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Spatial and temporal pattern of structure-function coupling of human brain connectome with development

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Abstract

Brain structural circuitry shapes a richly patterned functional synchronization, supporting for complex cognitive and behavioural abilities. However, how coupling of structural connectome (SC) and functional connectome (FC) develops and its relationships with cognitive functions and transcriptomic architecture remain unclear. We used multimodal magnetic resonance imaging data from 439 participants aged 5.7 to 21.9 years to predict functional connectivity by incorporating intracortical and extracortical structural connectivity, characterizing SC-FC coupling. Our findings revealed that SC-FC coupling was strongest in the visual and somatomotor networks, consistent with evolutionary expansion, myelin content, and functional principal gradient. As development progressed, SC-FC coupling exhibited heterogeneous alterations dominated by an increase in cortical regions, broadly distributed across the somatomotor, frontoparietal, dorsal attention, and default mode networks. Moreover, we discovered that SC-FC coupling significantly predicted individual variability in general intelligence, mainly influencing frontoparietal and default mode networks. Finally, our results demonstrated that the heterogeneous development of SC-FC coupling is positively associated with genes in oligodendrocyte-related pathways and negatively associated with astrocyte-related genes. This study offers insight into the maturational principles of SC-FC coupling in typical development.

eLife assessment

This study presents a **useful** exploration of the complex relationship between structure and function in the developing human brain using a large-scale imaging dataset from the Human Connectome Project in Development and gene expression profiles from the Allen Brain Atlas. The evidence supporting the claims of the authors is **solid**, although the inclusion of more systematic analyses of structural and functional connectivity with respect to myelin measures and oligodendrocyte-related genes, and also more details regarding the imaging analyses, cognitive scores, and design and validation strategies, would have strengthened the paper. The work will be of interest to developmental biologists and neuroscientists seeking to elucidate structure-function relationships in the human brain.

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Introduction

In neural circuitry, long-range (extracortical) interconnections among local (intracortical) microcircuits shape and constrain the large-scale functional organization of neural activity across the cortex[1–5]. The coupling of structural connectome (SC) and functional connectome (FC) varies greatly across different cortical regions reflecting anatomical and functional hierarchies[1, 6–9] and is regulated in part by genes[6, 8], as well as its individual differences relates to cognitive function[8, 9]. Despite its fundamental importance, our understanding of the changes in SC-FC coupling with development is currently limited. Specifically, the alterations in SC-FC coupling during development, its association with cognitive functions, and the underlying spatial transcriptomic mechanisms remain largely unknown.

Network modelling of the brain enables the characterization of complex information interactions at a system level and provides natural correspondences between structure and function in the cortex[7, 10]. Advances in diffusion MRI (dMRI) and tractography techniques have allowed the *in vivo* mapping of the white matter (WM) connectome (WMC), which depicts extracortical excitatory projections between regions[11]. The T1- to T2-weighted (T1w/T2w) ratio of MRI has been proposed as a means of quantifying microstructure profile covariance (MPC), which reflects a simplified recapitulation in cellular changes across intracortical laminar structure[6, 12–15]. Resting state functional MRI (rs-fMRI) can be used to derive the FC, which captures the synchronization of neural activity[16]. A variety of statistical[6, 8, 9], communication[1, 7], and biophysical[5, 17] models have been proposed to study the SC-FC coupling. The communication model is particularly useful because it not only depicts indirect information transmission but also takes into account biodynamic information within acceptable computational complexity[7, 18]. However, most studies have relied on WMC-derived extracortical communications as SC to predict FC, while ignoring the intracortical microcircuits, the MPC. In the present study, we propose that incorporating both intracortical and extracortical SC provides a more comprehensive perspective for characterizing the development of SC-FC coupling.

Previous studies in adults have revealed that the SC-FC coupling is strongest in sensory cortex regions and weakest in association cortex regions, following the general functional and cytoarchitectonic hierarchies of cortical organization[1]. This organization may occur due to structural constraints, wherein cortical areas with lower myelination and weaker WM connectivity tend to have more dynamic and complex functional connectivity[1, 8]. Large-

scale association networks emerged over evolution by breaking away from the rigid developmental programming found in lower order sensory systems[19], facilitating regional and individual specialization[20]. In terms of developmental changes in SC-FC coupling, a statistical model-based study[9] identified positive age-related changes in some regions, while fewer regions exhibited negative changes. Furthermore, there is evidence that SC-FC coupling is linked to cognitive functions in healthy children[21], adults[8, 22] and patients[23], suggesting that it may be a critical brain indicator that encodes individual cognitive differences. Nonetheless, a more comprehensive investigation is needed to understand the precise pattern of SC-FC coupling over development and its association with cognitive functions.

Cortical SC-FC coupling is highly heritable[8] and related to heritable connectivity profiles[6], suggesting that the development of coupling may be genetically regulated. The Allen Human Brain Atlas (AHBA)[24] is a valuable resource for identifying genes that co-vary with brain imaging phenotypes and for exploring potential functional pathways and cellular processes via enrichment analyses[25–27]. For instance, a myeloarchitectural study showed that enhanced myelin thickness in mid-to-deeper layers is specifically associated with the gene expression of oligodendrocytes[28]. Another functional study found that the expression levels of genes involved in calcium ion-regulated exocytosis and synaptic transmission are associated with the development of a differentiation gradient[29]. However, the transcriptomic architecture underlying the development of SC-FC coupling remains largely unknown.

In this study, we analysed data obtained from the Lifespan Human Connectome Project Development (HCP-D)[30], which enrolled healthy participants ranging in age from 5.7 to 21.9 years. Our main objective was to investigate the SC-FC coupling of brain connectome and characterize its developmental landscapes. Specifically, we aimed to determine whether the SC-FC coupling encodes individual differences in cognition during development. Finally, we explored the genetic and cellular mechanisms underlying the development of SC-FC coupling of brain connectome. To assess the reproducibility of our findings, sensitivity and replication analyses were performed with a different tractography algorithm and a split-half independent validation method.

Results

We selected 439 participants (5.7 – 21.9 years of age, 207 males) in the HCP-D dataset who met our inclusion criteria: available high-quality T1/T2, dMRI, and rs-fMRI data that met the quality control thresholds. For each participant, we generated multiple connectomes using 210 cortical regions from the Human Brainnetome Atlas (BNA)[31], which comprised MPC, WMC, and FC. Intracortical connectivity was represented by MPC. According to the WMC, twenty-seven weighted communication models[7] were calculated to characterize geometric, topological, or dynamic connectivity properties. Further details on these models can be found in Text S1. After analysis, we found that communicability[32], mean first passage times of random walkers[33], and flow graphs (timescales=1) provided the optimal combination of extracortical connectivity properties because of significantly predicting FC (p<0.05, 1,000 spin test permutations, Table S1). We used these three models to represent the extracortical connectivity properties in subsequent discovery and reproducibility analyses (Figure S1).

Spatial pattern of cortical SC-FC coupling

We used SCs (MPC and three WMC communication models) to predict FC per node based on a multilinear model[1] (**Figure 1**), and quantified the nodewise SC-FC coupling as an adjusted coefficient of determination r^2 . We observed that the grouped SC-FC coupling varied across cortical regions (mean adjusted r^2 = 0.14 ± 0.08, adjusted r^2 range = [0.03, 0.45], **Figure 2A**), and regions with significant coupling were located in the middle frontal gyrus, precentral gyrus,

paracentral lobule, superior temporal gyrus, superior parietal lobule, postcentral gyrus, cingulate gyrus, and occipital lobe (p<0.05, 1,000 spin test permutations, **Figure 2B**). Similar heterogeneous patterns of coupling were observed when categorizing cortical regions into seven functional subnetworks[34] (visual, somatomotor, dorsal attention, ventral attention, limbic, frontoparietal and default mode networks). In the visual, somatomotor, default mode and ventral attention networks, SC significantly predict FC variance (p<0.05, 1,000 spin test permutations, **Figure 2C**). The visual and somatomotor networks had higher coupling values than the other networks (p<0.05, Kruskal-Wallis ANOVA, **Figure 2C**). We further investigated the alignment between SC-FC coupling and three fundamental properties of brain organization: evolution expansion[35], myelin content[36], and functional principal gradient[37].

Our findings reveal a negative association between regional distribution of SC-FC coupling and evolution expansion (Spearman's r=-0.52, p<0.001, 1,000 spin test permutations, **Figure 2D**), as well as with the functional principal gradient (Spearman's r=-0.46, p<0.001, 1,000 spin test permutations, **Figure 2F**). Conversely, nodes exhibiting higher SC-FC coupling tended to exhibit higher myelin content (Spearman's r=0.49, p<0.001, 1,000 spin test permutations, **Figure 2E**). In addition, the coupling pattern based on other models (using only MPC or only SCs to predict FC) and the comparison between the models were shown in Figure S2A-C.

Additionally, we applied Haufe's inversion transform[38] to yield predictor weights of various SCs, where higher or lower values indicate stronger positive or negative correlations with FC. Our results demonstrated that different SCs had preferential contributions to FC variance across cortical regions to explain FC variance (p<0.05, FDR corrected, Kruskal-Wallis ANOVA, **Figure 2G**). Specifically, in the MPC, regions with positive correlation were the orbital gyrus, precentral gyrus, right middle temporal gyrus and temporoparietal junction, while regions with negative correlations were the left superior frontal gyrus, inferior parietal lobule and bilateral cingulate gyrus. Regarding WMC communication models, the communicability and flow graphs tended to stronger higher positive correlations in the visual, limbic and default mode networks, whereas the mean first passage time had stronger negative correlations in the somatomotor, limbic and frontoparietal networks.

Age-related changes in SC-FC coupling with development

To track changes in SC-FC coupling during development, we used a general linear model to assess the effect of age on nodal SC-FC coupling, while controlling for sex, intracranial volume, and in-scanner head motion. Our results revealed that the whole-cortex average coupling increased during development (β_{age}=1.05E-03, F=3.76, p=1.93E-04, r=0.20, p=3.20E-05, **Figure 3A**). Regionally, the SC-FC coupling of most cortical regions increased with age (p<0.05, FDR corrected, **Figure 3B**), particularly that in the frontal lobe, middle temporal gyrus, inferior temporal gyrus, parietal lobe, cingulate gyrus and lateral occipital cortex. Conversely, cortical regions with significantly decreased SC-FC coupling (p<0.05, FDR corrected, **Figure 3B**) were located in left orbital gyrus, left precentral gyrus, right superior and inferior temporal gyrus, left fusiform gyrus, left superior parietal lobule, left postcentral gyrus, insular gyrus, and cingulate gyrus. Age correlation coefficients distributed within functional subnetworks were shown in **Figure 3C**. Regarding mean SC-FC coupling within functional subnetworks, the somatomotor (β_{age}=2.39E-03, F=4.73, p=3.10E-06, r=0.25, p=1.67E-07, **Figure 3E**), dorsal attention (β_{age} =1.40E-03, F=4.63, p=4.86E-06, r=0.24, p=2.91E-07, **Figure 3F**), frontoparietal (β_{age}=2.11E-03, F=6.46, p=2.80E-10, r=0.33, p=1.64E-12, **Figure 3I**) and default mode (β_{age}=9.71E-04, F=2.90, p=3.94E-03, r=0.15, p=1.19E-03, **Figure 3J**) networks significantly increased with age and exhibited greater increase. No significant correlations were found between developmental changes in SC-FC coupling and the fundamental properties of cortical organization. Additionally, weights of different SCs varied with age, showing that MPC weight was positively correlated with age and that the weights of WMC communication models were stable (Figure S3-S6). The age-related patterns of SC-FC coupling based other coupling models were shown in Figure S2D-F.

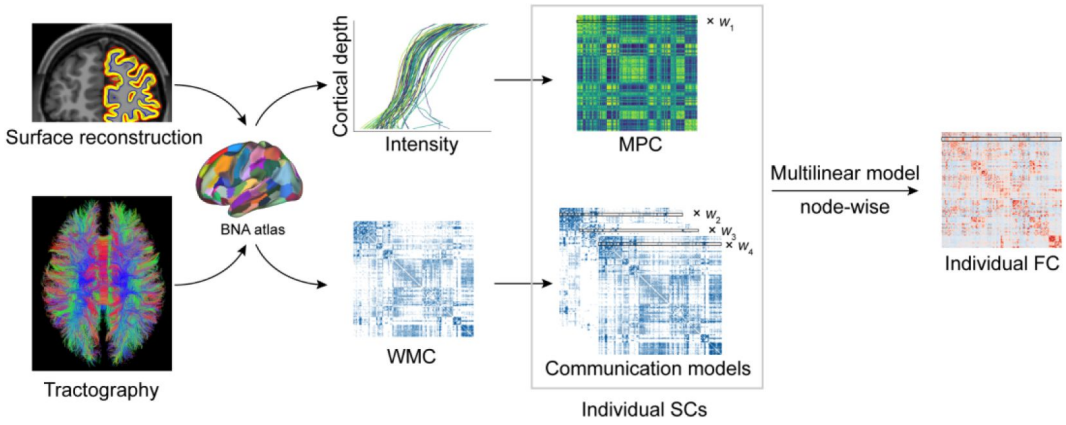

Figure 1.

SC-FC coupling framework.

The framework used to quantify nodal SC-FC coupling in the human brain. The MPC was used to map similarity networks of intracortical microstructure (voxel intensity sampled in different cortical depth) for each cortical node. The WMC represents the extracortical excitatory projection structure, and communication models were then constructed to represent the complex process of communication. A multilinear model was constructed to examine the association of individual nodewise SC (MPC and communication models) profiles with FC profiles.

