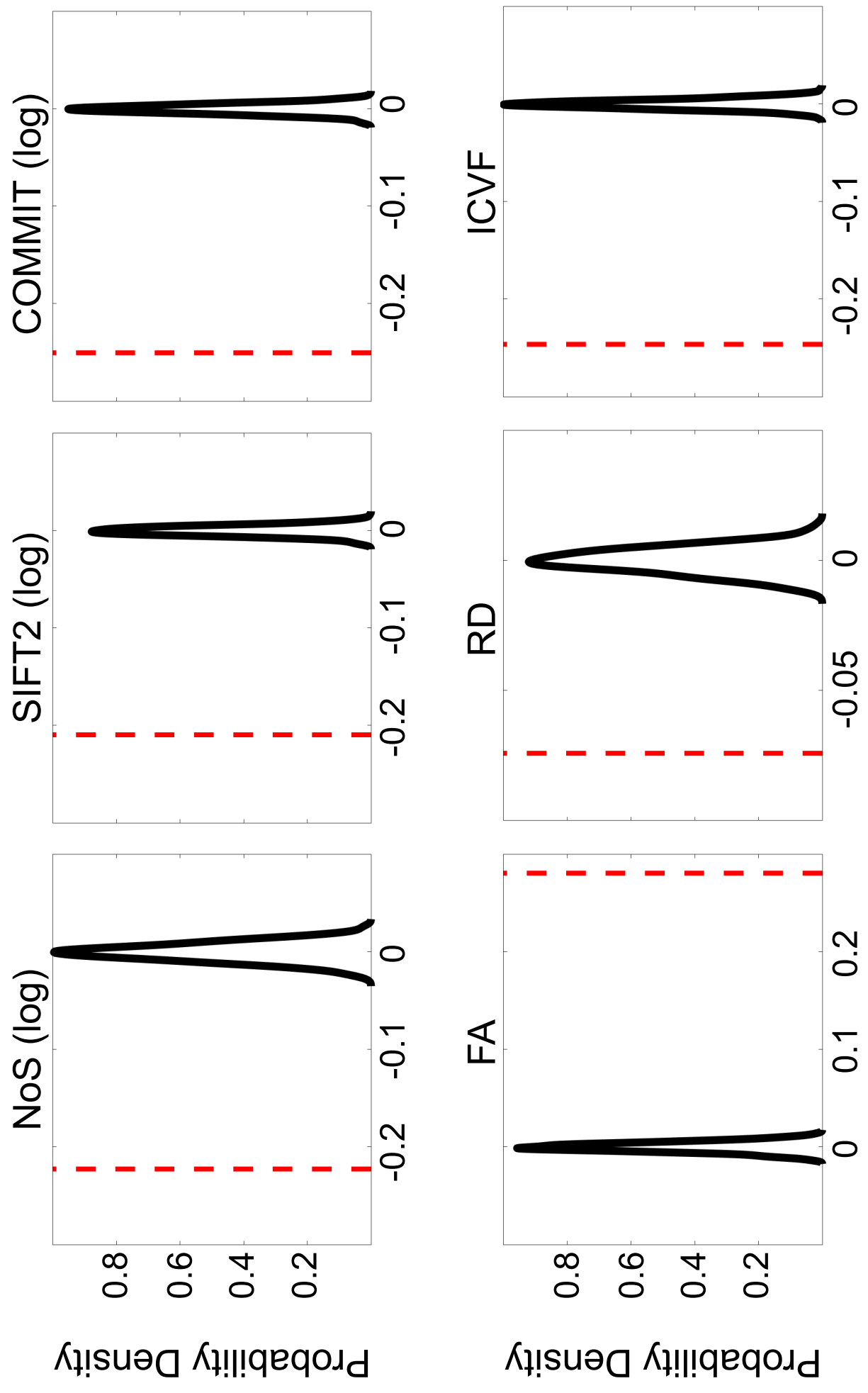