Development of structure–function coupling in human brain networks during youth

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The protracted development of structural and functional brain connectivity within distributed association networks coincides with improvements in higher-order cognitive processes such as executive function. However, it remains unclear how white-matter architecture develops during youth to directly support coordinated neural activity. Here, we characterize the development of structure–function coupling using diffusion-weighted imaging and *n*-back functional MRI data in a sample of 727 individuals (ages 8 to 23 y). We found that spatial variability in structure–function coupling aligned with cortical hierarchies of functional specialization and evolutionary expansion. Furthermore, hierarchy-dependent age effects on structure–function coupling localized to transmodal cortex in both cross-sectional data and a subset of participants with longitudinal data ($n = 294$). Moreover, structure–function coupling in rostrolateral prefrontal cortex was associated with executive performance and partially mediated age-related improvements in executive function. Together, these findings delineate a critical dimension of adolescent brain development, whereby the coupling between structural and functional connectivity remodels to support functional specialization and cognition.

brain development | MRI | connectome | cortical organization | structure–function

The human cerebral cortex is organized along a functional hierarchy extending from unimodal sensory cortex to transmodal association cortex (1, 2). This macroscale functional hierarchy is anchored by an anatomical backbone of white-matter pathways that coordinate synchronized neural activity and cognition. Both primate cortical evolution and human brain development have been characterized by the targeted expansion and remodeling of transmodal association areas (3, 4), which underpin the integration of sensory representations and abstract rules for executing goals. The protracted development of transmodal association cortex in humans provides an extended window for activity-dependent myelination (5) and synaptic pruning (6). This period of cortical plasticity sculpts functional specialization in transmodal association cortex and may be critical for developing higher-order executive functions such as working memory, mental flexibility, and inhibitory control (7).

Characterizing the functional specialization of cortical areas based on their patterns of connectivity has been central to understanding hierarchies of brain organization (8, 9). Network theory has provided a parsimonious framework for modeling structure–function mappings in neurobiological systems across species and spatial scales (10). Convergent evidence has highlighted the strong correspondence between measures of structural and functional brain connectivity at different spatiotemporal scales, including neural populations (11), specialized cortical regions (12), and large-scale brain networks (13–15). However, only sparse data exist regarding how the maturation of white-matter architecture during human brain development supports coordinated fluctuations in neural activity underlying cognition. Furthermore, aberrant development of structural constraints on functional communication could contribute to deficits in executive function and the emergence of neuropsychiatric disorders during adolescence (16–18).

Structure–function coupling describes structural support for functional communication and occurs when a cortical region's profile of interregional white-matter connectivity predicts the strength of interregional functional connectivity. Here, we describe the cortical topography of structure–function coupling and delineate how it evolves with development. To do this, we tested three related hypotheses. First, we hypothesized that structure–function coupling would reflect the functional specialization of a

Significance

The human brain is organized into a hierarchy of functional systems that evolve in childhood and adolescence to support the dynamic control of attention and behavior. However, it remains unknown how developing white-matter architecture supports coordinated fluctuations in neural activity underlying cognition. We document marked remodeling of structure–function coupling in youth, which aligns with cortical hierarchies of functional specialization and evolutionary expansion. Further, we demonstrate that structure–function coupling in rostrolateral prefrontal cortex supports age-related improvements in executive ability. These findings have broad relevance for accounts of experience-dependent plasticity in healthy development and abnormal development associated with neuropsychiatric illness.

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cortical area. Specifically, we predicted structure–function coupling would be high in somatosensory cortex, due to highly conserved programming that governs the early development of specialized sensory hierarchies (19). Conversely, we expected that structure–function coupling would be low in transmodal association cortex, where functional communication may have become untethered from genetic and anatomical constraints through rapid evolutionary expansion (19). Second, based on evidence of prolonged activity-dependent myelination during development (5), we hypothesized that developmental increases in structure–function coupling would be localized to transmodal association cortex. Third, under the premise that structure–function coupling reflects functional specialization of a cortical area (9), we hypothesized that higher structure–function coupling in frontoparietal association cortex would support specialized computations relevant for executive functioning (16, 20).