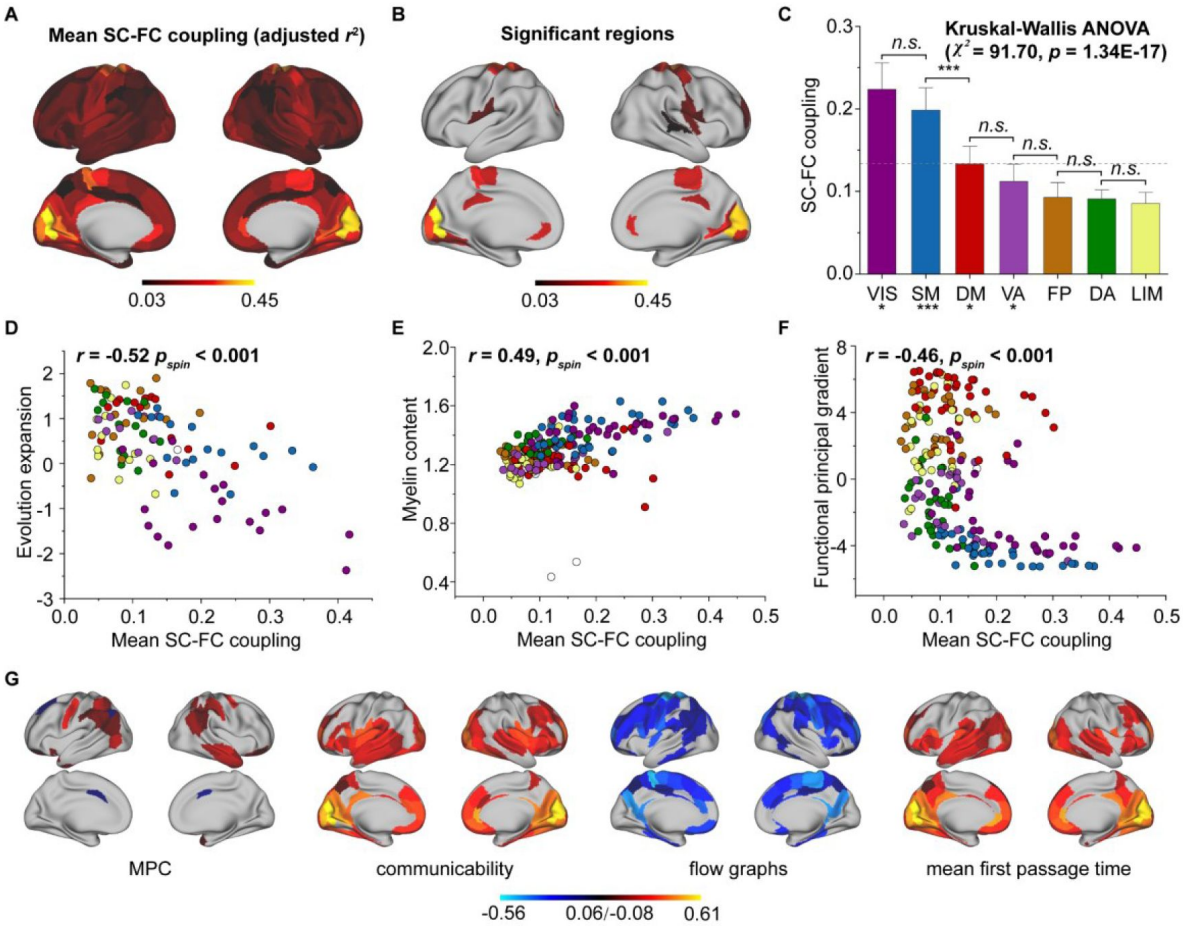

Figure 2.

Cortical SC-FC coupling in young individuals.

(A) Spatial pattern of SC-FC coupling. (B) Spatial patterns with significant predictions (p<0.05, spin test). (C) SC-FC coupling comparisons among functional networks. The error bars represent 95% confidence intervals. (D-F) SC-FC coupling aligns with evolution expansion, myelin content and functional principal gradient. (G) Preferential contributions of cortical regions across different structural connections. Note: ***: p<0.001; **: p<0.01; *: p<0.05; *n.s.*: p>0.05. VIS, visual network; SM, somatomotor network; DA, dorsal attention network; VA, ventral attention network; LIM, limbic network; FP, frontoparietal network; DM, default mode network.

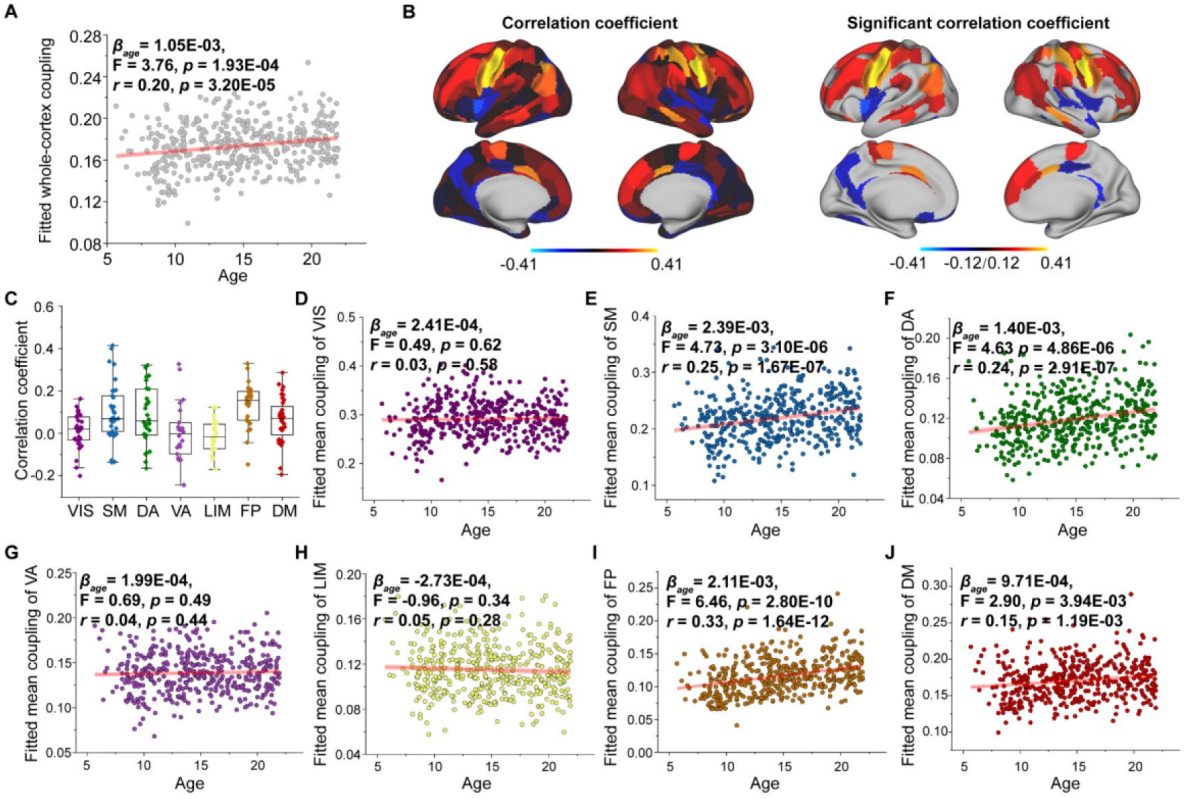

Figure 3.

Aged-related changes in SC-FC coupling.

(A) Increases in whole-brain coupling with age. (B) Correlation of age with SC-FC coupling across all regions and significant regions (p<0.05, FDR corrected). (C) Comparisons of age-related changes in SC-FC coupling among functional networks. The boxes show the median and interquartile range (IQR; 25–75%), and the whiskers depict 1.5× IQR from the first or third quartile. (D-J) Correlation of age with SC-FC coupling across the VIS, SM, DA, VA, LIM, FP and DM. VIS, visual network; SM, somatomotor network; DA, dorsal attention network; VA, ventral attention network; LIM, limbic network; FP, frontoparietal network; DM, default mode network.

SC-FC coupling predicts individual differences in cognitive functions

As we found that SC-FC coupling can encode brain maturation, we next evaluated the implications of coupling for individual cognition using Elastic-Net algorithm[11]. After controlling for sex, intracranial volume and in-scanner head motion, we found the SC-FC coupling significantly predicted individual differences in fluid intelligence, crystal intelligence and general intelligence (Pearson's r=0.3∼0.4, p<0.001, FDR corrected, **Figure 4A**). Furthermore, even after controlling for age, SC-FC coupling remained a significant predictor of general intelligence better than at chance (Pearson's r=0.11± 0.04, p=0.01, FDR corrected, **Figure 4A**). For fluid intelligence and crystal intelligence, the predictive performances of SC-FC coupling were not better than at chance (**Figure 4A**). The predictive performances for other cognitive subscores are shown in Figure S7. To identify the regions with the greatest contributions to individual differences in age-adjusted general intelligence, we utilized Haufe's inversion transform[38] to extract predictor weights across various regions. Our analysis revealed that SC-FC coupling within the prefrontal lobe, temporal lobe and lateral occipital lobe was the most predictive of individual differences in general intelligence (**Figure 4B**). In addition, we found that the weights of frontoparietal and default mode networks significantly contributed to the prediction of the general intelligence (p<0.01, 1,000 spin test permutations, **Figure 4C**).

Transcriptomic and cellular architectures of SC-FC coupling development

We employed partial least square (PLS) analysis[39] to establish a link between the spatial pattern of SC-FC coupling development and gene transcriptomic profiles (**Figure 5A**) obtained from the AHBA using a recommended pipeline[40]. The gene expression score of the first PLS component (PLS1) explained the most spatial variance, at 22.26%. After correcting for spatial autocorrelation[41], we found a positive correlation (Pearson's r=0.41, p=0.006, 10,000 spin test permutations, **Figure 5B**) between the PLS1 score of genes and the spatial pattern of SC-FC coupling development. In addition, we identified potential transcriptomic architectures using a Gene Ontology (GO) enrichment analysis of biological processes and pathway[42], analysing the significant positive and negative genes in PLS1. The positive weight genes (364 genes) were prominently enriched for "myelination", "monoatomic cation transport", "supramolecular fiber organization", etc (p<0.05, FDR corrected, **Figure 5C**). The negative correlation genes (456 genes) were relatively weakly enriched in "cellular macromolecule biosynthetic process" and other pathways (p<0.05, FDR corrected, **Figure 5C**).

To further investigate cell-specific expression patterns associated with SC-FC coupling development, the selected genes in the AHBA were agglomerated into seven canonical cell classes[43–48]: astrocytes, endothelial cells, excitatory neurons, inhibitory neurons, microglia, oligodendrocytes and oligodendrocyte precursors (OPCs). Our findings showed that the genes with positive weights were significantly expressed in oligodendrocytes (75 genes, p<0.001, permutation test, **Figure 5D**). The genes with negative weights were expressed in astrocytes (43 genes, p<0.001, permutation test, **Figure 5D**). Additionally, genes enriched in positive pathways were intensively overexpressed in oligodendrocytes, while genes enriched in three negative pathways were expressed in astrocytes, inhibitory neurons and microglia (p<0.05, permutation test, Figure S8).

Reproducibility analyses

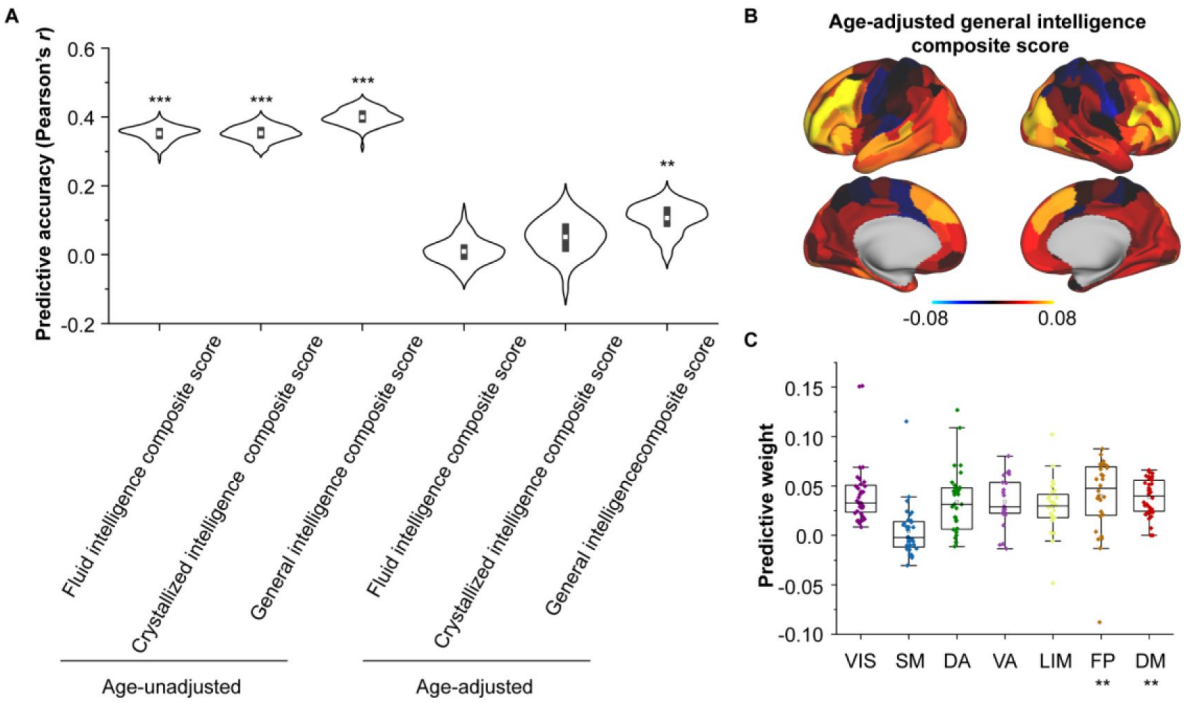

Figure 4.

Encoding individual differences in intelligence using regional SC-FC coupling.

(A) Predictive accuracy of fluid, crystallized, and general intelligence composite scores. (B) Regional distribution of predictive weight. (C) Predictive contribution of functional networks. The boxes show the median and interquartile range (IQR; 25–75%), and the whiskers depict the 1.5× IQR from the first or third quartile.