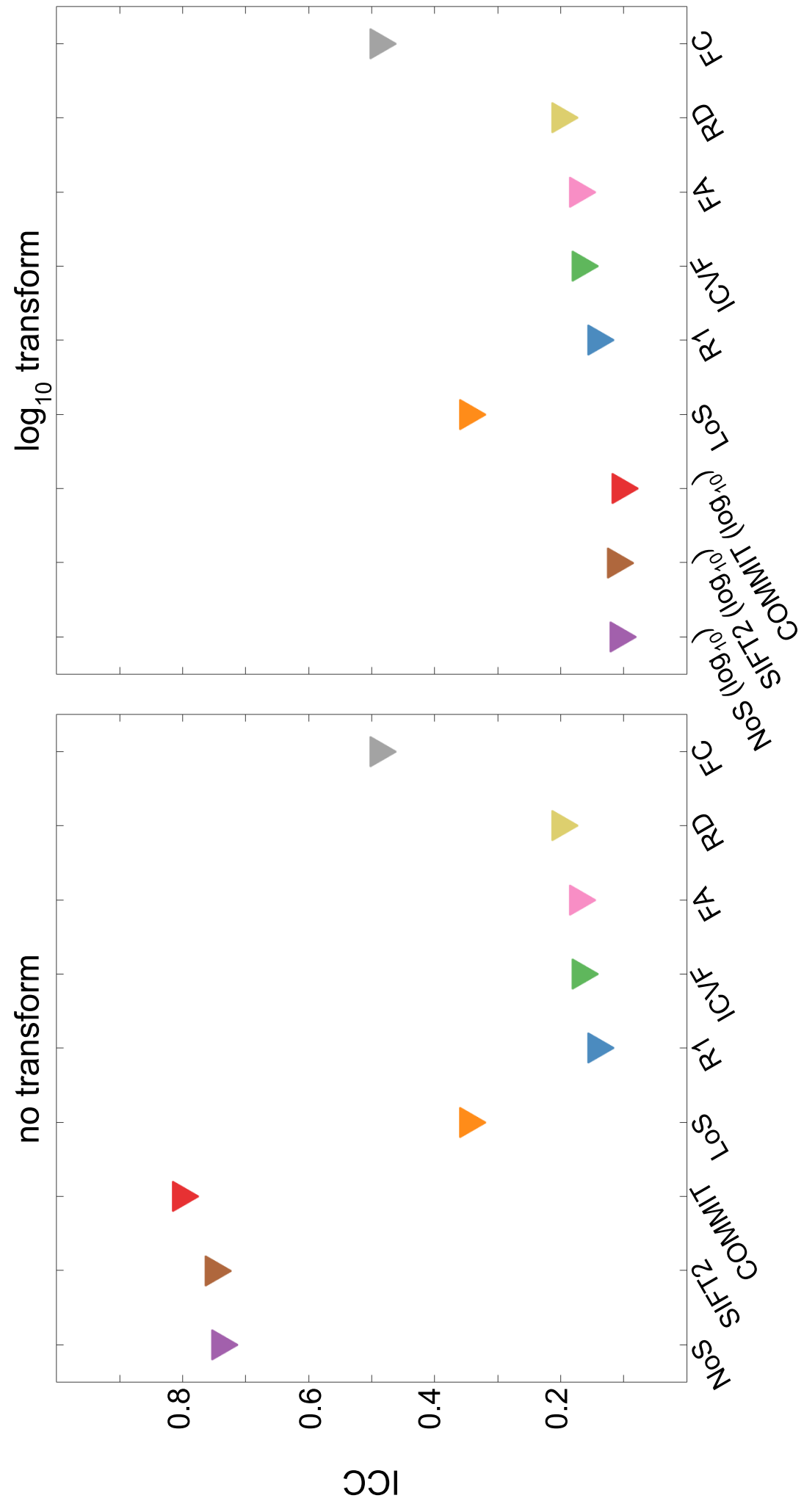
Supplemental Figure 9