Results

To characterize the development of structure–function coupling in youth, we quantified the degree to which a brain region's structural connections support coordinated fluctuations in neural activity. Leveraging multimodal neuroimaging data from 727 participants ages 8 to 23 y, we applied probabilistic diffusion tractography and estimated functional connectivity between each pair of cortical regions during a fractal *n*-back working memory task. While intrinsic functional connectivity estimated at rest reflects spontaneous fluctuations in neural activity during unconstrained cognitive states, functional connectivity measured during a working memory task can amplify individual differences in neural circuitry underlying executive performance (21). For each participant, two 400 × 400 weighted adjacency matrices were constructed using the same cortical parcellation (22), reflecting the structural and functional connectome. Structure–function coupling was measured as the Spearman rank correlation between the structural and functional connectivity profiles of each region (Fig. 1).

Variability in Structure–Function Coupling Reflects Gradients of Functional Specialization. As a first step, we assessed whether the spatial distribution of structure–function coupling aligns with fundamental properties of cortical organization. The spatial correspondence between structure–function coupling and other cortical properties was assessed using a conservative spatial permutation test, which generates a null distribution of randomly rotated brain maps that preserve the spatial covariance structure of the original data (associated *P* values are denoted p_{spin}) (23). Notably, the coupling between regional structural and functional connectivity profiles varied widely across the cortex (Fig. 2*A*), with higher coupling in primary sensory and medial prefrontal cortex compared to lateral temporal and frontoparietal regions with lower coupling. To assess the relationship between structure–function coupling and functional specialization, we calculated the participation coefficient, which is a graph measure that quantifies the diversity of connectivity across functionally specialized modules (24). Each brain region was assigned to one of seven canonical functional brain networks (25). Brain network nodes with a high participation coefficient exhibit diverse intermodular connectivity, and thus theoretically have the capacity to integrate information across distinct brain modules under some assumptions of module dynamics. In contrast, nodes with a low participation coefficient exhibit more locally segregated connectivity within that node's module. Variability in structure–function coupling was significantly associated with the participation coefficient for both structural ($r = -0.28$, $p_{spin} = 0.001$; Fig. 2*B*) and functional ($r = -0.17$, $p_{spin} = 0.037$; Fig. 2*C*) brain networks. Brain regions exhibiting relatively high structure–function coupling were localized in segregated regions of primary sensory and medial prefrontal cortex, while regions with diverse intermodular connectivity had relatively lower structure–function coupling.

Next, we evaluated whether variability in structure–function coupling reflects a macroscale functional hierarchy defined using an independent dataset (2) that captures a primary dimension of variance in intrinsic functional connectivity from unimodal sensory areas to transmodal association cortex. Structure–function

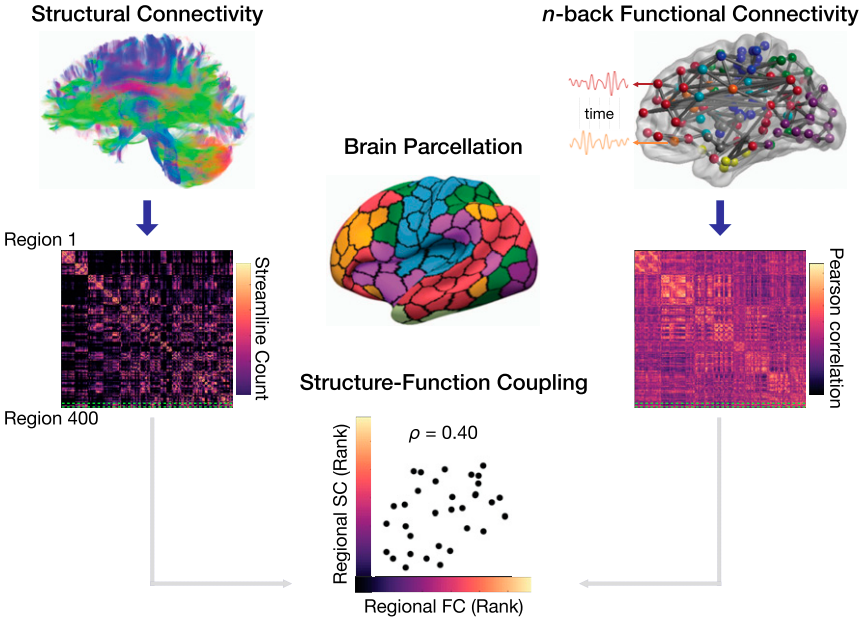

Fig. 1. Measuring structure–function coupling in human brain networks. Nodes in structural and functional brain networks were defined using a 400-region cortical parcellation based on functional homogeneity in fMRI data (22). For each participant, regional connectivity profiles were extracted from each row of the structural or functional connectivity matrix and represented as vectors of connectivity strength from a single network node to all other nodes in the network. Structure–function coupling was then measured as the Spearman rank correlation between nonzero elements of regional structural and functional connectivity profiles.

