CellPress

Neuron

Review

Neurodevelopment of the association cortices: Patterns, mechanisms, and implications for psychopathology

Valerie J. Sydnor,[1,2] Bart Larsen,[1,2] Danielle S. Bassett,[2,3,4,5,6,7] Aaron Alexander-Bloch,[2,8] Damien A. Fair,[9] Conor Liston,[10] Allyson P. Mackey,[11] Michael P. Milham,[12,13] Adam Pines,[1,2] David R. Roalf,[2] Jakob Seidlitz,[2,8] Ting Xu,[12] Armin Raznahan,[14] and Theodore D. Satterthwaite[1,2,15,*]

[1]Penn Lifespan Informatics and Neuroimaging Center (PennLINC), Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA
[2]Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA
[3]Department of Bioengineering, School of Engineering & Applied Science, University of Pennsylvania, Philadelphia, PA 19104, USA
[4]Department of Electrical & Systems Engineering, School of Engineering & Applied Science, University of Pennsylvania, Philadelphia, PA 19104, USA
[5]Department of Physics & Astronomy, College of Arts & Sciences, University of Pennsylvania, Philadelphia, PA 19104, USA
[6]Department of Neurology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA
[7]Santa Fe Institute, Santa Fe, NM 87501, USA
[8]Department of Child and Adolescent Psychiatry and Behavioral Science, The Children's Hospital of Philadelphia, Philadelphia, PA 19104, USA
[9]Masonic Institute for the Developing Brain, Institute of Child Development, College of Education and Human Development, Department of Pediatrics, Medical School, University of Minnesota, Minneapolis, MN 55414, USA
[10]Department of Psychiatry and Brain and Mind Research Institute, Weill Cornell Medicine, New York, NY 10065, USA
[11]Department of Psychology, University of Pennsylvania, Philadelphia, PA 19104, USA
[12]Center for the Developing Brain, Child Mind Institute, New York, NY 10022, USA
[13]Center for Biomedical Imaging and Neuromodulation, Nathan Kline Institute, Orangeburg, NY 10962, USA
[14]Section on Developmental Neurogenomics, NIMH Intramural Research Program, NIH, Bethesda, MD 20892, USA
[15]Center for Biomedical Image Computing and Analytics, University of Pennsylvania, Philadelphia, PA 19104, USA
*Correspondence: sattertt@pennmedicine.upenn.edu
https://doi.org/10.1016/j.neuron.2021.06.016

SUMMARY

The human brain undergoes a prolonged period of cortical development that spans multiple decades. During childhood and adolescence, cortical development progresses from lower-order, primary and unimodal cortices with sensory and motor functions to higher-order, transmodal association cortices subserving executive, socioemotional, and mentalizing functions. The spatiotemporal patterning of cortical maturation thus proceeds in a hierarchical manner, conforming to an evolutionarily rooted, sensorimotor-to-association axis of cortical organization. This developmental program has been characterized by data derived from multimodal human neuroimaging and is linked to the hierarchical unfolding of plasticity-related neurobiological events. Critically, this developmental program serves to enhance feature variation between lower-order and higher-order regions, thus endowing the brain's association cortices with unique functional properties. However, accumulating evidence suggests that protracted plasticity within late-maturing association cortices, which represents a defining feature of the human developmental program, also confers risk for diverse developmental psychopathologies.

INTRODUCTION

The human brain supports unique cognitive, socioemotional, and mentalizing capabilities. These capabilities emerged as part of recent evolutionary development and are sculpted and enhanced in each individual by the process of neurodevelopment. Such human-specific faculties are subserved by the association cortices of the brain: phylogenetically newer regions of cortex that exhibit protracted neurodevelopment throughout childhood and adolescence. Maturation of the association cortices partially underlies the significant intellectual, emotional, and behavioral changes observed during the first decades of life, with maturational variability contributing to inter-individual differences in executive and psychosocial functioning.

The brain's association cortices—composed of prefrontal, cingulate, inferior parietal, precuneal, and middle temporal areas, often referred to collectively as "association cortex"—are expansive and integrative regions of cortex that can be principally contrasted against primary sensory and motor cortices. Primary sensorimotor regions (i.e., primary visual, auditory, somatosensory, and motor cortices) are unimodal, functionally specific, and involved in processes of sensation, perception,

and action. Regions of association cortex, in contrast, tend to be multimodal or transmodal (though unimodal association areas exist), functionally flexible, and recruited for information integration, perceptually decoupled cognition, or internal thought (Margulies et al., 2016; Murphy et al., 2019; Yeo et al., 2015). Moreover, primary regions are located most distant on the cortex from transmodal association regions that support higher-order psychological, social, and executive functions, with uni- and multi-modal cortices occupying spatially intermediate positions (Huntenburg et al., 2018; Margulies et al., 2016; Mesulam, 2008). This distance-dependent layout of the cortex ultimately corresponds to a large-scale axis of cortical feature organization—an axis that repeatedly manifests when examining spatial variation in diverse features across the cortex and that informs our understanding of the timing and consequences of cortical development.