Subject Edge Weight Distributions
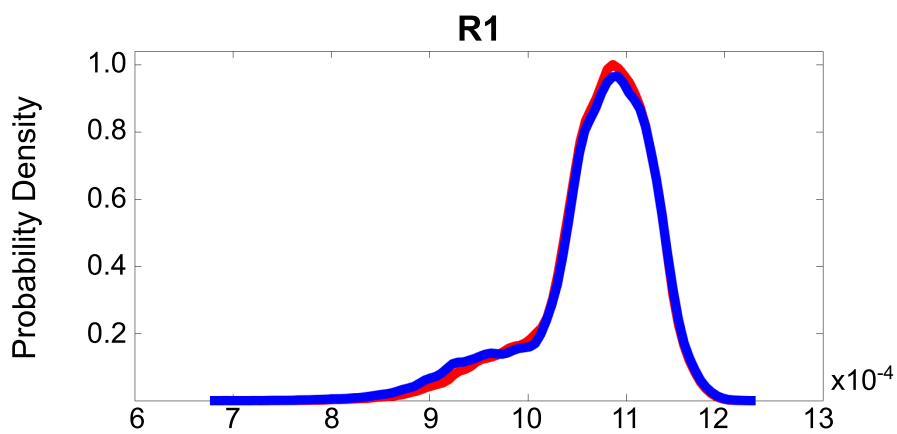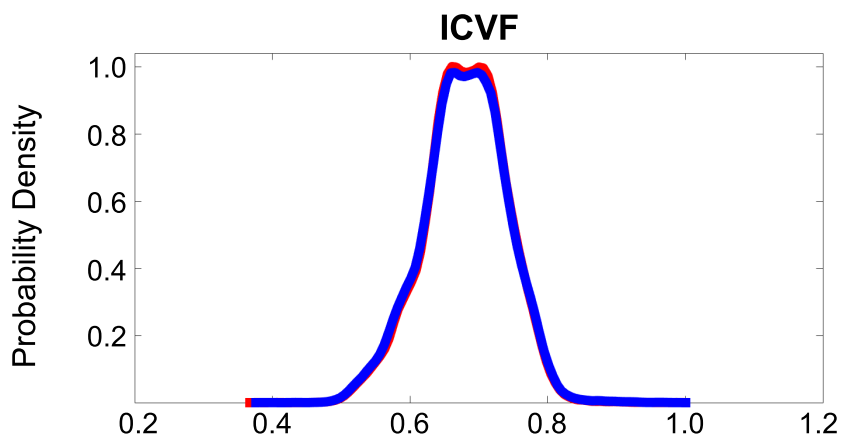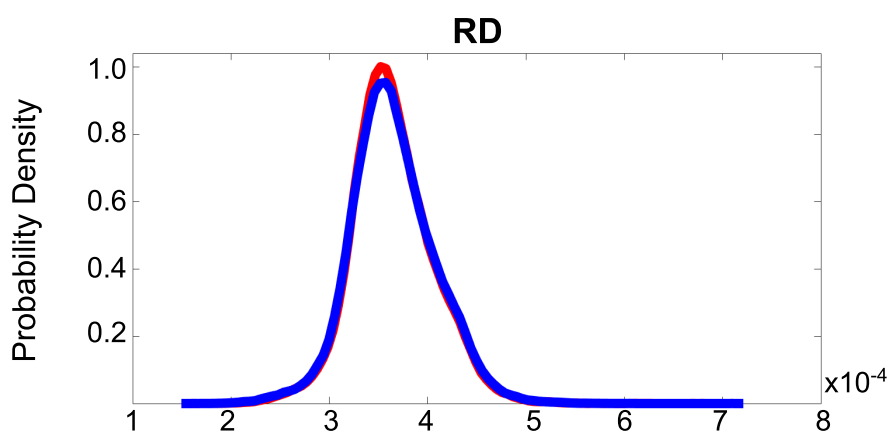