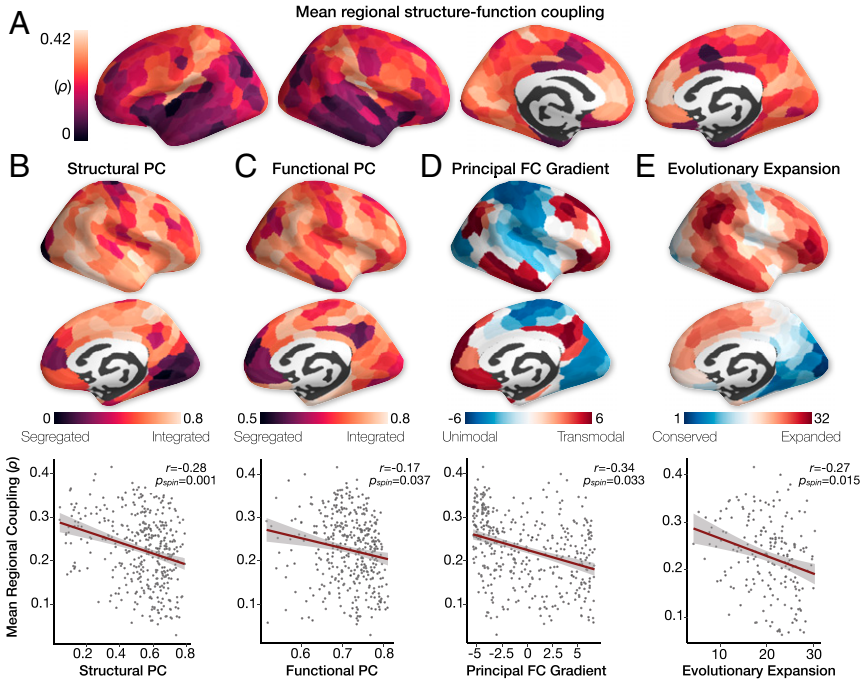

Fig. 2. Variability in structure–function coupling reflects cortical hierarchies of functional specialization. The coupling between regional structural and functional connectivity profiles during the *n*-back working memory task varied widely across the cortex. (*A*) Primary sensory and medial prefrontal cortex exhibited relatively high structure–function coupling, while lateral temporal and frontoparietal regions had relatively low coupling. (*B*) Structure–function coupling was significantly associated with the structural participation coefficient (PC) and the functional participation coefficient (*C*), a measure of the diversity of intermodule connectivity. (*D*) Variability in structure–function coupling reflected a brain region's position along the macroscale functional gradient from unimodal to transmodal processing, and (*E*) recapitulated patterns of evolutionary expansion in cortical surface area from macaques to humans. The significance of regional correlations was evaluated using nonparametric spatial permutation testing, and associated *P* values are denoted p_{spin}.

coupling aligned significantly with the principal gradient of functional connectivity: Unimodal sensory regions exhibited relatively strong structure–function coupling, while transmodal regions at the apex of the functional hierarchy exhibited weaker coupling ($r = -0.34$, $p_{spin} = 0.033$; Fig. 2*D*). We also tested the hypothesis that functionally specialized somatosensory cortex with evolutionarily conserved organization would exhibit strong structure–function coupling, while highly expanded transmodal cortex would exhibit relatively low structure–function coupling to facilitate functional diversity and cognitive flexibility. Our results were consistent with such an account, as structure–function coupling was significantly correlated with evolutionary expansion of cortical surface area ($r = -0.27$, $p_{spin} = 0.015$; Fig. 2*E*). Highly conserved sensory areas had relatively strong structure–function coupling, while highly expanded transmodal areas had weaker coupling. Together, our results demonstrate that structure–function coupling reflects cortical hierarchies of functional specialization and evolutionary expansion.

Hierarchy-Dependent Development of Structure–Function Coupling. While previous work has largely focused on global relationships between group-averaged structural and functional brain networks in adults, here we sought to understand how regional structure–function coupling develops from childhood through adulthood. Regional associations between structure–function coupling and age were assessed using generalized additive models (GAM) with penalized splines, including sex and in-scanner head motion as covariates. Age-related differences in structure–function coupling were broadly distributed across lateral temporal, inferior parietal, and prefrontal cortex (Fig. 3*A*). Notably, age-related increases in coupling were disproportionately enriched within a unique subset of functionally segregated areas of the default mode network ($F = 12.54$, $P < 1 \times 10^{-10}$; Fig. 3*B*). Moreover, the magnitude of age-related differences in structure–function coupling was significantly correlated with the functional participation coefficient ($r = -0.19$, $p_{spin} = 0.013$; Fig. 3*C*) and the functional gradient from unimodal to transmodal processing ($r = 0.28$, $p_{spin} = 0.009$; Fig. 3*D*). The spatial distribution of age-related differences in structure–function coupling also recapitulated patterns of evolutionary cortical expansion. Age-related increases in coupling were observed primarily in highly expanded association cortex, while age-related decreases in coupling were observed in highly conserved sensory motor cortex ($r = 0.39$, $p_{spin} = 0.002$; Fig. 3*E*).