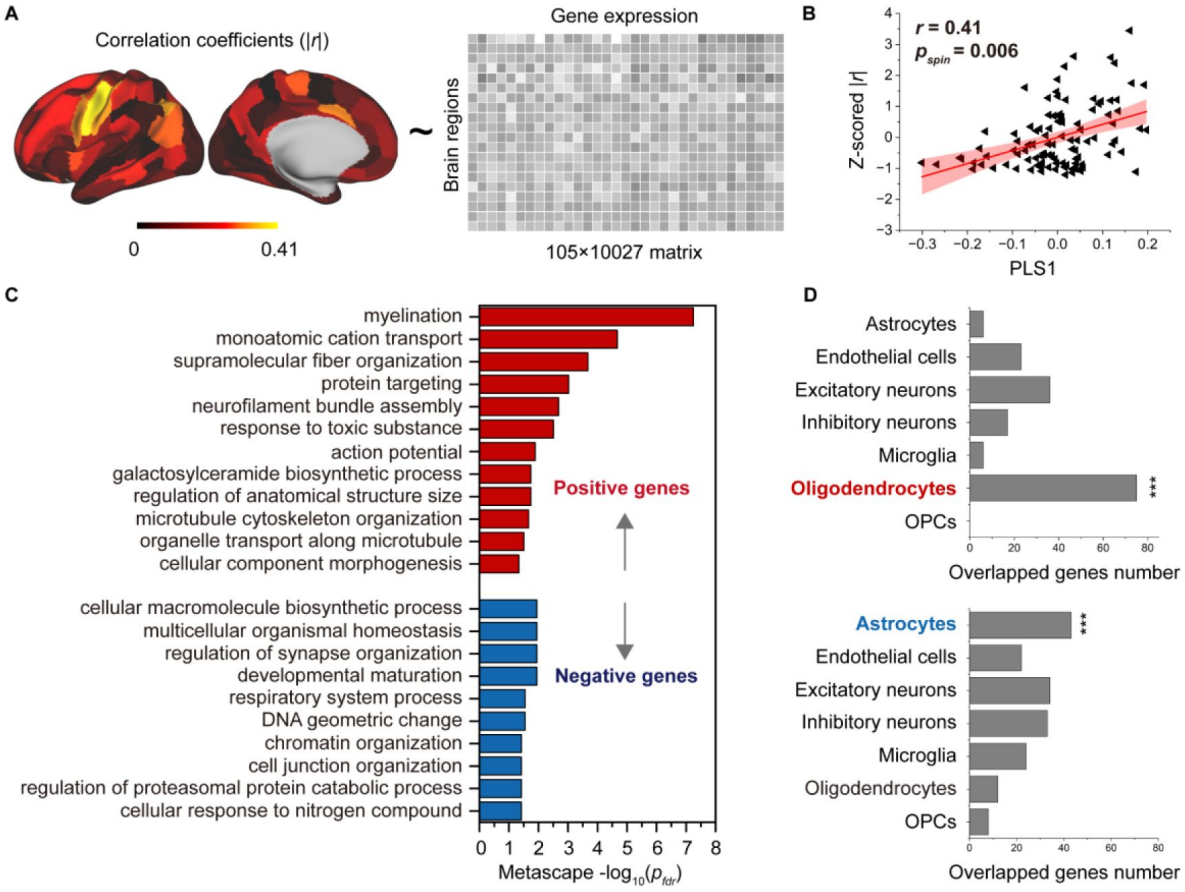

Figure 5.

Association between developmental changes in SC-FC coupling and gene transcriptional profiles.

(A) The map of developmental changes (absolute value of correlation coefficients) in SC-FC coupling across 105 left brain regions (left panel), and the normalized gene transcriptional profiles containing 10,027 genes in 105 left brain regions (right panel). (B) The correlation between developmental changes in SC-FC coupling and the first PLS component from the PLS regression analysis. (C) Enriched terms of significant genes. (D) Cell type-specific expression of significant genes. Note, p_{spin}: spin test; p_{fdr}: FDR corrected.

Different parcellation templates

To evaluate the robustness of our findings to different parcellation templates, using the multimodal parcellation from the Human Connectome Project (HCPMMP)[49], we repeated the analyses of the cortical patterns of SC-FC coupling, correlation of age with SC-FC coupling, and gene weights. We observed a similar distribution in SC-FC coupling in which visual and somatomotor networks had higher coupling values than other networks (Figure S9A). The SC-FC coupling of most cortical regions increased with age (Figure S9B), and the significant regions were similar to those in the main findings (Figure S9C, $p<0.05$, FDR corrected). The gene weights of HCPMMP was consistent with that of BNA ($r = 0.25$, $p < 0.001$).

Different tractography strategies

To evaluate the sensitivity of our results to tractography strategies, we reconstructed fibres using deterministic tractography with a ball-and-stick model and generated a fibre number-weighted network for each participant. This same pipeline was employed for subsequent SC-FC coupling, prediction, and gene analyses. These two tractography strategies yielded similar findings, as indicated by significant correlations in the mean SC-FC coupling (r=0.85, p<0.001, spin test, Figure S10A), the correlation of between age and SC-FC coupling (r=0.79, p<0.001, spin test, Figure S10B), predictive weights on the general intelligence (r=0.85, p<0.001, spin test, Figure S10C), and gene weights (r=0.80, p<0.001, Figure S10D).

Split-half validation

To assess the reproducibility of our findings, we performed a split-half independent validation using the whole dataset (WD). Specifically, we randomly partitioned WD into two independent subsets (S1 and S2), and this process was repeated 1,000 times to mitigate any potential bias due to data partitioning. We then quantified SC-FC coupling, correlation between age and SC-FC coupling, and gene weights in S1 and S2 using the same procedures. Remarkably, we observed high levels of agreement among the datasets (S1, S2, and the WD) as demonstrated in Figure S11.

Discussion

In the present study, we characterized alterations of SC-FC coupling of brain connectome during development by combining intracortical and extracortical SC to predict FC based on the HCP-D dataset. We observed that SC-FC coupling was stronger in the visual and somatomotor networks than in other networks, and followed fundamental properties of cortical organization. With development, SC-FC coupling exhibited heterogeneous changes in cortical regions, with significant increases in the somatomotor, frontoparietal, dorsal attention and default mode networks. Furthermore, we found that SC-FC coupling can predict individual differences in general intelligence, mainly with the frontoparietal and default mode networks contributing higher weights. Finally, we demonstrated that the spatial heterogeneity of changes in SC-FC coupling with age was associated with transcriptomic architectures, with genes with positive weights enriched in oligodendrocyte-related pathways and genes with negative weights expressed in astrocytes.

Together, these findings characterized the spatial and temporal pattern of SC-FC coupling of brain connectome during development and the heterogeneity in the development of SC-FC coupling is associated with individual differences in intelligence and transcriptomic architecture.

Intracortical microcircuits are interconnected through extracortical WM connections, which give rise to richly patterned functional networks[1, 3]. Despite extensive research on this topic, the relationship between SC and FC remains unclear. Although many studies have attempted to

directly correlate FC with the WMC, this correspondence is far from perfect due to the presence of polysynaptic (indirect) structural connections and circuit-level modulation of neural signals[2, 9, 16, 50]. Biological models can realistically generate these complex structural interconnections, but they have significant temporal and spatial complexity when solving for model parameters[51–54]. Communication models using the WMC integrate the advantages of different communication strategies and are easy to construct[18]. As there are numerous communication models, we identified an optimal combination consisting of three decentralized communication models based on predictive significance: communicability, mean first passage times of random walkers and flow graphs. We excluded a centralized model (shortest paths), which was not biologically plausible since it requires global knowledge of the shortest path structure[7, 55, 56]. In our study, we excluded the Euclidean distance and geodesic distance because spatial autocorrelation is inhibited. This study provides a complementary perspective (in addition to the role of WMC in shaping FC) that emphasizes the importance of intrinsic properties within intracortical circuit in shaping the large-scale functional organization of the human cortex. MPC can link intracortical circuits variance at specific cortical depths from a graph-theoretical perspective, enabling reflection of intracortical microcircuit differentiation at molecular, cellular, and laminar levels[6, 12–15]. Coupling models that incorporate these microarchitectural properties yield more accurate predictions of FC from SC[3, 57].

SC-FC coupling may reflect anatomical and functional hierarchies. SC-FC coupling in association areas, which have lower structural connectivity, was lower than that in sensory areas. This configuration effectively releases the association cortex from strong structural constraints imposed by early activity cascades, promoting higher cognitive functions that transcend simple sensori-motor exchanges[19]. A macroscale functional principal gradient[37, 58] in the human brain has been shown to align with anatomical hierarchies. Our study revealed a similar pattern, where SC-FC coupling was positively associated with evolutionary expansion and myelin content, and negatively associated with functional principal gradient during development. These findings are consistent with previous studies on WMC-FC coupling[9] and MPC-FC coupling[6]. Notably, we also found that the coupling pattern differed from that in adults, as illustrated by the moderate coupling of the sensorimotor network in the adult population[8]. SC-FC coupling is dynamic and changes throughout the lifespan[7], particularly during adolescence[6, 9], suggesting that perfect SC-FC coupling may require sufficient structural descriptors. Moreover, our results suggested that regional preferential contributions across different SCs lead to variations in the underlying communication process. Interestingly, the two extremes of regions in terms of MPC correlations corresponded to the two anchor points of the gradient[28]. The preferential regions in WM communication models were consistent with the adult results[7].

In addition, we observed developmental changes in SC-FC coupling dominated by a positive increase in cortical regions[9], broadly distributed across somatomotor, frontoparietal, dorsal attention, and default mode networks[9]. In a lifespan study, the global SC-FC coupling alterations with age were driven by reduced coupling in the sensorimotor network[7]. This finding is consistent across age ranges, indicating that sensorimotor coupling changes appear throughout development and ageing. Furthermore, we investigated the relationships of coupling alterations with evolutionary expansion and functional principal gradient but found no significant correlations, in contrast to a previous study[9]. These discrepancies likely arise from differences in coupling methods. We also found the SC-FC coupling with age across regions within subnetworks has more variability than the differences between networks, suggesting that the coupling with age is more likely region-dependent than network-dependent.

The neural circuits in the human brain support a wide repertoire of human behaviour[59]. Our study demonstrates that the degree of SC-FC coupling in cortical regions can significantly predict cognitive scores across various domains, suggesting that it serves as a sensitive indicator of brain maturity. Moreover, even after controlling for age effects, SC-FC coupling significantly predicted

general intelligence, suggesting that it can partly explain individual differences in intelligence, as shown in previous studies[8]. In another study[9], positive correlations between executive function and SC-FC coupling were mainly observed in the rostro-lateral frontal and medial occipital regions, whereas negative associations were found in only the right primary motor cortex. While SC-FC coupling was not found to predict age-adjusted executive function in our study, we observed that the frontoparietal network and the default mode network specifically contributed higher positive prediction weights for general intelligence, whereas the somatomotor network had negative prediction weights[8]. The maturation of the frontoparietal network and default mode network continues into early adulthood, providing an extended window for the activity-dependent reconstruction of distributed neural circuits in the cross-modal association cortex[19]. As we observed increasing coupling in these networks, this may have contributed to the improvements in general intelligence, highlighting the flexible and integrated role of these networks.

Classic twin studies have reported that the heritability of coupling differs among cortical regions, with higher heritability in the visual network than in other cortical networks[8]. An inverse correlation between the pattern of SC-FC coupling and heritable connectivity profiles has been reported[6]. This led us to hypothesize that the development of SC-FC coupling may be influenced by the expression patterns of the genetic transcriptome across various cell types with different spatial distributions. Our findings suggest that the spatial development of SC-FC coupling is associated with underlying transcriptome structure. Specifically, genes positively associated with the development of SC-FC coupling were enriched in oligodendrocyte-related pathways. Oligodendrocytes, specialized glial cells in the central nervous system, play a crucial role in myelination by producing myelin sheaths that enable saltatory conduction and provide metabolic support to axons[60]. Defects in myelination have been linked to developmental disorders[61]. This seems to indicate that significant alterations in SC-FC coupling during development may reflect neural plasticity, such as activity-dependent myelination of axons connecting functionally coupled regions[62, 63]. Conversely, we found that genes negatively correlated with SC-FC coupling were enriched in two specific gene pathways within astrocytes, inhibitory neurons and microglia. Both astrocytes and microglia have been implicated in synaptic pruning, a critical developmental process for the formation of fully functional neuronal circuits that eliminates weak and inappropriate synapses[64–66]. Importantly, the precise establishment of synapses is crucial for establishing the intercellular connectivity patterns of GABAergic neurons[67]. These findings suggest that the subtle alterations observed in SC-FC coupling are closely associated with the refinement of mature neural circuits.

Several methodological issues must be addressed. First, we implemented a conservative quality control procedure to address head motion, which unavoidably resulted in the loss of some valuable data. Given the confounding influence of head motion in fMRI studies, especially those involving developing populations, we applied censoring of high-motion frames and included motion as a covariate in the GLM analysis and cognitive prediction to minimize its effects[7, 59, 68, 69]. Second, Second, although we observed SC-FC coupling across development by integrating intra- and extracortical SC to predict FC, it is worth noting that combining deep learning models[2], biophysical models[5, 17], or dynamic coupling[3, 13] perspectives may provide complementary insights. Third, the appropriateness of structurally defined regions for the functional analysis is also a topic of important debate. Fourth, we focused solely on cortico-cortical pathways, excluding subcortical nuclei from analysis. This decision stemmed from the difficulty of reconstructing the surface of subcortical regions[70] and characterizing their connections using MPC technique, as well as the challenge of accurately resolving the connections of small structures within subcortical regions using whole-brain diffusion imaging and tractography techniques[71, 72]. In addition, the reconstruction of short connections between hemispheres is a notable challenge. Fifth, it is important to acknowledge that changes in gene expression levels during development may introduce bias in the results. Finally, validation of sensitivity across independent datasets is a crucial step in

ensuring the reliability of our results. To address this, we employed an alternative split-half validation strategy and the results supported the reliability of the current findings. However, future verification of current findings on independent datasets are still needed.

Conclusions

Overall, this study sheds light on the development of SC-FC coupling in the brain and its relationship to cognitive function and gene expression patterns. The results improve our understanding of the fundamental principles of brain development and provide a basis for future research in this area. Further investigations are needed to fully explore the clinical implications of SC-FC coupling for a range of developmental disorders.

Materials and Methods

Participants

We selected 439 participants (207 males, mean age = 14.8 ± 4.2 years, age range = [5.7, 21.9]) from the HCP-D Release 2.0 data (*https://www.humanconnectome.org/study/hcp-lifespan-development*) after conducting rigorous checks for data completeness and quality control.

The HCP-D dataset comprised 652 healthy participants who underwent multimodal MRI scans and cognitive assessments, and the detailed inclusion and exclusion criteria for this cohort have been described in[30]. All participants or their parents (for participants under the age of 18 years) provided written informed consent and assent. The study was approved by the Institutional Review Board of Washington University in St. Louis.

Cognitive scores

We included 11 cognitive scores which were assessed with the National Institutes of Health (NIH) Toolbox Cognition Battery (*https://www.healthmeasures.net/exploremeasurement-systems/nih-toolbox*), including episodic memory, executive function/cognitive flexibility, executive function/inhibition, language/reading decoding, processing speed, language/vocabulary comprehension, working memory, fluid intelligence composite score, crystal intelligence composite score, early child intelligence composite score and total intelligence composite score. Distributions of these cognitive scores and their relationship with age are illustrated in Figure S12.