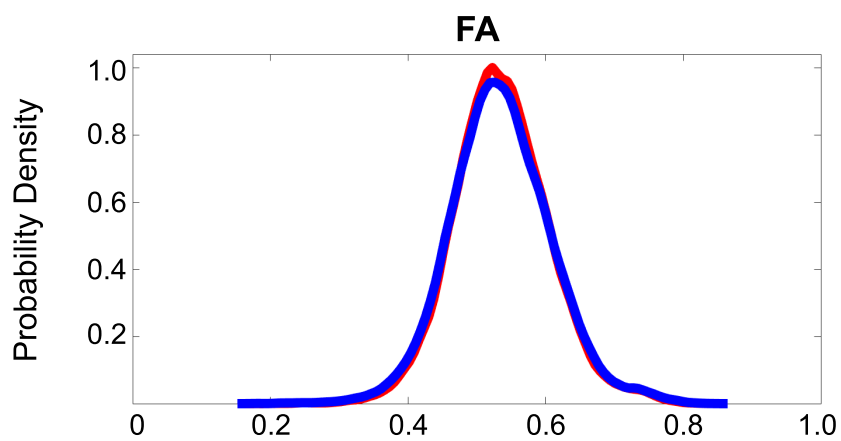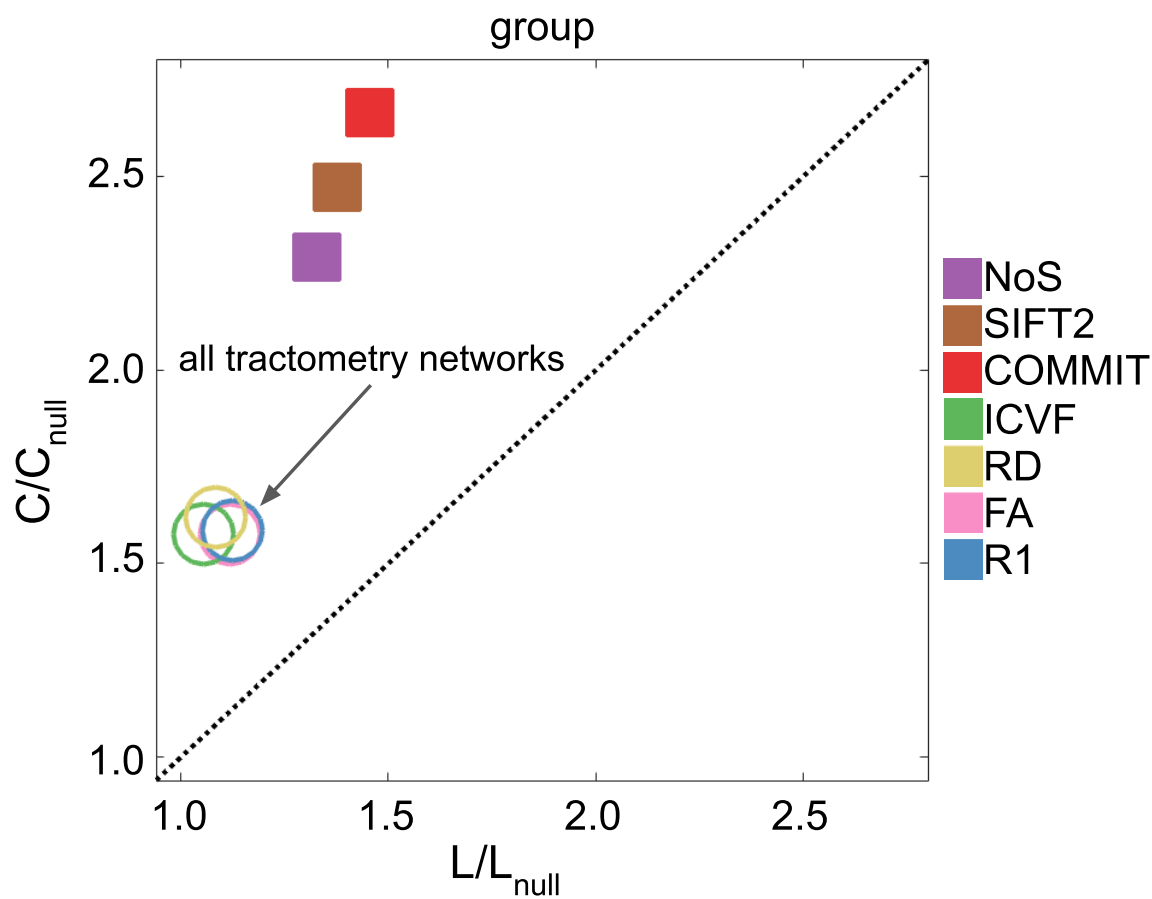
A residual edge weight correlations with FC