Longitudinal Increases in Structure–Function Coupling Are Associated with Changes in the Regional Diversity of Functional Connectivity. To determine whether age-related changes in structure–function coupling were reliably capturing intraindividual developmental change, we evaluated longitudinal changes in structure–function coupling using a subsample of participants who returned for follow-up ∼1.7 y after baseline assessment ($n = 294$). We observed a significant correspondence between cross-sectional and longitudinal age effects on structure–function coupling estimated with a linear mixed effects model ($r = 0.65$, $p_{spin} < 0.001$; Fig. 4*A*).

Next, we evaluated how intraindividual development of structure–function coupling was associated with intraindividual changes in the diversity of regional connectivity. We focused on developmental changes in the participation coefficient because it captures how a brain region's connections are distributed across functionally specialized subnetworks underlying perception, attention, and executive control (26). We used linear regression to test whether longitudinal change in structure–function coupling (Fig. 4*B*) was associated with longitudinal change in the functional participation coefficient (Fig. 4*C*). Notably, we found that longitudinal changes in coupling were associated with longitudinal changes in the functional participation coefficient in distributed

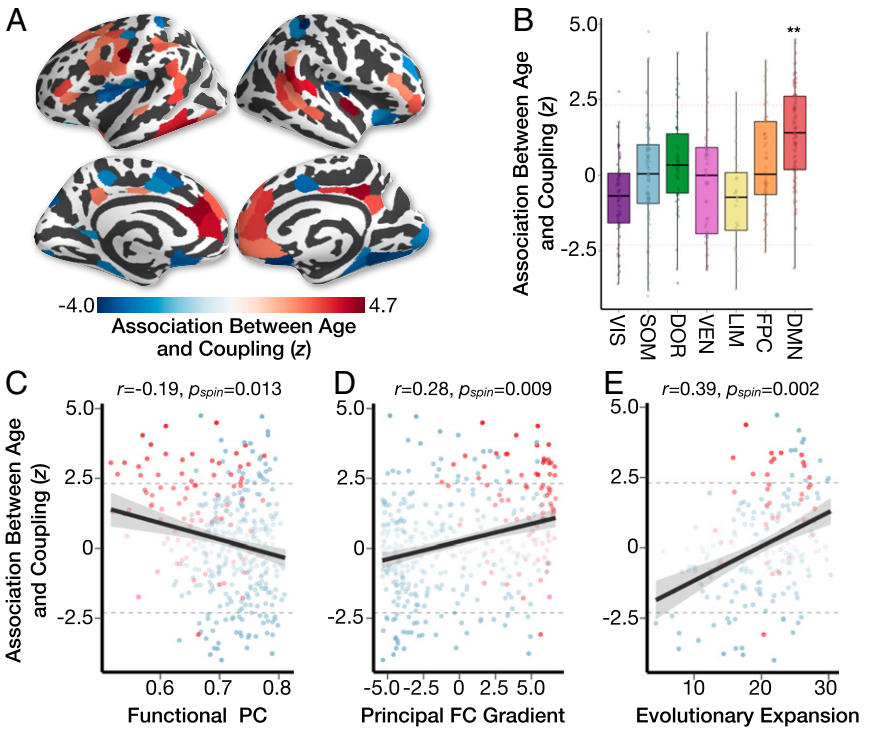

Fig. 3. Hierarchy-dependent development of structure–function coupling. Age-related differences in structure–function coupling were broadly distributed across the cerebral cortex. (*A*) Age-related increases in structure–function coupling were observed bilaterally in the temporoparietal junction and prefrontal cortex, while age-related decreases in coupling were observed in visual, motor, and insular cortex. (*B*) Notably, age-related increases in coupling were disproportionately enriched within the default mode network compared to other functional systems ($F = 12.54$, $P < 10^{-10}$). (*C*) The magnitude of age-related differences in structure–function coupling was significantly correlated with the functional participation coefficient (PC), (*D*) the functional gradient from unimodal to transmodal processing, and (*E*) evolutionary expansion of cortical surface area. The significance of regional correlations was evaluated using nonparametric spatial permutation testing, and associated *P* values are denoted p_{spin}. Red points in *C*–*E* correspond to default mode regions, and blue points correspond to brain regions in other functional systems. Asterisks in *B* indicate $P < 0.001$. VIS, visual; SOM, somatomotor; DOR, dorsal attention; VEN, ventral attention; LIM, limbic; FPC, frontoparietal control; DMN, default mode network.