Imaging acquisition

The MRI data were obtained with a Siemens 3T Prisma with a 32-channel phased array head coil, and detailed imaging parameters are available in[73]. High-resolution T1w images were acquired using a 3D multiecho MPRAGE sequence (0.8 mm isotropic voxels, repetition time (TR)/inversion time (TI) = 2500/1000 ms, echo time (TE) = 1.8/3.6/5.4/7.2 ms, flip angle = 8°, up to 30 reacquired TRs). The structural T2w images were collected with a variable-flip-angle turbo-spin–echo 3D SPACE sequence (0.8 mm isotropic voxels, TR/TE = 3200/564 ms, up to 25 reacquired TRs). The dMRI scans included four consecutive runs with a 2D 4× multiband spin– echo echo-planar imaging (EPI) sequence (1.5 mm isotropic voxels, 185 diffusion directions with b = 1500/3000 s/mm^2 and 28 b = 0 s/mm^2 volumes, TR = 3.23 s, flip angle = 78°). The rs-fMR images were acquired using a 2D 8× multiband gradient-recalled echo EPI sequence (2.0 mm isotropic voxels, TR/TE = 800/37 ms, flip angle = 52°). Each rs-fMRI scan duration was 26 minutes (four runs of 6.5 minutes) for participants over 8 years old and 21 minutes (six runs of 3.5 minutes) for participants who were 5~7 years old.

Imaging preprocessing

All structural, diffusion and functional images underwent minimal preprocessing[70]. We specifically processed dMRI data referring to the publicly available code from *https://github.com/Washington-University/HCPpipelines* since the HCP-D has not released preprocessed dMRI results. Briefly, structural T1w and T2w images went through gradient distortion correction, alignment, bias field correction, registration to Montreal Neurological Institute (MNI) space, white matter and pial surface reconstruction, segment structures, and surface registration and downsampling to 32k_fs_LR mesh. A T1w/T2w ratio image, which indicates intracortical myelin, was produced for each participant[36]. The BNA[31] was projected on native space according to the official scripts (*http://www.brainnetome.org/resource/*) and the native BNA was checked by visual inspection. Regarding fMRI data, the preprocessing pipeline included spatial distortion correction, motion correction, EPI distortion correction, registration to MNI space, intensity normalization, mapping volume time series to 32k_fs_LR mesh, and smoothing using a 2 mm average surface vertex. Following our previous methodological evaluation study[11], the dMRI procedures consisted of intensity normalization of the mean b0 image, correction of EPI distortion and eddy current, motion correction, gradient nonlinearity correction, and linear registration to T1w space.

Network computation

Microstructure profile covariance (MPC)

The MPC can capture cytoarchitectural similarity between cortical areas[12]. We first reconstructed 14 cortical surfaces from the white matter to the pial surface using a robust equivolumetric model[12, 74]. Then, the T1w/T2w ratio image was used to sample intracortical myelin intensities at these surfaces. We averaged the intensity profiles of vertices over 210 cortical regions according to the BNA[31]. Finally, we computed pairwise partial correlations between regional intensity profiles, while controlling for the average intensity profile. After removing negative correlations, we used Fisher's r-to-z-transformation to generate an individual MPC.

White matter connectome (WMC)

Following our previous methodological evaluation study[11], the ball-and-stick model estimated from the bedpostx command-line in the FDT toolbox of FSL (*https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FDT*) was used to estimate fibre orientations (three fibres modelled per voxel)[75–78]. The BNA atlas was applied to individual volume space by inverse transformation derived from preprocessed steps. Next, probabilistic tractography (probtrackx)[77, 79] was implemented in the FDT toolbox to estimate the probability of connectivity between two regions by sampling 5,000 fibres for each voxel within each region, correcting for distance, dividing by the total fibres number in source region, and calculating the average bidirectional probability[11]. Notably, the connections in subcortical areas were removed. A consistency-based thresholding approach (weight of the coefficient of variation at the 75th percentile) was used to remove spurious connections, and retain consistently reconstructed connections across subjects[9, 80]. Finally, twenty-seven communication models[7] were subsequently derived from the weighted probabilistic network, including shortest path length (gamma values = {0.12, 0.25, 0.5, 1, 2, 4}), communicability[32], cosine similarity, search information (weight-to-cost transformations = {0.12, 0.25, 0.5, 1, 2, 4})[81], path transitivity (weight-to-cost transformations = {0.12, 0.25, 0.5, 1, 2, 4})[55], matching index[82], greedy navigation[83], mean first passage times of random walkers[33], and flow graphs (timescales = {1, 2.5, 5, 10})[84]; for more details see Text S1.

Functional network (FC)

To further clean the functional signal, we performed frame censoring, regressed out nuisance variables (including white matter, cerebrospinal fluid, global signal, and 12 motion parameters), and executed temporal bandpass filtering (0.01~0.1 Hz). Specifically, we identified censored frames with motion greater than 0.15 mm[7] based on the Movement_RelativeRMS.txt file. We flagged one frame before and two frames after each censored frame, along with any uncensored segments of fewer than five contiguous frames, as censored frames as well[69]. We discarded fMRI runs with more than half of the frames flagged as censored frames, and excluded participants with fewer than 300 frames (less than 4 minutes). The nuisance variables were removed from time series based on general linear model. We averaged the time series of vertices into 210 cortical regions according to the BNA[31]. We then computed pairwise Pearson's correlations between regional time series, and applied Fisher's r-to-z-transformation to the resulting correlations to generate individual FC.

Quality control

The exclusion of participants in the whole multimodal data processing pipeline was depicted in Figure S13. In the context of fMRI data, we computed Pearson's correlation between motion and age, as well as between the number of remaining frames and age, for the included participants aged 5 to 22 years and 8 to 22 years, respectively. These correlations were presented in Figure S14.

SC-FC coupling

A multilinear model[1] was constructed to examine the relationship of individual nodewise SC profiles and FC profiles. For a given node, the predictive variable was nodal SC $\mathbf{S} = \{\boldsymbol{s}_1, \boldsymbol{s}_2, \cdots, \boldsymbol{s}_i, \cdots, \boldsymbol{s}_n\}$, $\boldsymbol{s}_i \in \mathrm{R}^m$ where $\boldsymbol{s}_i$ is the ith SC profiles, n is the number of SC profiles, and m is the node number. The nodal functional profile $\boldsymbol{f}$ is the dependent variable.

$$\boldsymbol{f} = b_0 + b_1\boldsymbol{s}_1 + b_2\boldsymbol{s}_2 + \cdots + b_i\boldsymbol{s}_i + \cdots + b_n\boldsymbol{s}_n \quad (1)$$

where the intercept b_0 and regression coefficients b_i are estimated model parameters. For each participant, goodness of fit per node represents the nodal coupling between SC and FC, quantified as the adjusted coefficient of determination[7]

$$R^2_{adjusted} = 1 - \frac{(1 - R^2)(N_c - 1)}{N_c - N_p - 1} \quad (2)$$

where R^2 is the unadjusted coefficient of determination, N_c is the number of connection (N_c = 245 for BNA), and N_p is the number of predictors.

In the present study, WMC communication models that represented diverse geometric, topological, or dynamic factors, were used to explain nodal FC variation. Notably, too many predictors will result in overfitting and blindly increase the explained variance. And covariance structure among the predictors may lead to unreliable predictor weights. Thus, we applied Haufe's inversion transform[38] to address these issues and identified reliable communication mechanisms. Specifically, we used all twenty-seven communication models to predict FC at the node level for each participant. We applied Haufe's inversion transform[38] to obtain predictor weights for each model, with higher or lower values indicating stronger positive or negative correlations with FC. Next, we generated 1,000 FC permutations through a spin test[85] for each nodal prediction in each subject and obtained random distributions of model weights. These weights were averaged over the group and were investigated the enrichment of the highest weights per region to assess whether the number of highest weights across communication models was significantly larger than that in a random discovery.

The significant communication models were used to represent WMC communication properties and to predict functional profiles in conjunction with MPC as structural profiles (predictors). To test the significance of the resulting adjusted R^2 values and system-specific of coupling, we generated a null predictive model using a spin test[85] with 1,000 spatially-constrained repetitions. We also used Kruskal-Wallis nonparametric one-way analysis of variance (Kruskal-Wallis ANOVA) to compare coupling differences between systems. To investigate the contributions of various structural predictors, we applied Kruskal-Wallis ANOVA to test the predictive weights derived by Haufe's inversion transform, identifying optimal predictors across regions. We corrected for multiple comparisons using FDR correction. Additionally, we used a general linear model to explore age-related developmental patterns of SC-FC coupling, while controlling for sex, intracranial volume, and in-scanner head motion. Similarly, the system-specific significance of coupling alteration was calculated based on the 1,000 repetitions of the spin test. In addition, we have constructed the models using only MPC or SCs to predict FC, respectively. Spearman's correlation was used to assess the consistency between spatial patterns based on different models.

We examined the associations of SC-FC coupling and its developmental pattern with evolution expansion[35], myelin content[36], and functional principal gradient[37]. Spearman's correlation analyses were used to quantify the strength of correlations, with significance corrected for spatial autocorrelation with 1,000 repetitions of the spin test.

Prediction of cognitive function

Based on our predictive evaluation work[11], the Elastic-Net algorithm was applied to predict cognitive performance using nodal SC-FC coupling, which tends to yield robust prediction performance across various dimensions of cognitive tasks. The objective function is as follows:

$$L(\mathbf{Y}, f(\mathbf{X}, \mathbf{w})) = \sum_{i=0}^{n} (y_i - f(\boldsymbol{x}_i))^2 + \alpha \sum_{j=1}^{m} (\beta |w_j| + \frac{1}{2}(1-\beta) ||w_j||^2) \quad (3)$$

where $\boldsymbol{X} = \{\boldsymbol{x}_1, \boldsymbol{x}_2, ..., \boldsymbol{x}_n\}$ represents an observation set (e.g., SC-FC coupling) with a sample size of n, and $\boldsymbol{Y} = \{y_1, y_2, ..., y_n\}$ is a label set (e.g., cognitive measure). The model solves the fitting coefficient $\boldsymbol{W} = (w_1, w_2, ..., w_m)$ under the minimization objective function $L(\mathbf{Y}, f(\mathbf{X}, \mathbf{W}))$. The L1 regularization term $|\cdot|$ and L2 regularization term $||\cdot||^2$ constraint the fitting coefficient to ensure model generalization ability. α represents regularization strength, controlling the compression loss scale, and β denotes a trade-off parameter between the L1 and L2 terms.

We employed a nested fivefold cross validation (CV) framework comprising an external CV and an internal CV[11]. In the external CV, observations were randomly partitioned into five folds, with four of them included in the training set used to develop the model and the remaining fold used as a testing set to assess the predictive accuracy of the model. This process was repeated 100 times, and the final model performance was evaluated by averaging the predictive accuracy across the 100 models. In the internal CV, the hyperparameter spaces were first defined as $\alpha \in \{x \mid x = 2^n, n \in \mathbf{Z}, n \in [-10,5]\}$ and $\beta \in \{x \mid x = 0.1n, n \in \mathbf{Z}, n \in [0,10]\}$. Then, the training set was further divided into five folds. Four folds composed the internal training set, which was used to generate models by successively applying 16×11 hyperparametric combinations, and the remaining fold was defined as the validation set and used to find the optimal combination. Subsequently, we retrained the model on the training set using the optimal hyperparametric combination and assessed its predictive performance on the testing set by performing Pearson's correlation analyses of the relationship between the predicted and labelled values.

Prior to applying the nested fivefold cross-validation framework to each behaviour measure, we regressed out covariates including sex, intracranial volume, and in-scanner head motion from the behaviour measure[59, 69]. Specifically, we estimated the regression coefficients of the

covariates using the training set and applied them to the testing set. This regression procedure was repeated for each fold. Additionally, we conducted control analyses using age-adjusted behavioral measures to investigate the effect of age on the predictive performance of SC-FC coupling.

To evaluate whether our model performed better than at chance on each behaviour measure, we performed 1,000 permutation tests by randomly shuffling the behaviour measure across participants, generating a null model of predicted performance using the same procedures. We then used the corrected resampled *t* test to determine statistical significance[86, 87]. We corrected for multiple comparisons using FDR correction. For model interpretability, we applied Haufe's inversion transform[38] to obtain predicted weights for various brain regions. The significance of the weights for each system was assessed by comparing them to those generated by a spin test[85] with 1,000 repetitions.

Association between alterations of SC-FC coupling and gene expression

We preprocessed the anatomic and genomic information of the Allen Human Brain Atlas (AHBA) dataset following a recommended pipeline[40]. Specifically, we used FreeSurfer (*https://surfer.nmr.mgh.harvard.edu/fswiki/*) to generate preprocessed structural data for each donor and projected the BNA template onto native fsaverage space using official scripts (*http://www.brainnetome.org/resource/*). Finally, we produced an averaged gene expression profile for 10,027 genes covering 105 left cortical regions. Restricting analyses to the left hemisphere will minimize variability across regions (and hemispheres) in terms of the number of samples available[40].

PLS analysis[39] was performed to mine the linear association between the spatial development pattern of SC-FC coupling and gene expression profiles. We used absolute values of the correlation between age and SC-FC coupling in 105 left cortical regions as predicted variables and the gene expression profiles of the corresponding regions as predictor variables. Pearson's correlation coefficient was calculated to determine the association between the PLS score and the absolute correlation value between age and SC-FC coupling. To correct for spatial autocorrelation, we compared the empirically observed value to spatially constrained null models generated by 10,000 spin permutations[85]. We then transformed the gene weight on PLS1 into a z score by dividing the standard deviation of the corresponding weights estimated from bootstrapping, and ranked all genes accordingly. We identified significant genes at a threshold of $p < 0.05$ and classified them as having positive or negative gene weights. To understand the functional significance of these genes, we performed gene functional enrichment analysis (GO analysis of biological processes and pathways) using Metascape[42]. We focused on the selected genes with positive or negative weights and retained enrichment pathways with an FDR-corrected < 0.05.

To investigate the cell type-specific expression of the selected genes, we assigned them to 58 cell types derived from five studies[43–47] focusing on single-cell research using the human postnatal cortex. To avoid potential bias in cell-type assignment, we grouped these cell types into seven canonical classes: astrocytes, endothelial cells, excitatory neurons, inhibitory neurons, microglia, oligodendrocytes, and OPCs[48, 88]. We generated a null model by performing 10,000 random resamplings of genes within each cell type. We then tested the significance of our results against this null model. Additionally, we subjected the genes associated with each enriched term to the same analysis to explore the specificity of the cell type.

Reproducibility analyses

To evaluate the robustness of our findings under different parcellation templates, we computed MPC, SCs (WMC, communicability[32], mean first passage times of random walkers[33], and flow graphs (timescales=1)) and FC using the multimodal parcellation from the Human Connectome Project (HCPMMP)[49]. We used the multilinear model to examine the association of individual nodewise SC profiles and FC profiles. Then, a general linear model was used to

explore age-related developmental patterns of SC-FC coupling, while controlling for sex, intracranial volume, and in-scanner head motion. We corrected for multiple comparisons using FDR correlation. Finally, we produced an averaged gene expression profile for 10,027 genes covering 176 left cortical regions based on HCPMMP and obtained the gene weights by PLS analysis. We performed Pearson's correlation analyses to assess the consistency of gene weights between HCPMMP and BNA.