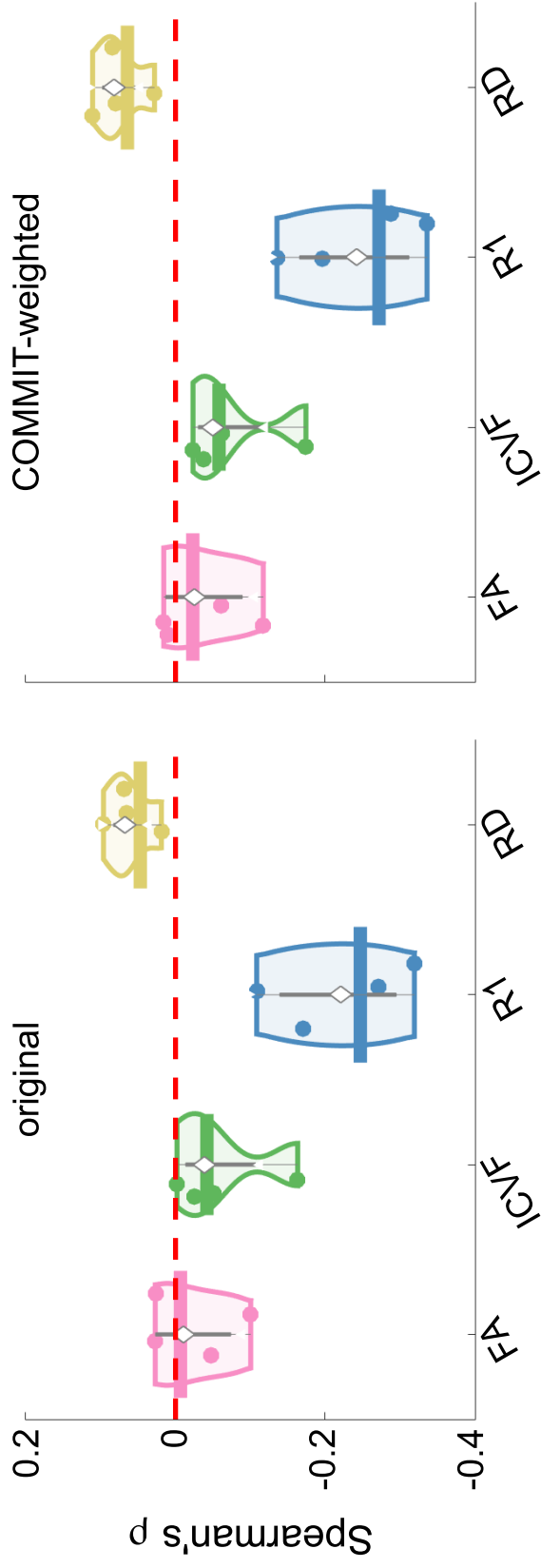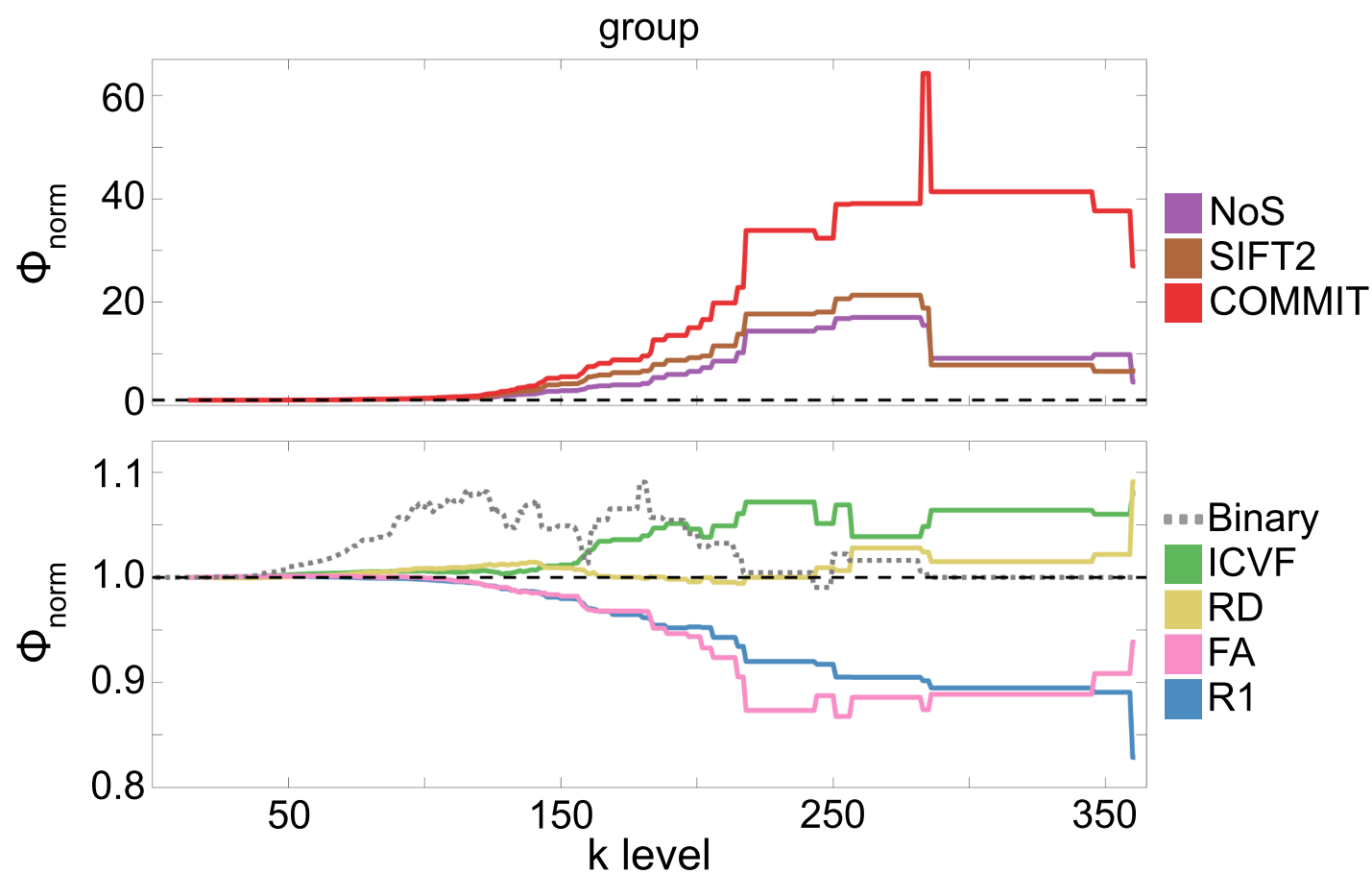
B residual edge weight correlations with R1