higher-order association areas, including dorsal and medial prefrontal cortex, inferior parietal cortex, and lateral temporal cortex (Fig. 4*D*). Specifically, longitudinal increases in coupling within dorsal prefrontal and inferior parietal regions were associated with increased intermodular integration, while increased coupling in medial occipital and medial prefrontal cortex was associated with decreased intermodular diversity (functional segregation). We observed significant associations between longitudinal change in structure–function coupling and the functional participation coefficient in some cortical regions that showed no observable age-related differences in the larger cross-sectional sample (*SI Appendix*, Fig. S1). These intraindividual changes in brain connectivity were observed over a narrow developmental window (0.5 to 3.5 y) compared to cross-sectional age-related differences and may reflect plasticity over shorter timescales (*SI Appendix*).

Individual Differences in Structure–Function Coupling Are Associated with Executive Function. Next, we sought to understand the implications of individual differences in structure–function coupling for behavior. Specifically, we investigated whether structure–function coupling during a working memory task could explain executive performance measured on a computerized cognitive battery administered separately from the scanning session. While controlling for age, sex, and in-scanner head motion, we found that better executive performance was associated with higher structure–function coupling in the rostrolateral prefrontal cortex (rlPFC), posterior cingulate, and medial occipital cortex (Fig. 5*A*); better performance was also associated with lower structure–function coupling in somatosensory cortex. Regional associations between coupling and in-scanner performance on the *n*-back working memory task (*d'*) were highly consistent (*SI Appendix*, Fig. S2). Notably, the strength of this association between regional coupling and executive performance was significantly correlated with that region's position along the functional hierarchy from unimodal to transmodal processing: Higher structure–function coupling in transmodal regions of frontoparietal and default networks was associated with better performance on executive tasks ($r = 0.25$, $p_{spin} = 0.005$). Furthermore, higher structure–function coupling in the right rlPFC partially mediated age-related improvements in executive function (Fig. 5*B*; bootstrapped $P = 0.01$). Regional associations between coupling and cognitive performance were most robust within the executive domain: We observed no associations between coupling and social cognition, and structure–function coupling was associated with episodic memory performance in only four cortical regions (*SI Appendix*, Fig. S3). These results suggest that structure–function coupling in transmodal regions during task conditions may in part underpin individual differences in executive processes.

Sensitivity Analyses. As a final step, we performed sensitivity analyses to evaluate whether our results were robust to a number of methodological variations. Spatial variability and age-related changes in structure–function coupling were highly consistent across methodological approaches, including 1) applying consistency-based thresholds to structural connectivity matrices (*SI Appendix*, Fig. S4), 2) using deterministic tractography and network communicability as a measure of structural connectivity strength that captures communication through indirect connections (*SI Appendix*, Fig. S5), 3) extracting functional connectivity only from task blocks with high working memory load (one-back and two-back) instead of the full task time series (*SI Appendix*, Fig. S6), 4) accounting for