To evaluate the sensitivity of our results to deterministic tractography, we used the Camino toolbox (*http://camino.cs.ucl.ac.uk/*) to reconstruct fibres with a ball-and-stick model estimated from bedpostx results[78] and to generate a fibre number-weighted network using the BNA atlas. We then calculated the communication properties of the WMC including communicability, mean first passage times of random walkers, and flow graphs (timescales=1). The same pipeline was used for subsequent SC-FC coupling, prediction, and gene analysis. To assess the consistency of our results between deterministic tractography and probabilistic tractography, we performed Pearson's correlation analyses with significance corrected for spatial autocorrelation through 1,000 repetitions of the spin test.

To evaluate the generalizability of our findings, we adopted a split-half cross-validation strategy by randomly partitioning the whole dataset (WD) into two independent subsets (S1 and S2). This process was repeated 1,000 times to minimize bias due to data partitioning. Based on MPC, three communication properties of the WMC, and FC, we then used the same procedures to quantify SC-FC coupling, the correlation between age and SC-FC coupling and gene weights in both S1 and S2. Finally, we assessed the consistency of results by calculating Pearson's correlation coefficients of the relationships between S1 and WD, S2 and WD, and S1 and S2.

Data and Code availability

The HCP-D 2.0 release data that support the findings of this study are publicly available at *https://www.humanconnectome.org/study/hcp-lifespan-development.R4.1.2* software (*https://www.r-project.org/*) was used to construct the general linear model. MATLAB scripts used for preprocessing of the AHBA dataset can be found at *https://github.com/BMHLab/AHBAprocessing*. Python scripts used to perform PLS regression can be found at *https://scikit-learn.org/stable/modules/generated/sklearn.cross_decomposition.PLSRegression.html#sklearn.cross_decomposition.PLSRegression*. The minimal preprocessing pipelines can be accessed at *https://github.com/Washington-University/HCPpipelines*. The code relevant to this study can be accessed through the following GitHub repository: *https://github.com/FelixFengCN/SC-FC-coupling-development*.

Credit Authorship Contribution Statement

G.F. performed acquisition and analysis of data, contributed new analytic tools, drafted and revised the paper. Y.W., W.H., H.C. and J.C. performed acquisition and analysis of data. N.S. contributed to the design of the work, performed analysis of data, and revised the paper.

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There are no conflicts of interest including any financial, personal, or other relationships with people or organizations for any of the authors related to the work described in the article.

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Editors

Reviewing Editor
Susie Huang
Massachusetts General Hospital, Charlestown, United States of America

Senior Editor
Jonathan Roiser
University College London, London, United Kingdom

Reviewer #1 (Public Review):

Summary:

This work studies spatio-temporal patterns of structure-function coupling in developing brains, using a large set of imaging data acquired from children aged 5-22. Magnetic resonance imaging data of brain structure and function were obtained from a publicly available database, from which structural and functional features and measures were derived. The authors examined the spatial patterns of structure-function coupling and how they evolve with brain development. This work further sought correlations of brain structure-function coupling with behavior and explored evolutionary, microarchitectural and genetic bases that could potentially account for the observed patterns.

Strength:

The strength of this work is the use of currently available state-of-the-art analysis methods, along with a large set of high-quality imaging data, and comprehensive examinations of

structure-function coupling in developing brains. The results are comprehensive and illuminating.

Weakness:

As with most other studies, transcriptomic and cellular architectures of structure-function coupling were characterized only on the basis of a common atlas in this work.

The authors have achieved their aims in this study, and the findings provide mechanistic insights into brain development, which will inspire further basic and clinical studies along this line.

https://doi.org/10.7554/eLife.93325.2.sa0

Author response:

The following is the authors' response to the original reviews.

> ***Recommendations for the authors:***
>
> ***Reviewer #1 (Recommendations For The Authors):***
>
> *(1) Lines 40-42: The sentence "The coupling of structural connectome (SC) and functional connectome (FC) varies greatly across different cortical regions reflecting anatomical and functional hierarchies as well as individual differences in cognitive function, and is regulated by genes" is a misstatement. Regional variations of structure-function coupling do not really reflect differences in cognitive function among individuals, but inter-subject variations do.*

Thank you for your comment. We have made revisions to the sentence to correct its misstatement. Please see lines 40-43: "The coupling of structural connectome (SC) and functional connectome (FC) varies greatly across different cortical regions reflecting anatomical and functional hierarchies[1, 6-9] and is regulated by genes[6, 8], as well as its individual differences relates to cognitive function[8, 9]."

> *(2) In Figure 1, the graph showing the relation between intensity and cortical depth needs explanation.*

Thank you for your comment. We have added necessary explanation, please see lines 133-134: "The MPC was used to map similarity networks of intracortical microstructure (voxel intensity sampled in different cortical depth) for each cortical node."

> *(3) Line 167: Change "increased" to "increase".*

We have corrected it, please see lines 173-174: "…networks significantly increased with age and exhibited greater increase."

> *(4) Line 195: Remove "were".*

We have corrected it, please see line 204: "…default mode networks significantly contributed to the prediction…"

> *(5) Lines 233-240, Reproducibility analyses: Comparisons of parcellation templates were not made with respect to gene weights. Is there any particular reason?*

Thank you for your comment. We have quantified the gene weights based on HCPMMP using the same procedures. We identified a correlation (r = 0.25, p<0.001) between the gene weights in HCPMMP and BNA. Given that this is a relatively weak correlation, we need to clarify the following points.

Based on HCPMMP, we produced an averaged gene expression profile for 10,027 genes covering 176 left cortical regions[1]. The excluding 4 cortical regions that had an insufficient number of assigned samples may lead to different templates having a relatively weak correlation of gene associations. Moreover, the effect of different template resolutions on the results of human connectome-transcriptome association is still unclear.

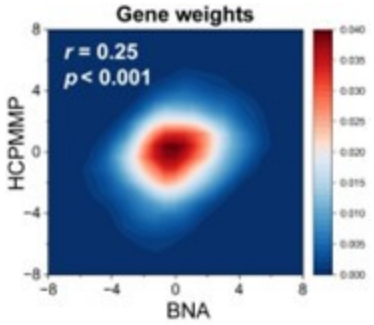
In brain connectome analysis, the choice of parcellation templates can indeed influence the subsequent findings to some extent. A methodological study[2] provided referenced correlations about 0.4~0.6 for white matter connectivity and 0.2~0.4 for white matter nodal property between two templates (refer to Figure 4 and 5 in [2]). Therefore, the age-related coupling changes as a downstream analysis was calculated using multimodal connectome and correlated with gene expression profiles, which may be influenced by the choice of templates.

We have further supplemented gene weights results obtained from HCPMMP to explicitly clarify the dependency of parcellation templates.

Please see lines 251-252: “The gene weights of HCPMMP was consistent with that of BNA (r = 0.25, p < 0.001).”

Author response image 1.

The consistency of gene weights between HCPMMP and BNA.



Please see lines 601-604: “Finally, we produced an averaged gene expression profile for 10,027 genes covering 176 left cortical regions based on HCPMMP and obtained the gene weights by PLS analysis. We performed Pearson's correlation analyses to assess the consistency of gene weights between HCPMMP and BNA.”

> ***Reviewer #2 (Recommendations For The Authors):***
>
> *Your paper is interesting to read and I found your efforts to evaluate the robustness of the results of different parcellation strategies and tractography methods very valuable. The work is globally easy to navigate and well written with informative good-quality figures, although I think some additional clarifications will be useful to improve readability. My suggestions and questions are detailed below (I aimed to group them by topic which did not always succeed so apologies if the comments are difficult to navigate, but I hope they will be useful for reflection and to incorporate in your work).*

> ** L34: 'developmental disorder'*
>
> *** As far as I understand, the subjects in HCP-D are mostly healthy (L87). Thus, while your study provides interesting insights into typical brain development, I wonder if references to 'disorder' might be premature. In the future, it would be interesting to extend your approach to the atypical populations. In any case, it would be extremely helpful and appreciated if you included a figure visualising the distribution of behavioural scores within your population and in relationship to age at scan for your subjects (and to include a more detailed description of the assessment in the methods section) given that large part of your paper focuses on their prediction using coupling inputs (especially given a large drop of predictive performance after age correction). Such figures would allow the reader to better understand the cognitive variability within your data, but also potential age relationships, and generally give a better overview of your cohort.*

We agree with your comment that references to 'disorder' is premature. We have made revisions in abstract and conclusion.

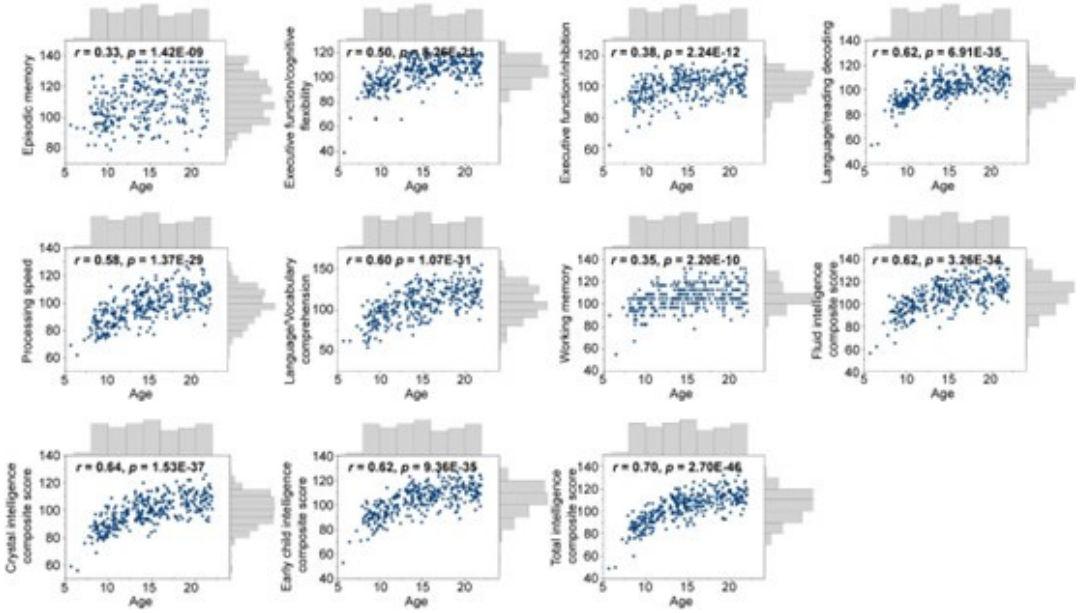
Please see lines 33-34: “This study offers insight into the maturational principles of SC-FC coupling in typical development.”

Please see lines 395-396: “Further investigations are needed to fully explore the clinical implications of SC-FC coupling for a range of developmental disorders.”

In addition, we have included a more detailed description of the cognitive scores in the methods section and provided a figure to visualize the distributions of cognitive scores and in relationship to age for subjects. Please see lines 407-413: “Cognitive scores. We included 11 cognitive scores which were assessed with the National Institutes of Health (NIH) Toolbox Cognition Battery (https://www.healthmeasures.net/exploremeasurement-systems/nih-toolbox), including episodic memory, executive function/cognitive flexibility, executive function/inhibition, language/reading decoding, processing speed, language/vocabulary comprehension, working memory, fluid intelligence composite score, crystal intelligence composite score, early child intelligence composite score and total intelligence composite score. Distributions of these cognitive scores and their relationship with age are illustrated in Figure S12.”

Author response image 2.

Cognitive scores and age distributions of scans.



** SC-FC coupling*

*** L162: 'Regarding functional subnetworks, SC-FC coupling increased disproportionately with age (Figure 3C)'.*

**** As far as I understand, in Figure 3C, the points are the correlation with age for a given ROI within the subnetwork. Is this correct? If yes, I am not sure how this shows a disproportionate increase in coupling. It seems that there is great variability of SC-FC correlation with age across regions within subnetworks, more so than the differences between networks. This would suggest that the coupling with age is regionally dependent rather than network-dependent? Maybe you could clarify?*

The points are the correlation with age for a given ROI within the subnetwork in Figure 3C. We have revised the description, please see lines 168-174: “Age correlation coefficients distributed within functional subnetworks were shown in Figure 3C. Regarding mean SC-FC coupling within functional subnetworks, the somatomotor (βage=2.39E-03, F=4.73, p=3.10E-06, r=0.25, p=1.67E07, Figure 3E), dorsal attention (βage=1.40E-03, F=4.63, p=4.86E-06, r=0.24, p=2.91E-07, Figure 3F), frontoparietal (βage =2.11E-03, F=6.46, p=2.80E-10, r=0.33, p=1.64E-12, Figure 3I) and default mode (βage =9.71E-04, F=2.90, p=3.94E-03, r=0.15, p=1.19E-03, Figure 3J) networks significantly increased with age and exhibited greater increase.” In addition, we agree with your comment that the coupling with age is more likely region-dependent than network-dependent. We have added the description, please see lines 329-332: “We also found the SC-FC coupling with age across regions within subnetworks has more variability than the differences between networks, suggesting that the coupling with age is more likely region-dependent than network-dependent.” This is why our subsequent analysis focused on regional coupling.