A normalized small-worldness

B normalized rich club
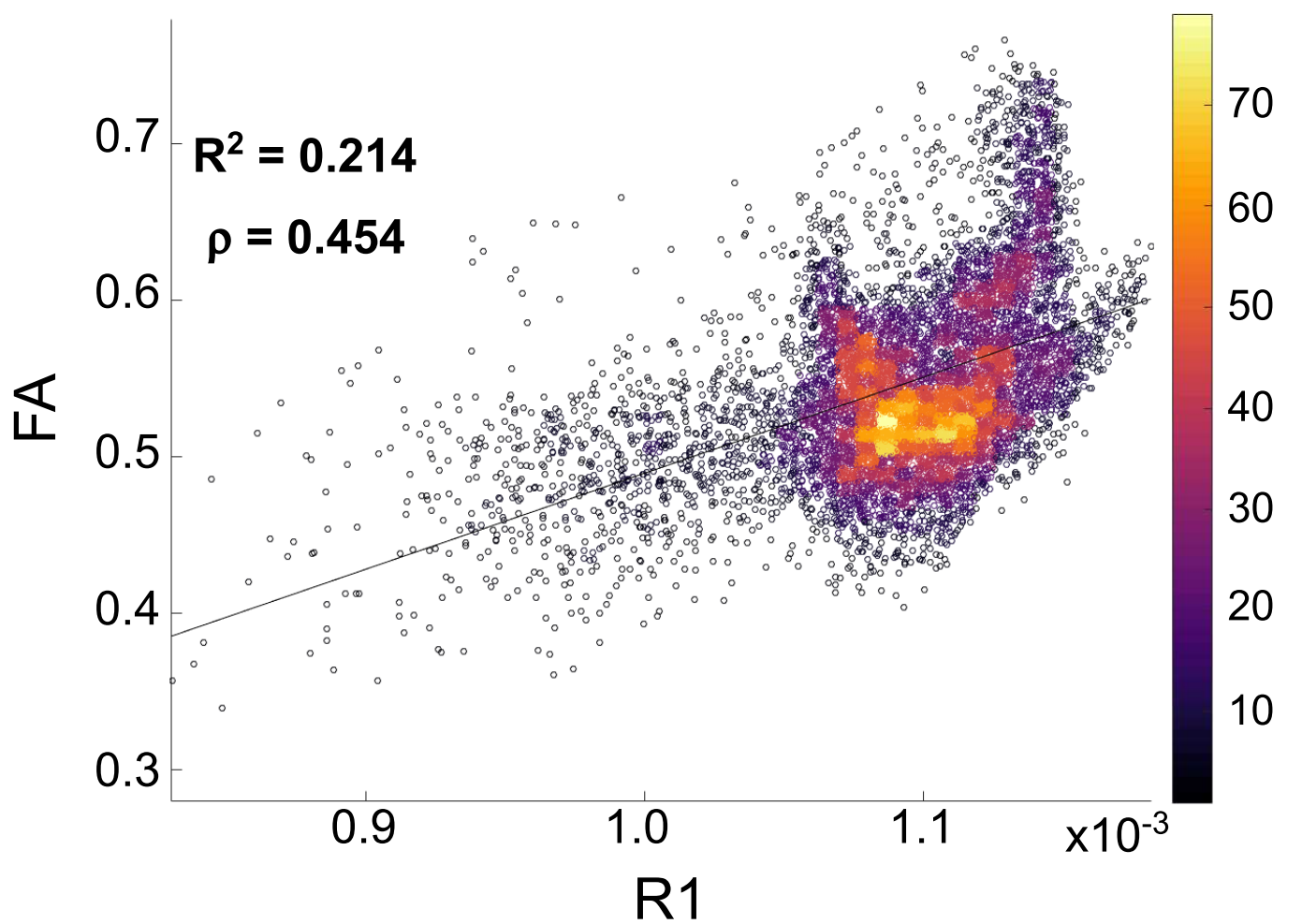