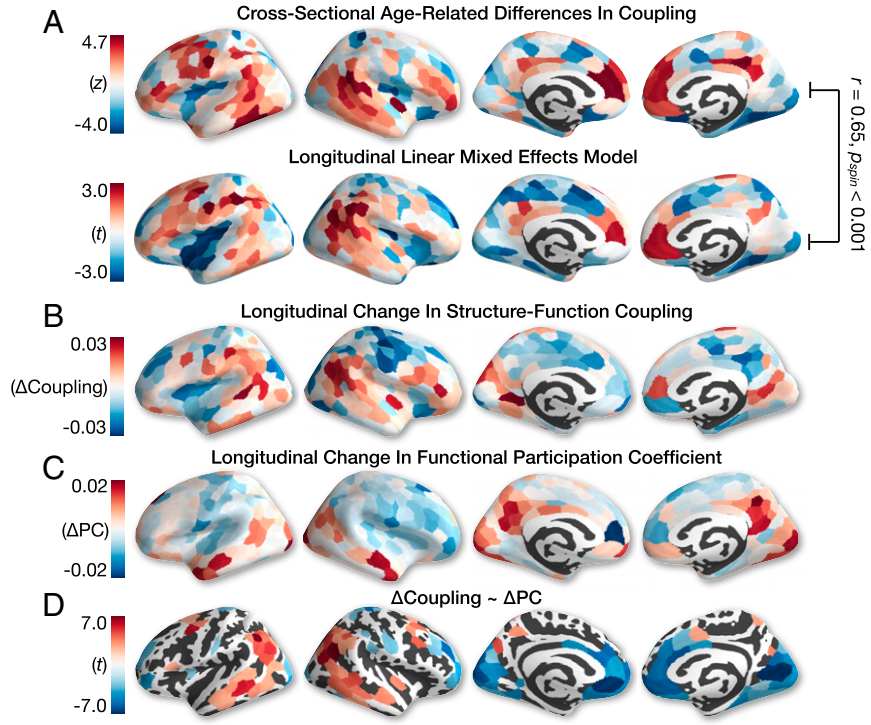

Fig. 4. Longitudinal change in structure–function coupling is associated with longitudinal change in the diversity of regional functional connectivity. (*A*) We observed a significant correspondence between cross-sectional ($n = 727$) and longitudinal age effects on structure–function coupling estimated with a linear mixed-effects model ($n = 294$). We used linear regression to test whether longitudinal change in structure–function coupling (*B*) was associated with longitudinal change in the functional participation coefficient (*C*). Longitudinal increases in coupling were associated with increased participation coefficient (functional integration) in lateral frontoparietal and temporal regions and decreased participation coefficient (functional segregation) in medial visual and prefrontal regions (*D*).

interregional distance when quantifying structure–function coupling (*SI Appendix*, Fig. S7), 5) accounting for nodal degree when evaluating age-related differences in structure–function coupling (*SI Appendix*, Fig. S8), and 6) accounting for nodal strength when evaluating age-related differences in structure–function coupling (*SI Appendix*, Fig. S9).

We also evaluated whether regional patterns of structure–function coupling showed a similar organization during the *n*-back working memory task and at rest. The spatial distribution of structure–function coupling was globally similar during *n*-back and rest when averaging across individuals ($r = 0.95$, $p_{spin} < 0.001$; *SI Appendix*, Fig. S10). However, we observed greater intraindividual variability in regional coupling when assessing the correlation between *n*-back and resting-state coupling for each participant (mean $r = 0.53$; *SI Appendix*, Fig. S10). Further, regional variability in structure–function coupling during *n*-back was more robustly associated with individual differences in executive performance compared to coupling during rest (*SI Appendix*, *SI Results*).

Discussion

We leveraged multimodal neuroimaging in a large sample of youths to characterize how structure–function coupling evolves in development and reflects macroscale cortical hierarchies. Consistent with previous work characterizing the targeted expansion and remodeling of transmodal cortex in both primate evolution and human development, we observed age-related differences in coupling localized within a unique subset of transmodal regions spanning higher-order association networks. These findings fill a critical gap in our understanding of how white-matter architecture develops during human adolescence to support coordinated neural activity underlying executive processing.

Cortical hierarchy has provided a unifying principle for understanding the multiscale organization of primate cortical anatomy and function (2, 8, 27). Anatomical hierarchies of intracortical myelin (28) and laminar patterns of interareal projections (29) have been shown to align with hierarchies of functional (2) and transcriptional (28) specialization. Here, we provide evidence that these cortical hierarchies are in part determined by anatomical constraints on functional communication, whereby highly myelinated sensory areas exhibit strong structure–function coupling, and less myelinated association areas exhibit weak structure–function coupling. The convergence of structural and functional connectivity profiles in unimodal sensory regions suggests that functional communication is directly supported by local white-matter pathways. In contrast, the divergence of structural and functional connectivity profiles in transmodal regions suggests that functional communication is untethered by structural constraints, relying on polysynaptic (indirect) structural connections or circuit-level modulation of neural signals.

Lower structure–function coupling in transmodal brain regions may also support functional flexibility and dynamic recruitment during diverse task demands (30). One important exception to this trend was observed in transmodal regions of the default mode network, such as the medial prefrontal cortex, which exhibited both functional segregation and strong structure–function coupling. Tightly coupled structural and functional connectivity within transmodal regions of the medial prefrontal cortex could support efficient communication among strongly interconnected association areas within the default mode network. Further, high structure–function coupling in local hubs of the default network could reduce competitive interference between the (task-positive) central executive and (task-negative) default mode networks (31), allowing for the suppression of internally generated thoughts while maintaining and manipulating information in working memory.