**** Additionally, we see from Figure 3C that regions within networks have very different changes with age. Given this variability (especially in the subnetworks where you show both positive and negative correlations with age for specific ROIs (i.e. all of them)), does it make sense then to show mean coupling over regions within the subnetworks which erases the differences in coupling with age relationships across regions (Figures 3D-J)?*

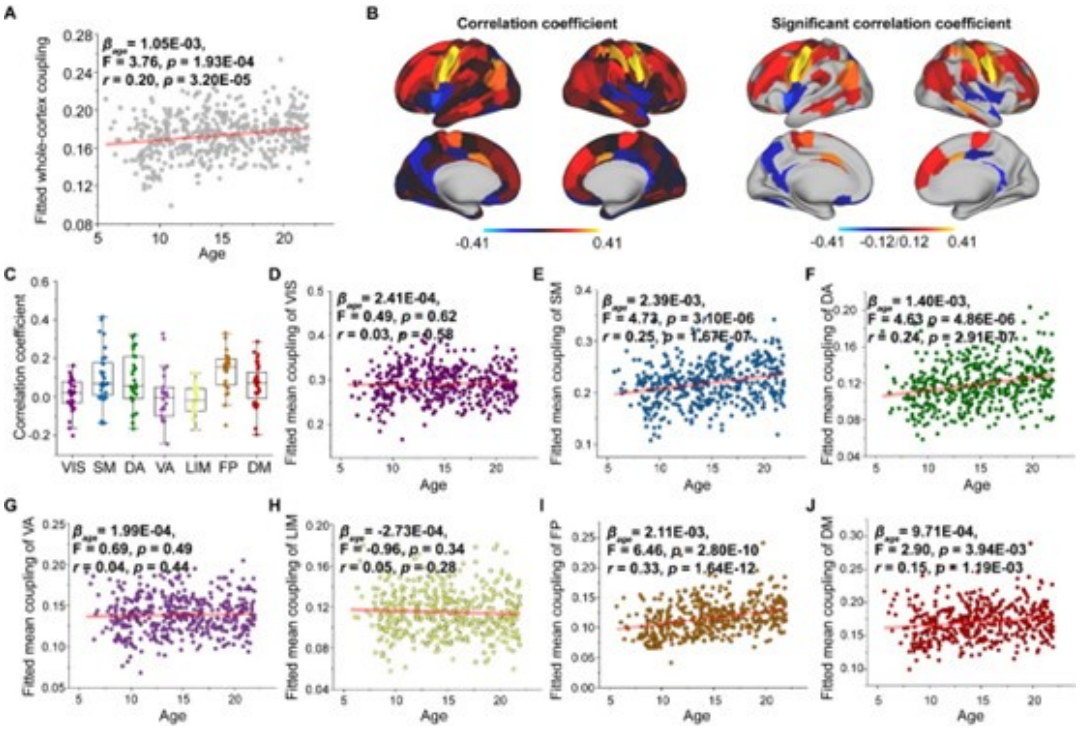
Considering the interest and interpretation for SC-FC coupling, showing the mean coupling at subnetwork scales with age correlation is needed, although this eliminates variability at regional scale. These results at different scales confirmed that coupling changes with age at this age group are mainly increased.

> **** Also, I think it would be interesting to show correlation coefficients across all regions, not only the significant ones (3B). Is there a spatially related tendency of increases/decreases (rather than a 'network' relationship)? Would it be interesting to show a similar figure to Figure S7 instead of only the significant regions?*

As your comment, we have supplemented the graph which shows correlation coefficients across all regions into Figure 3B. Similarly, we supplemented to the other figures (Figure S3-S6).

Author response image 3.

Aged-related changes in SC-FC coupling. (A) Increases in whole-brain coupling with age. (B) Correlation of age with SC-FC coupling across all regions and significant regions (p<0.05, FDR corrected). (C) Comparisons of age-related changes in SC-FC coupling among functional networks. The boxes show the median and interquartile range (IQR; 25–75%), and the whiskers depict 1.5× IQR from the first or third quartile. (D-J) Correlation of age with SC-FC coupling across the VIS, SM, DA, VA, LIM, FP and DM. VIS, visual network; SM, somatomotor network; DA, dorsal attention network; VA, ventral attention network; LIM, limbic network; FP, frontoparietal network; DM, default mode network.



> **** For the quantification of MPC.*
>
> ***** L421: you reconstructed 14 cortical surfaces from the wm to pial surface. If we take the max thickness of the cortex to be 4.5mm (Fischl & Dale, 2000), the sampling is above the resolution of your anatomical images (0.8mm). Could you expand on what the*

> *interest is in sampling such a higher number of surfaces given that the resolution is not enough to provide additional information?*

The surface reconstruction was based on state-of-the-art equivolumetric surface construction techniques[3] which provides a simplified recapitulation of cellular changes across the putative laminar structure of the cortex. By referencing a 100-μm resolution Merkerstained 3D histological reconstruction of an entire post mortem human brain (BigBrain: https://bigbrain.loris.ca/main.php), a methodological study[4] systematically evaluated MPC stability with four to 30 intracortical surfaces when the resolution of anatomical image was 0.7 mm, and selected 14 surfaces as the most stable solution. Importantly, it has been proved the *in vivo* approach can serve as a lower resolution yet biologically meaningful extension of the histological work[4].

> ***** L424: did you aggregate intensities over regions using mean/median or other statistics?*

It might be useful to specify.

Thank you for your careful comment. We have revised the description in lines 446-447: “We averaged the intensity profiles of vertices over 210 cortical regions according to the BNA”.

> ***** L426: personal curiosity, why did you decide to remove the negative correlation of the intensity profiles from the MPC? Although this is a common practice in functional analyses (where the interpretation of negatives is debated), within the context of cortical correlations, the negative values might be interesting and informative on the level of microstructural relationships across regions (if you want to remove negative signs it might be worth taking their absolute values instead).*

We agree with your comment that the interpretation of negative correlation is debated in MPC. Considering that MPC is a nascent approach to network modeling, we adopted a more conservative strategy that removing negative correlation by referring to the study [4] that proposed the approach. As your comment, the negative correlation might be informative. We will also continue to explore the intrinsic information on the negative correlation reflecting microstructural relationships.

> ***** L465: could you please expand on the notion of self-connections, it is not completely evident what this refers to.*

We have revised the description in lines 493-494: “Nc is the number of connection (Nc = 245 for BNA)”.

> ***** Paragraph starting on L467: did you evaluate the multicollinearities between communication models? It is possibly rather high (especially for the same models with similar parameters (listed on L440-444)). Such dependence between variables might affect the estimates of feature importance (given the predictive models only care to minimize error, highly correlated features can be selected as a strong predictor while the impact of other features with similarly strong relationships with the target is minimized thus impacting the identification of reliable 'predictors').*

We agree with your comment. The covariance structure (multicollinearities) among the communication models have a high probability to lead to unreliable predictor weights. In our study, we applied Haufe's inversion transform[5] which resolves this issue by computing the covariance between the predicted FC and each communication models in the training set. More details for Haufe's inversion transform please see [5]. We further clarified in the

manuscript, please see in lines 497-499: “And covariance structure among the predictors may lead to unreliable predictor weights. Thus, we applied Haufe's inversion transform[38] to address these issues and identify reliable communication mechanisms.”

> ***** L474: I am not completely familiar with spin tests but to my understanding, this is a spatial permutation test. I am not sure how this applies to the evaluation of the robustness of feature weight estimates per region (if this was performed per region), it would be useful to provide a bit more detail to make it clearer.*

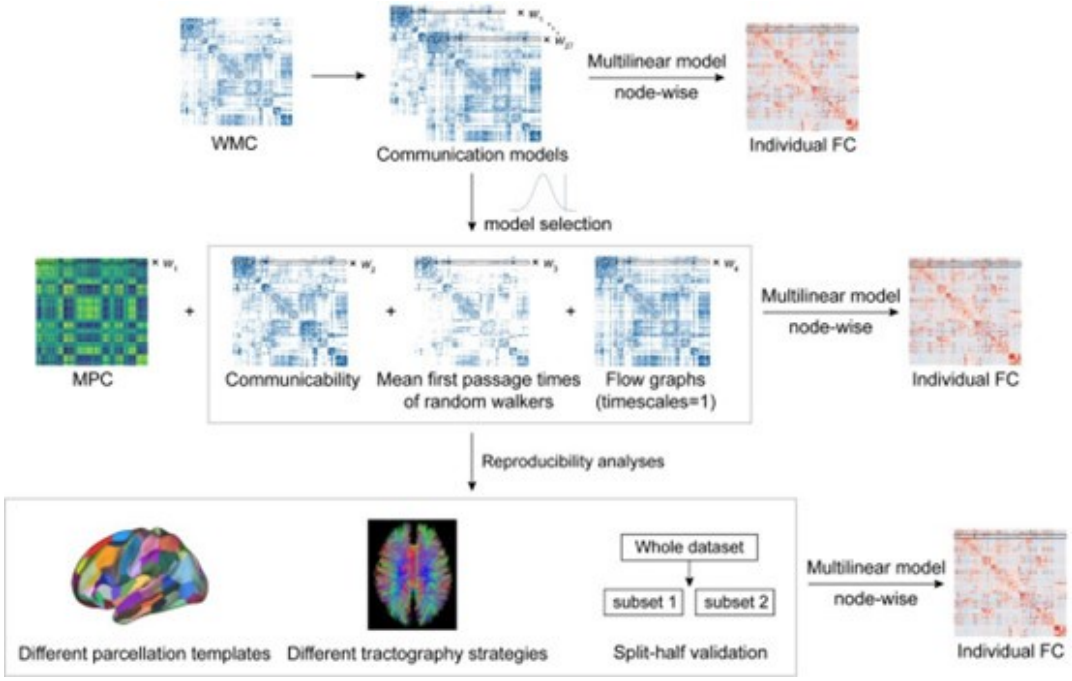
As your comment, we have supplemented the detail, please see lines 503-507: “Next, we generated 1,000 FC permutations through a spin test[86] for each nodal prediction in each subject and obtained random distributions of model weights. These weights were averaged over the group and were investigated the enrichment of the highest weights per region to assess whether the number of highest weights across communication models was significantly larger than that in a random discovery.”

> ***** L477: 'significant communication models were used to represent WMC...', but in L103 you mention you select 3 models: communicability, mean first passage, and flow graphs. Do you want to say that only 3 models were 'significant' and these were exactly the same across all regions (and data splits/ parcellation strategies/ tractography methods)? In the methods, you describe a lot of analysis and testing but it is not completely clear how you come to the selection of the final 3, it would be beneficial to clarify. Also, the final 3 were selected on the whole dataset first and then the pipeline of SC-FC coupling/age assessment/behaviour predictions was run for every (WD, S1, S2) for both parcellations schemes and tractography methods or did you end up with different sets each time? It would be good to make the pipeline and design choices, including the validation bit clearer (a figure detailing all the steps which extend Figure 1 would be very useful to understand the design/choices and how they relate to different runs of the validation).*

Thank you for your comment. In all reproducibility analyses, we used the same 3 models which was selected on the main pipeline (probabilistic tractography and BNA parcellation). According to your comment, we produced a figure that included the pipeline of model selection as the extend of Figure 1. And the description please see lines 106-108: “We used these three models to represent the extracortical connectivity properties in subsequent discovery and reproducibility analyses (Figure S1).”

Author response image 4.

Pipeline of model selection and reproducibility analyses.



> ***** Might the imbalance of features between structural connectivity and MPC affect the revealed SC-FC relationships (3 vs 1)? Why did you decide on this ratio rather than for example best WM structural descriptor + MPC?*

We understand your concern. The WMC communication models represent diverse geometric, topological, or dynamic factors. In order to describe the properties of WMC as best as possible, we selected three communication models after controlling covariance structure that can significantly predict FC from the 27 models. Compared to MPC, this does present a potential feature imbalance problem. However, this still supports the conclusion that coupling models that incorporate microarchitectural properties yield more accurate predictions of FC from SC[6, 7]. The relevant experiments are shown in Figure S2 below. If only the best WM structural descriptor is used, this may lose some communication properties of WMC.

> ***** L515: were intracranial volume and in-scanner head motion related to behavioural measures? These variables likely impact the inputs, do you expect them to influence the outcome assessments? Or is there a mistake on L518 and you actually corrected the input features rather than the behaviour measures?*

The in-scanner head motion and intracranial volume are related to some age-adjusted behavioural measures, as shown in the following table. The process of regression of covariates from cognitive measures was based on these two cognitive prediction studies [8, 9]. Please see lines 549-554: “Prior to applying the nested fivefold cross-validation framework to each behaviour measure, we regressed out covariates including sex, intracranial volume, and in-scanner head motion from the behaviour measure[59, 69]. Specifically, we estimated the regression coefficients of the covariates using the training set and applied them to the testing set. This regression procedure was repeated for each fold.”

Author response table 1.

	In-scanner head motion		Intracranial volume	
	r value	*p* value	r value	*p* value
Episodic memory	-0.04	0.494825	0.00	0.963828
Executive function/cognitive flexibility	-0.13	0.017108	-0.02	0.729339
Executive function/inhibition, language/reading decoding	0.00	0.985376	-0.01	0.911467
Language/reading decoding	-0.09	0.124475	0.03	0.596947
Processing speed	-0.07	0.215465	0.11	0.049091
Language/vocabulary comprehension	-0.15	0.007839	0.01	0.835508
Working memory	-0.02	0.767743	0.08	0.16235
Fluid intelligence composite score	-0.12	0.034428	0.02	0.695776
Crystal intelligence composite score	-0.09	0.112609	0.08	0.153797
Early child intelligence composite score	-0.09	0.107082	0.04	0.503285
Total intelligence composite score	-0.12	0.037287	0.07	0.219497

Age-adjusted cognitive score

> *** Additionally, in the paper, you propose that the incorporation of cortical microstructural (myelin-related) descriptors with white-matter connectivity to explain FC provides for 'a more comprehensive perspective for characterizing the development of SC-FC coupling' (L60). This combination of cortical and white-matter structure is indeed interesting, however the benefits of incorporating different descriptors could be studied further. For example, comparing results of using only the white matter connectivity (assessed through selected communication models) ~ FC vs (white matter + MPC) ~ FC vs MPC ~ FC. Which descriptors better explain FC? Are the 'coupling trends' similar (or the same)? If yes, what is the additional benefit of using the more complex combination? This would also add strength to your statement at L317: 'These discrepancies likely arise from differences in coupling methods, highlighting the complementarity of our methods with existing findings'. Yes, discrepancies might be explained by the use of different SC inputs. However, it is difficult to see how discrepancies highlight complementarity - does MCP (and combination with wm) provide additional information to using wm structural alone?~*

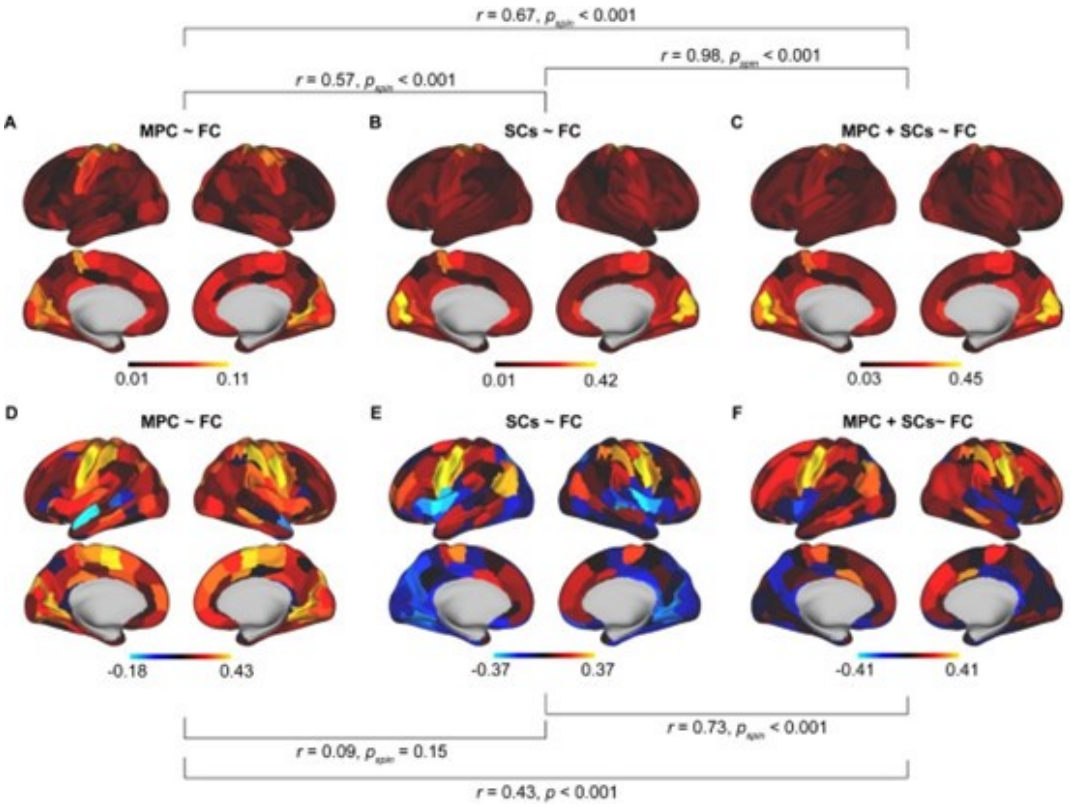
According to your comment, we have added the analyses based on different models using only the myelin-related predictor or WM connectivity to predict FC, and further compared the results among different models. please see lines 519-521: “In addition, we have constructed the models using only MPC or SCs to predict FC, respectively. Spearman’s correlation was used to assess the consistency between spatial patterns based on different models.”