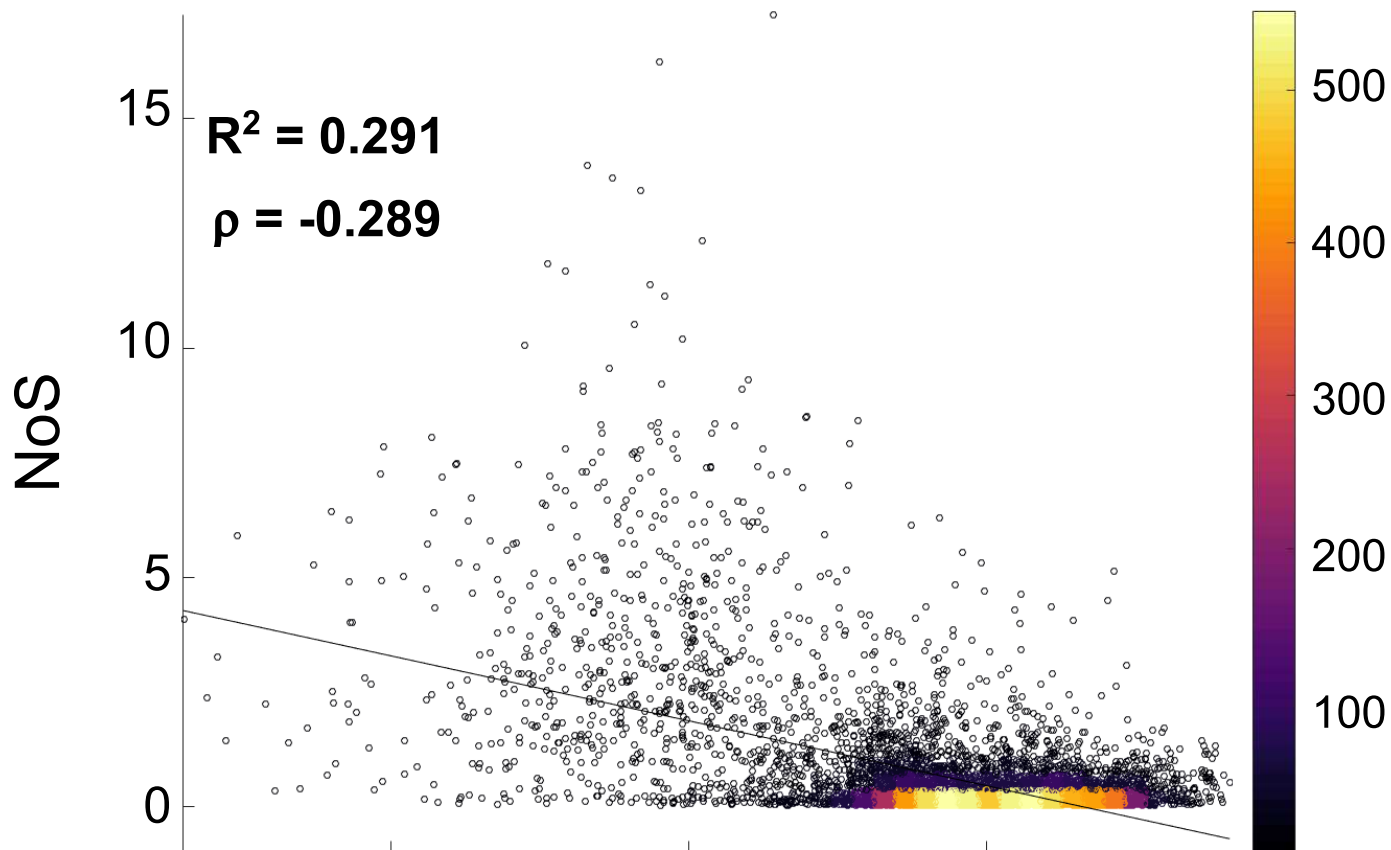
Edgewise Relationship of Edge Weights (not residuals)