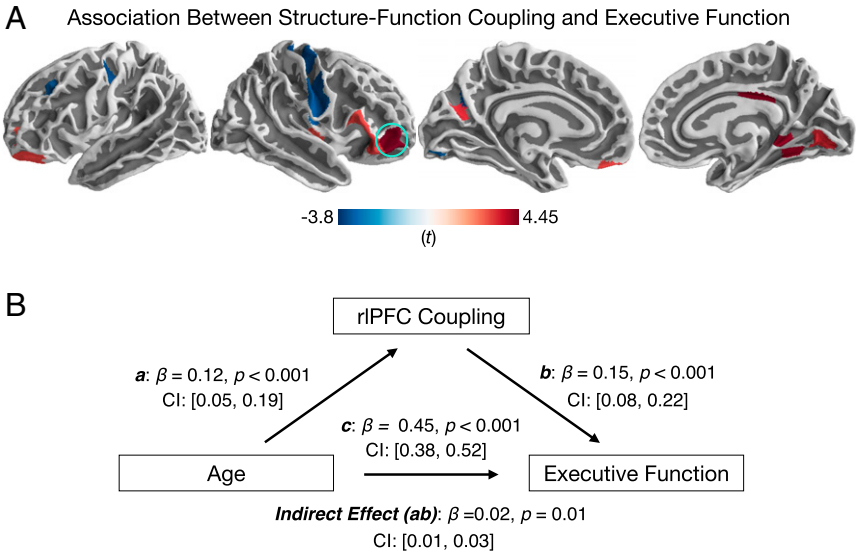

Fig. 5. Individual differences in structure–function coupling are associated with executive function. (*A*) We found that executive performance was associated with higher structure–function coupling in the rlPFC, anterior insula, posterior cingulate, and medial occipital cortex, while better performance was associated with lower structure–function coupling in areas of somatomotor cortex. (*B*) Higher structure–function coupling in the rlPFC (circled in *A*) partially mediated age-related improvements in executive function. Mediation results are reported as standardized regression coefficients, and statistical significance was assessed using 95% bootstrapped CIs.

Our findings of regional variability in structure–function coupling are consistent with recent work that has described similar hierarchical differences between structural and functional connectivity (32) and between microstructural covariance profiles and functional connectivity (33). While these studies report convergent structure–function coupling in primary sensory cortex and divergent structure–function coupling in transmodal association cortex, the focus on group-averaged data precluded investigating how structure–function coupling changes over the course of brain development, and whether it is relevant for individual differences in cognitive ability. One recent study in adults found that lower switch costs during a cognitive switching task were linked with individual differences in the alignment between blood-oxygen-level-dependent signals and the eigenspectrum of structural brain networks (34). By demonstrating age-related differences in regional patterns of structure–function coupling that are linked with executive function, our findings build upon prior accounts of structure–function relationships in human neocortex.

Developmental changes in coupling were preferentially localized within transmodal areas of frontoparietal and default mode networks, recapitulating evolutionary patterns of cortical areal expansion. In addition to having expanded association cortex relative to other primates, humans exhibit slower axonal myelination in association cortex during childhood, characterized by a prolonged period of maturation that extends into early adulthood (5). As posited by the tethering hypothesis (19), this protracted development provides an extended window for the activity-dependent remodeling of distributed neural circuits in transmodal association cortex, which may be critical for the maturation of complex cognitive abilities in humans. In our study, longitudinal changes in structure–function coupling in transmodal cortex were associated with developmental increases in the diversity of intermodular functional connectivity, underscoring the flexible and integrative role of these brain regions within the network.

One outstanding question concerns whether existing white-matter architecture drives future changes in functional connectivity, or whether functional circuit changes sculpt the development of specific wiring patterns. We speculate that developmental changes in structure–function coupling could reflect processes of neural plasticity, such as the activity-dependent myelination of axons linking functionally coupled regions (35, 36). Alternatively, early myelination of axons could enhance signal conduction velocity and fidelity, enhancing neural signal-to-noise ratio and the coordination of distributed neural activity (36). Longitudinal inferences in our study were limited by only two time points of imaging data, precluding the characterization of lead–lag relationships between structural and functional brain connectivity. Future studies could leverage dense sampling of individuals during sensitive periods of development to delineate lead–lag relationships in the maturation of structural and functional connectivity within specialized circuits.