Please see lines 128-130: “In addition, the coupling pattern based on other models (using only MPC or only SCs to predict FC) and the comparison between the models were shown in Figure S2A-C.” Please see lines 178-179: “The age-related patterns of SC-FC coupling based other coupling models were shown in Figure S2D-F.”

Although we found that there were spatial consistencies in the coupling patterns between different models, the incorporation of MPC with SC connectivity can improve the prediction of FC than the models based on only MPC or SC. For age-related changes in coupling, the differences between the models was further amplified. We agree with you that the complementarity cannot be explicitly quantified and we have revised the description, please see line 329: “These discrepancies likely arise from differences in coupling methods.”

Author response image 5.

Comparison results between different models. Spatial pattern of mean SC-FC coupling based on MPC ~ FC (A), SCs ~ FC (B), and MPC + SCs ~ FC (C). Correlation of age with SC-FC coupling across cortex based on MPC ~ FC (D), SCs ~ FC (E), and MPC + SCs ~ FC (F).



*** For the interpretation of results: L31 'SC-FC coupling is positively associated with genes in oligodendrocyte-related pathways and negatively associated with astrocyte-related gene'; L124: positive myelin content with SC-FC coupling…and similarly on L81, L219, L299, L342, and L490:*

****You use a T1/T2 ratio which is (in large part) a measure of myelin to estimate the coupling between SC and FC. Evaluation with SC-FC coupling with myeline described in Figure 2E is possibly biased by the choice of this feature. Similarly, it is possible that reported positive associations with oligodendrocyte-related pathways and SC-FC coupling in your work could in part result from a bias introduced by the 'myelin descriptor' (conversely, picking up the oligodendrocyte-related genes is a nice*

> *corroboration for the T1/T2 ration being a myelin descriptor, so that's nice). However, it is possible that if you used a different descriptor of the cortical microstructure, you might find different expression patterns associated with the SCFC coupling (for example using neurite density index might pick up neuronal-related genes?). As mentioned in my previous suggestions, I think it would be of interest to first use only the white matter structural connectivity feature to assess coupling to FC and assess the gene expression in the cortical regions to see if the same genes are related, and subsequently incorporate MPC to dissociate potential bias of using a myelin measure from genetic findings.*

Thank you for your insightful comments. In this paper, however, the core method of measuring coupling is to predict functional connections using multimodal structural connections, which may yield more information than a single modal. We agree with your comment that separating SCs and MPC to look at the genes involved in both separately could lead to interesting discoveries. We will continue to explore this in the future.

> *** Generally, I find it difficult to understand the interpretation of SC-FC coupling measures and would be interested to hear your thinking about this. As you mention on L290-294, how well SC predicts FC depends on which input features are used for the coupling assessment (more complex communication models, incorporating additional microstructural information etc 'yield more accurate predictions of FC' L291) - thus, calculated coupling can be interpreted as a measure of how well a particular set of input features explain FC (different sets will explain FC more or less well) ~ coupling is related to a measure of 'missing' information on the SC-FC relationship which is not contained within the particular set of structural descriptors - with this approach, the goal might be to determine the set that best, i.e. completely, explains FC to understand the link between structure and function. When you use the coupling measures for comparisons with age, cognition prediction etc, the 'status' of the SC-FC changes, it is no longer the amount of FC explained by the given SC descriptor set, but it's considered a descriptor in itself (rather than an effect of feature selection / SC-FC information overlap) - how do you interpret/argue for this shift of use?*

Thank you for your comment. In this paper, we obtain reasonable SC-FC coupling by determining the optimal set of structural features to explain the function. The coupling essentially measures the direct correspondence between structure and function. To study the relationship between coupling and age and cognition is actually to study the age correlation and cognitive correlation of this direct correspondence between structure and function.

> *** In a similar vein to the above comment, I am interested to hear what you think: on L305 you mention that 'perfect SC-FC coupling may be unlikely'. Would this reasoning suggest that functional activity takes place through other means than (and is therefore somehow independent of) biological (structural) substrates? For now, I think one can only say that we have imperfect descriptors of the structure so there is always information missing to explain function, this however does not mean the SC and FC are not perfectly coupled (only that we look at insufficient structural descriptors - limitations of what imaging can assess, what we measure etc). This is in line with L305 where you mention that 'Moreover, our results suggested that regional preferential contributions across different SCs lead to variations in the underlying communication process'. This suggests that locally different areas might use different communication models which are not reflected in the measures of SC-FC coupling that was employed, not that the 'coupling' is lower or higher (or coupling is not perfect). This is also a change in approach to L293: 'This configuration effectively releases the association cortex from strong structural constraints' - the 'release' might only be in light of the particular structural descriptors you use - is it conceivable that a different communication model would be more appropriate (and show high coupling) in these areas.*

Thank you for your insightful comments. We have changed the description, please see lines 315317: “SC-FC coupling is dynamic and changes throughout the lifespan[7], particularly during adolescence[6,9], suggesting that perfect SC-FC coupling may require sufficient structural descriptors.”

> **Cognitive predictions:*
>
> *** From a practical stand-point, do you think SC-FC coupling is a better (more accurate) indicator of cognitive outcomes (for example for future prediction studies) than each modality alone (which is practically easier to obtain and process)? It would be useful to check the behavioural outcome predictions for each modality separately (as suggested above for coupling estimates). In case SC-FC coupling does not outperform each modality separately, what is the benefit of using their coupling? Similarly, it would be useful to compare to using only cortical myelin for the prediction (which you showed to increase in importance for the coupling). In the case of myelin->coupling-> intelligence, if you are able to predict outcomes with the same performance from myelin without the need for coupling measures, what is the benefit of coupling?*

From a predictive performance point of view, we do not believe that SC-FC coupling is a better indicator than a single mode (voxel, network or other indicator). Our starting point is to assess whether SC-FC coupling is related to the individual differences of cognitive performances rather than to prove its predictive power over other measures. As you suggest, it's a very interesting perspective on the predictive power of cognition by separating the various modalities and comparing them. We will continue to explore this issue in the future study.

> *** The statement on L187 'suggesting that increased SC-FC coupling during development is associated with higher intelligence' might not be completely appropriate before age corrections (especially given the large drop in performance that suggests confounding effects of age).*

According to your comment, we have removed the statement.

> *** L188: it might be useful to report the range of R across the outer cross-validation folds as from Figure 4A it is not completely clear that the predictive performance is above the random (0) threshold. (For the sake of clarity, on L180 it might be useful for the reader if you directly report that other outcomes were not above the random threshold).*

According to your comment, we have added the range of R and revised the description, please see lines 195-198: “Furthermore, even after controlling for age, SC-FC coupling remained a significant predictor of general intelligence better than at chance (Pearson’s r=0.11±0.04, p=0.01, FDR corrected, Figure 4A). For fluid intelligence and crystal intelligence, the predictive performances of SC-FC coupling were not better than at chance (Figure 4A).”

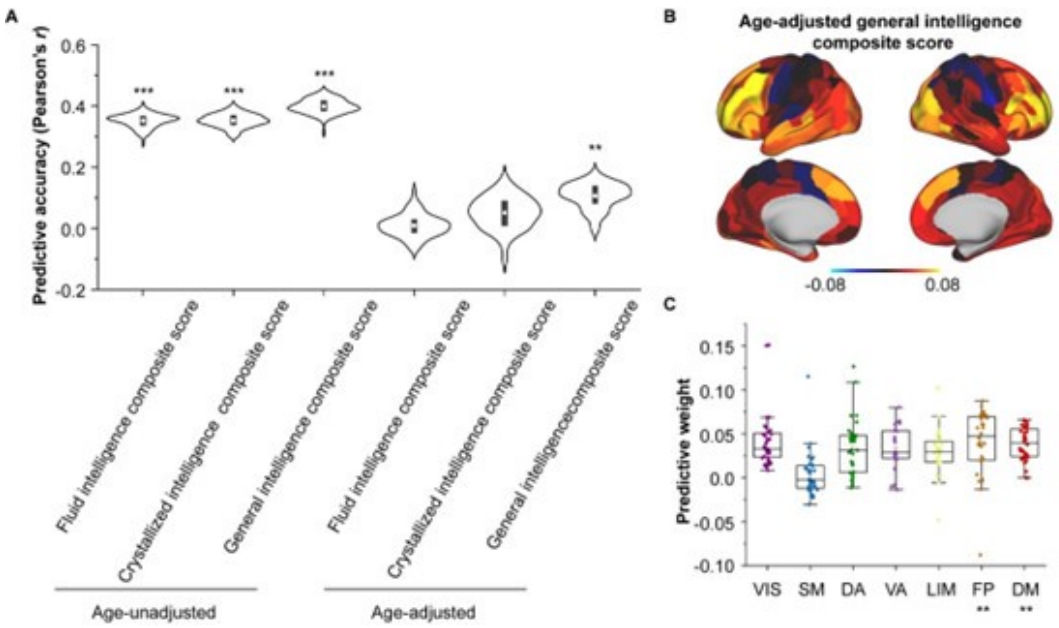
> *In a similar vein, in the text, you report Pearson's R for the predictive results but Figure 4A shows predictive accuracy - accuracy is a different (categorical) metric. It would be good to homogenise to clarify predictive results.*

We have made the corresponding changes in Figure 4.

Author response image 6.

Encoding individual differences in intelligence using regional SC-FC coupling. (A) Predictive accuracy of fluid, crystallized, and general intelligence composite scores. (B) Regional

distribution of predictive weight. (C) Predictive contribution of functional networks. The boxes show the median and interquartile range (IQR; 25–75%), and the whiskers depict the 1.5× IQR from the first or third quartile.



> **Methods and QC:*
>
> *-Parcellations*
>
> *** It would be useful to mention briefly how the BNA was applied to the data and if any quality checks were performed for the resulting parcellations, especially for the youngest subjects which might be most dissimilar to the population used to derive the atlas (healthy adults HCP subjects) ~ question of parcellation quality.*

We have added the description, please see lines 434-436: “The BNA[31] was projected on native space according to the official scripts (http://www.brainnetome.org/resource/) and the native BNA was checked by visual inspection.”

> *** Additionally, the appropriateness of structurally defined regions for the functional analysis is also a topic of important debate. It might be useful to mention the above as limitations (which apply to most studies with similar focus).*

We have added your comment to the methodological issues, please see lines 378-379: “Third, the appropriateness of structurally defined regions for the functional analysis is also a topic of important debate.”

> *- Tractography*
>
> *** L432: it might be useful to name the method you used (probtrackx).*

We have added this name to the description, please see lines 455-456: “probabilistic tractography (probtrackx)[78, 79] was implemented in the FDT toolbox …”

> *** L434: 'dividing the total fibres number in source region' - dividing by what?*

We have revised the description, please see line 458: “dividing by the total fibres number in source region.”

> *** L436: 'connections in subcortical areas were removed' - why did you trace connections to subcortical areas in the first place if you then removed them (to match with cortical MPC areas I suspect)? Or do you mean there were spurious streamlines through subcortical regions that you filtered?*

On the one hand we need to match the MPC, and on the other hand, as we stated in methodological issues, the challenge of accurately resolving the connections of small structures within subcortical regions using whole-brain diffusion imaging and tractography techniques[10, 11].

> *** Following on the above, did you use any exclusion masks during the tracing? In general, more information about quality checks for the tractography would be useful. For example, L437: did you do any quality evaluations based on the removed spurious streamlines? For example, were there any trends between spurious streamlines and the age of the subject? Distance between regions/size of the regions?*

We did not use any exclusion masks. We performed visual inspection for the tractography quality and did not assess the relationship between spurious streamlines and age or distance between regions/size of the regions.

> *** L439: 'weighted probabilistic network' - this was weighted by the filtered connectivity densities or something else?*

The probabilistic network is weighted by the filtered connectivity densities.

> *** I appreciate the short description of the communication models in Text S1, it is very useful.*

Thank you for your comment.

> *** In addition to limitations mentioned in L368 - during reconstruction, have you noticed problems resolving short inter-hemispheric connections?*

We have not considered this issue, we have added it to the limitation, please see lines 383-384: “In addition, the reconstruction of short connections between hemispheres is a notable challenge.”

> *- Functional analysis:*
>
> *** There is a difference in acquisition times between participants below and above 8 years (21 vs 26 min), does the different length of acquisition affect the quality of the processed data?*

We have made relatively strict quality control to ensure the quality of the processed data.