group - Schaefer-200 - cortex only

$R^2 = 0.291$

$\rho = -0.289$

$R^2 = 0.214$

$\rho = 0.454$

NoS

FA

R1

Table

Short name	Long name	Method	Data source	Interpretation
LoS	Length of Streamlines	streamline-specific	diffusion MRI	Mean length of all streamlines connecting two nodes
NoS	Number of Streamlines	streamline-specific	diffusion MRI	Number of streamlines connecting two nodes; connection strength
SIFT2	Spherical-deconvolution Informed Filtering of Tractograms	streamline-specific	diffusion MRI	Fiber density from spherical deconvolution summed across streamlines; connection strength
COMMIT	Convex Optimization Modeling for Microstructure Informed Tractography	streamline-specific	diffusion MRI	Total intra-axonal cross-sectional area summed across streamlines; connection strength
R1	longitudinal relaxation rate	tractometry	multi-modal (diffusion + relaxometry)	$R_1 = 1/T_1$; index of tissue myelin content
FA	Fractional Anisotropy	tractometry	diffusion MRI	Diffusion directional dependence
RD	Radial Diffusivity	tractometry	diffusion MRI	Diffusion perpendicular to the principal axis
ICVF	Intra-Cellular Volume Fraction	tractometry	diffusion MRI	Neurite density

AUTHOR SUMMARY

For computational network models to provide mechanistic links between brain structure and function, they must be informed by networks in which edge weights quantify structural features relevant to brain function. Here, we characterized several weighted structural networks capturing multiscale features of white matter connectivity including total intra-axonal cross-sectional area and myelin density. We describe these networks in terms of edge weight distribution, variance and network topology, as well as their relationships with each other, edge length and function. Overall, these findings support the joint use of structural networks weighted by the total intra-axonal cross-sectional area and myelin content of white matter tracts in structure-function models. This thorough characterization serves as a benchmark for future investigations of weighted structural brain networks.