Our results also suggest that structure–function coupling has implications for individual differences in executive function. The rlPFC has been consistently linked with abstract reasoning (37) and the hierarchical control of goal-directed behavior (38). From childhood through early adulthood, the development of structural and functional connectivity between the rlPFC and lateral parietal cortex has been associated with improvements in abstract reasoning ability (37, 39). In this study, we extend these findings by showing that individual differences in rlPFC structure–function coupling partially mediate age-related improvements in executive functioning. The capacity of rlPFC to support executive processing may be understood through its role in integrating information between frontoparietal and dorsal attention networks to regulate perceptual attention (40).

Despite the strengths of this study, potential limitations should be noted. First, accurately reconstructing the complexity of human white-matter pathways from diffusion MRI and tractography remains challenging. Diffusion tractography algorithms face a well-characterized trade-off between connectome specificity and sensitivity (41). In this study, we attempted to overcome these limitations by replicating results with both deterministic and probabilistic tractography methods, while also applying a consistency-based thresholding procedure to minimize the influence of false-positive connections (42). Second, motion artifact remains an important confound for all neuroimaging-based studies of brain development (43, 44). In addition to rigorous quality assurance protocols and extensively validated image processing designed to mitigate the influence of head motion on functional connectivity (45), we address this issue by quantifying and controlling for the influence of in-scanner head motion in all group-level analyses. Third, while our approach for quantifying regional patterns of

structure–function coupling allowed us to evaluate age-related differences and associations with cognitive ability, this approach was limited in its ability to discern the influence of individual network connections on regional measures.

Conclusion

By quantifying regional patterns of structure–function coupling and characterizing their development during adolescence, our results inform network-level mechanisms of plasticity that support cognitive maturation. Describing how underlying white-matter architecture develops to support coordinated neural activity underlying executive function may offer critical insights into the basis for many sources of adolescent morbidity and mortality, such as risk taking and diverse neuropsychiatric syndromes which are prominently associated with failures of executive function.

Materials and Methods

Neuroimaging was completed as part of the Philadelphia Neurodevelopmental Cohort (46). All participants, or their parent or guardian, provided informed consent, and minors provided assent; study procedures were approved by the institutional review boards of both the University of Pennsylvania and the Children's Hospital of Philadelphia. All participants included in this study were medically healthy, were not taking psychotropic medication at the time of study, and passed strict quality-assurance procedures for four imaging modalities including T1-weighted structural images, diffusion-weighted imaging, resting-state functional MRI (fMRI), and *n*-back fMRI. The final sample included 727 youths ages 8 to 23 y (420 females; mean = 15.9 y, SD = 3.2 y). From the original study sample, 147 typically developing youths returned for longitudinal neuroimaging assessments ∼1.7 y after baseline (83 females; 294 total scans). For further details regarding image preprocessing and brain network construction see *SI Appendix*, *SI Methods*.

To evaluate the relationship between structure–function coupling and previously characterized cortical hierarchies, evolutionary cortical areal expansion (3) and the principal gradient of intrinsic functional connectivity (2) were extracted from publicly available atlases. The significance of the spatial correspondence between brain maps was estimated using a conservative spatial permutation test, which generates a null distribution of randomly rotated brain maps that preserve spatial covariance structure of the original data (23).

We used penalized splines within a GAM to estimate linear and nonlinear age-related changes in structure–function coupling for each brain region. Importantly, the GAM estimates nonlinearities using restricted maximum likelihood, penalizing nonlinearity in order to avoid overfitting the data (47). To evaluate regional associations between structure–function coupling and executive function, executive performance was measured as a factor score summarizing accuracy across mental flexibility, attention, working memory, verbal reasoning, and spatial ability tasks administered as part of the Penn Computerized Neurocognitive Battery (*SI Appendix*, *SI Methods*).

Longitudinal developmental change in structure–function coupling was evaluated with two approaches. First, we estimated longitudinal age effects on coupling within a linear mixed effects model, including a random subject intercept in addition to other covariates. Second, we used linear regression models with longitudinal change scores. Longitudinal intraindividual change in coupling (ΔCoupling) and the participation coefficient (ΔPC) were calculated as the difference in regional brain measures between time points. Baseline age, sex, mean relative framewise displacement, and the number of years between time points were included as additional covariates in linear regression models.

The data reported in this paper have been deposited in the database of Genotypes and Phenotypes under accession number dbGaP: phs000607.v2.p2 (https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs000607.v2.p2).

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