> *** L446 'regressed out nuisance variables' - it would be informative to describe in more detail what you used to perform this.*

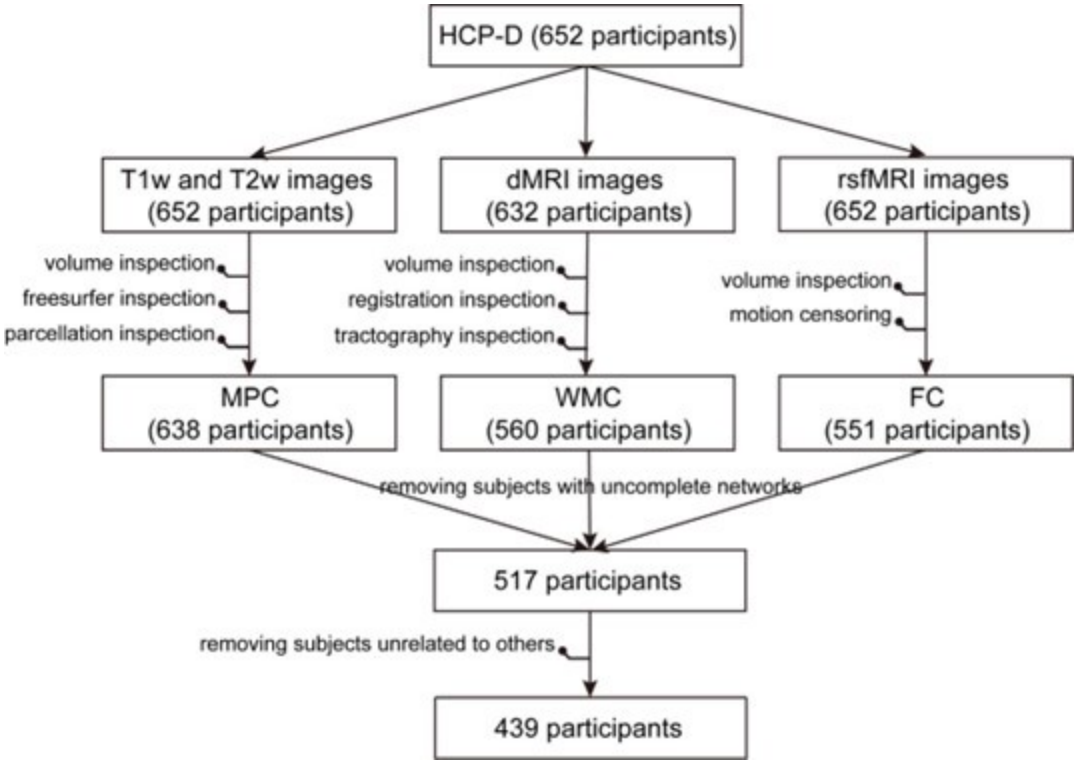
We have provided more detail about the regression of nuisance variables, please see lines 476-477: “The nuisance variables were removed from time series based on general linear model.”

> *** L450-452: it would be useful to add the number of excluded participants to get an intuition for the overall quality of the functional data. Have you checked if the quality is associated with the age of the participant (which might be related to motion etc). Adding a distribution of remaining frames across participants (vs age) would be useful to see in the supplementary methods to better understand the data you are using.*

We have supplemented the exclusion information of the subjects during the data processing, and the distribution and aged correlation of motion and remaining frames. Please see lines 481-485: "Quality control. The exclusion of participants in the whole multimodal data processing pipeline was depicted in Figure S13. In the context of fMRI data, we computed Pearson's correlation between motion and age, as well as between the number of remaining frames and age, for the included participants aged 5 to 22 years and 8 to 22 years, respectively. These correlations were presented in Figure S14."

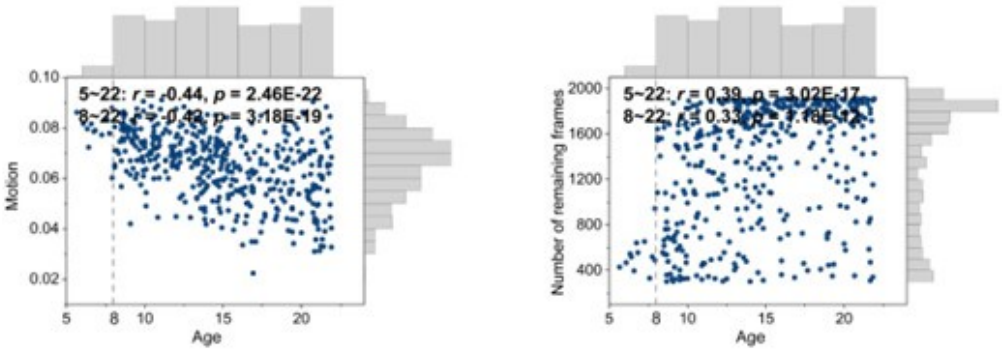
Author response image 7.

Exclusion of participants in the whole multimodal data processing pipeline.



Author response image 8.

Figure S14. Correlations between motion and age and number of remaining frames and age.



> *** L454: 'Pearson's correlation's... ' In contrast to MPC you did not remove negative correlations in the functional matrices. Why this choice?*

Whether the negative correlation connection of functional signal is removed or not has always been a controversial issue. Referring to previous studies of SC-FC coupling[12-14], we find that the practice of retaining negative correlation connections has been widely used. In order to retain more information, we chose this strategy. Considering that MPC is a nascent approach to network modeling, we adopted a more conservative strategy that removing negative correlation by referring to the study [4] that proposed the approach.

> *- Gene expression:*
>
> *** L635, you focus on the left cortex, is this common? Do you expect the gene expression to be fully symmetric (given reported functional hemispheric asymmetries)? It might be good to expand on the reasoning.*

An important consideration regarding sample assignment arises from the fact that only two out of six brains were sampled from both hemispheres and four brains have samples collected only in the left. This sparse sampling should be carefully considered when combining data across donors[1]. We have supplemented the description, please see lines 569-571: “Restricting analyses to the left hemisphere will minimize variability across regions (and hemispheres) in terms of the number of samples available[40].”

> *** Paragraph of L537: you use evolution of coupling with age (correlation) and compare to gene expression with adults (cohort of Allen Human Brain Atlas - no temporal evolution to the gene expressions) and on L369 you mention that 'relative spatial patterns of gene expressions remain stable after birth'. Of course this is not a place to question previous studies, but would you really expect the gene expression associated with the temporary processes to remain stable throughout the development? For example, myelination would follow different spatiotemporal gradient across brain regions, is it reasonable to expect that the expression patterns remain the same? How do you then interpret a changing measure of coupling (correlation with age) with a gene expression assessed statically?*

We agree with your comment that the spatial expression patterns is expected to vary at different periods. We have revised the previous description, please see lines 383-386: “Fifth, it is important to acknowledge that changes in gene expression levels during development may introduce bias in the results.”

> *- Reproducibility analyses:*

> *** Paragraph L576: are we to understand that you performed the entire pipeline 3 times (WD, S1, S2) for both parcellations schemes and tractography methods (~12 times) including the selection of communication models and you always got the same best three communication models and gene expression etc? Or did you make some design choices (i.e. selection of communication models) only on a specific set-up and transfer to other settings?*

The choice of communication model is established at the beginning, which we have clarified in the article, please see lines 106-108: “We used these three models to represent the extracortical connectivity properties in subsequent discovery and reproducibility analyses (Figure S1).” For reproducibility analyses (parcellation, tractography, and split-half validation), we fixed other settings and only assessed the impact of a single factor.

> *** Paragraph of L241: I really appreciate you evaluated the robustness of your results to different tractography strategies. It is reassuring to see the similarity in results for the two approaches. Did you notice any age-related effects on tractography quality for the two methods given the wide age range (did you check?)*

In our study, the tractography quality was checked by visual inspection. Using quantifiable tools to tractography quality in future studies could answer this question objectively.

> *** Additionally, I wonder how much of that overlap is driven by the changes in MPC which is the same between the two methods... especially given its high weight in the SC-FC coupling you reported earlier in the paper. It might be informative to directly compare the connectivity matrices derived from the two tracto methods directly. Generally, as mentioned in the previous comments, I think it would be interesting to assess coupling using different input settings (with WM structural and MPC separate and then combined).*

As your previous comment, we have examined the coupling patterns, coupling differences, coupling age correlation, and spatial correlations between the patterns based on different models, as shown in Figure S2. Please see our response to the previous comment for details.

> *** L251 - I also wonder if the random splitting is best adapted to validation in your case given you study relationships with age. Would it make more sense to make stratified splits to ensure a 'similar age coverage' across splits?*

In our study, we adopt the random splitting process which repeated 1,000 times to minimize bias due to data partitioning. The stratification you mentioned is a reasonable method, and keeping the age distribution even will lead to higher verification similarity than our validation method. However, from the validation results of our method, the similarity is sufficient to explain the generalization of our findings.

> *Minor comments*
>
> *L42: 'is regulated by genes'*
>
> *** Coupling (if having a functional role and being regulated at all) is possibly resulting from a complex interplay of different factors in addition to genes, for example, learning/environment, it might be more cautious to use 'regulated in part by genes' or similar.*

We have corrected it, please see line 42.

> *L43 (and also L377): 'development of SC-FC coupling'*
>
> *** I know this is very nitpicky and depends on your opinion about the nature of SC-FC coupling, but 'development of SC-FC coupling' gives an impression of something maturing that has a role 'in itself' (for example development of eye from neuroepithelium to mature organ etc.). For now, I am not sure it is fully certain that SC-FC coupling is more than a byproduct of the comparison between SC and FC, using 'changes in SC-FC coupling with development' might be more apt.*

We have corrected it, please see lines 43-44.

> *L261 'SC-FC coupling was stronger ... [] ... and followed fundamental properties of cortical organization.' vs L168 'No significant correlations were found between developmental changes in SC-FC coupling and the fundamental properties of cortical organization'.*
>
> ***Which one is it? I think in the first you refer to mean coupling over all infants and in the second about correlation with age. How do you interpret the difference?*

Between the ages of 5 and 22 years, we found that the mean SC-FC coupling pattern has become similar to that of adults, consistent with the fundamental properties of cortical organization. However, the developmental changes in SC-FC coupling are heterogeneous and sequential and do not follow the mean coupling pattern to change in the same magnitude.

> *L277: 'temporal and spatial complexity'*
>
> *** Additionally, communication models have different assumptions about the flow within the structural network and will have different biological plausibility (they will be more or less*
>
> *'realistic').*

Here temporal and spatial complexity is from a computational point of view.

> *L283: 'We excluded a centralized model (shortest paths), which was not biologically plausible' ** But in Text S1 and Table S1 you specify the shortest paths models. Does this mean you computed them but did not incorporate them in the final coupling computations even if they were predictive?*
>
> *** Generally, I find the selection of the final 3 communication models confusing. It would be very useful if you could clarify this further, for example in the methods section.*

We used all twenty-seven communication models (including shortest paths) to predict FC at the node level for each participant. Then we identified three communication models that can significantly predict FC. For the shortest path, he was excluded because he did not meet the significance criteria. We have further added methodological details to this section, please see lines 503-507.

> *L332 'As we observed increasing coupling in these [frontoparietal network and default mode network] networks, this may have contributed to the improvements in general intelligence, highlighting the flexible and integrated role of these networks' vs L293 'SC-FC coupling in association areas, which have lower structural connectivity, was lower than that in sensory areas. This configuration effectively releases the association cortex from strong structural constraints imposed by early activity cascades, promoting higher cognitive functions that transcend simple sensori-motor exchanges'*

> *** I am not sure I follow the reasoning. Could you expand on why it would be the decoupling promoting the cognitive function in one case (association areas generally), but on the reverse the increased coupling in frontoparietal promoting the cognition in the other (specifically frontoparietal)?*

We tried to explain the problem, for general intelligence, increased coupling in frontoparietal could allow more effective information integration enable efficient collaboration between different cognitive processes.

> ** Formatting errors etc.*
>
> *L52: maybe rephrase?*

We have rephrased, please see lines 51-53: “The T1- to T2-weighted (T1w/T2w) ratio of MRI has been proposed as a means of quantifying microstructure profile covariance (MPC), which reflects a simplified recapitulation in cellular changes across intracortical laminar structure[6, 1215].”

> *L68: specialization1,[20].*

We have corrected it.

> *L167: 'networks significantly increased with age and exhibited greater increased' - needs rephrasing.*

We have corrected it.

> *L194: 'networks were significantly predicted the general intelligence' - needs rephrasing.*

We have corrected it, please see lines 204-205: “we found that the weights of frontoparietal and default mode networks significantly contributed to the prediction of the general intelligence.”

> *L447: 'and temporal bandpass filtering' - there is a verb missing.*

We have corrected it, please see line 471: “executed temporal bandpass filtering.”

> *L448: 'greater than 0.15' - unit missing.*

We have corrected it, please see line 472: “greater than 0.15 mm”.

> *L452: 'After censoring, regression of nuisance variables, and temporal bandpass filtering,' - no need to repeat the steps as you mentioned them 3 sentences earlier.*

We have removed it.

> *L458-459: sorry I find this description slightly confusing. What do you mean by 'modal'? Connectional -> connectivity profile. The whole thing could be simplified, if I understand correctly your vector of independent variables is a set of wm and microstructural 'connectivity' of the given node... if this is not the case, please make it clearer.*

We have corrected it, please see line 488: “where s_i is the ith SC profiles, n is the number of SC profiles”.

> *L479: 'values and system-specific of 480 coupling'.*

We have corrected it.

> *L500: 'regular' - regularisation.*

We have changed it to “regularization”.

> *L567: Do you mean that in contrast to probabilistic with FSL you use deterministic methods within Camino? For L570, you introduce communication models through 'such as': did you fit all models like before? If not, it might be clearer to just list the ones you estimated rather than introduce through 'such as'.*

We have changed the description to avoid ambiguity, please see lines 608-609: “We then calculated the communication properties of the WMC including communicability, mean first passage times of random walkers, and flow graphs (timescales=1).”

> *Citation [12], it is unusual to include competing interests in the citation, moreover, Dr. Bullmore mentioned is not in the authors' list - this is most likely an error with citation import, it would be good to double-check.*

We have corrected it.

> *L590: Python scripts used to perform PLS regression can 591 be found at https://scikitlearn.org/. The link leads to general documentation for sklearn.*

We have corrected it, please see lines 627-630: “Python scripts used to perform PLS regression can be found at https://scikit-learn.org/stable/modules/generated/sklearn.cross_decomposition.PLSRegression.html#sklearn.cro ss_decomposition.PLSRegression.”

> *P26 and 27 - there are two related sections: Data and code availability and Code availability - it might be worth merging into one section if possible.*

We have corrected it, please see lines 623-633.

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(2) Zhong S, He Y, Gong G. Convergence and divergence across construction methods for human brain white matter networks: an assessment based on individual differences. Hum Brain Mapp. 2015;36(5):1995-2013. Epub 2015/02/03. doi: 10.1002/hbm.22751. PubMed PMID: 25641208; PubMed Central PMCID: PMCPMC6869604.

(3) Waehnert MD, Dinse J, Weiss M, Streicher MN, Waehnert P, Geyer S, et al. Anatomically motivated modeling of cortical laminae. Neuroimage. 2014;93 Pt 2:210-20. Epub 2013/04/23. doi: 10.1016/j.neuroimage.2013.03.078. PubMed PMID: 23603284.

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