An axis is a unidimensional ordering of cortical regions, determined by quantifying patterns of variability in one or more cortical properties. Cortical regions that occupy nearby positions along an axis—regardless of their distance across the cortex—are similar with respect to a given property, whereas those that define the two opposing ends of an axis are maximally divergent. When visualized across the cortical surface, axes of organization offer insight into the global arrangement of cortical properties and the degree of similarity among regions, augmenting the information derived from characterization of local properties. Critically, efforts to delineate axes of organization for a multitude of different cortical properties have revealed that the principal axis of organization commonly spans from primary and unimodal sensory and motor cortices, to multimodal cortices, and finally to transmodal association cortices that support advanced mental functions, defining a "sensorimotor-association (S-A) cortical axis." Cortical features derived from remarkably varied data types including non-invasive neuroimaging (Burt et al., 2018; Huntenburg et al., 2018; Margulies et al., 2016; Paquola et al., 2019a; Raut et al., 2020), histology (Beul and Hilgetag, 2019; Paquola et al., 2019a; Scholtens et al., 2014), transcriptomics (Burt et al., 2018; Hansen et al., 2021; Krienen et al., 2016), receptor autoradiography (Froudist-Walsh et al., 2021; Goulas et al., 2021), and electrophysiology (Gao et al., 2020; Honey et al., 2012; Murray et al., 2014) conform to this principal S-A axis. Hence, joint spatial variation observed across numerous neurobiological features reflects a hierarchical axis of cortical function that transitions from lower-order sensorimotor to highest-order associative functions: from action to cognition, from perception to introspection, from sensation to self-awareness.

In this review, we discuss how the spatial and temporal patterning of cortical maturation proceeds along the S-A axis throughout childhood and adolescence, and describe how this developmental sequence systematically enhances functional variation across the cortical mantle. To this end, we first synthesize data from analyses conducted across scales and species that reveal a unified, principal sensorimotor-to-associative axis of cortical organization. This axis elegantly captures known diversity in cortical anatomy, physiology, gene expression, and function and provides a framework for understanding the progression and the biobehavioral outcomes of cortical development. We next review relevant evidence from studies that have harnessed advanced *in vivo* neuroimaging in humans, which have begun to characterize the unfolding of cortical maturation from early childhood to adulthood. Specifically, we highlight work from structural, diffusion, functional, and chemical neuroimaging that has documented differences in maturational patterns across sensorimotor and associative cortices. We further explore relationships between neuroimaging, histological, physiological, and transcriptomics findings in brain development, in an effort to link macroscale spatiotemporal developmental patterns to microscale mechanisms involved in cortical plasticity. Finally, we consider major causes and consequences of inter-individual maturational variability.

Taken together, existing literature supports a model of human brain development wherein maturation occurs along a dominant, hierarchical organizational axis. In this developmental program, transmodal association cortices develop over a more protracted period of time than sensorimotor cortices, exhibiting sustained development-associated changes through infancy, childhood, and adolescence, and completing their course of maturation comparatively later in development. This developmental program is critical for shaping many of the structural, functional, and computational properties that differentiate transmodal associative cortices from the rest of the cortical landscape. However, the prolonged plasticity seen in higher-order association cortices—which is a defining feature of the brain's developmental program—makes these cortical areas particularly vulnerable to the effects of developmental insults and puts humans at risk for developmental psychopathology.

HIERARCHICAL CORTICAL TOPOGRAPHY AND THE SENSORIMOTOR-ASSOCIATION AXIS

A hierarchical axis of cortical organization

A central goal of neuroscience is to understand intrinsic patterns of cortical organization and topography (i.e., the spatial distribution of cortical areas) and relationships to cortical functioning. Decades of research dedicated to this goal have revealed how patterns of anatomical and functional organization can be understood as conforming to large-scale cortical hierarchies, defined by ordered rankings of cortical areas (Hilgetag and Goulas, 2020). Research has established the importance of three such cortical hierarchies—hierarchies that are described by cortical *anatomy*, cortical *function*, and cortical *evolution*. Foundational studies of cortical anatomy examining architectonic differentiation and the laminar origins of cortico-cortical connections helped identify a dominant cortical hierarchy (Barbas, 1986; Felleman and Van Essen, 1991). In this anatomically defined cortical hierarchy, regions lowest in the hierarchy are those with high neuron density and a greater proportion of supragranular-originating connections involved in feedforward communication (García-Cabezas et al., 2019; Hilgetag and Goulas, 2020; Hilgetag et al., 2019). Conversely, cortical regions highest in the hierarchy are those with lowest neuron density and a predominance of infragranular-originating connections that facilitate feedback communication. The anatomical hierarchy, originally described in the macaque visual system (Felleman and Van Essen, 1991; Markov et al., 2014) and subsequently expanded to the entire primate cortex (Burt et al., 2018;

Chaudhuri et al., 2015; Hilgetag and Goulas, 2020; Hilgetag et al., 2019), revealed how complex facets of cortical organization and communication can be understood through a graded ordering of features along a simplified spatial dimension.

On the basis of theories of function following structure, it was proposed that the anatomical hierarchy would facilitate hierarchical information processing proceeding from lower hierarchy regions involved in externally oriented perception to higher hierarchy regions involved in internally focused cognitive processes (Mesulam, 1998). A wealth of cross-species research—using diverse techniques such as *in vivo* neural recordings, lesion mapping, neuromodulation, and task-based functional MRI—has substantiated the relationship between a region's position in the anatomically defined hierarchy and its function. It is now apparent that cortical areas lowest in the anatomical hierarchy map to sensory and motor regions, whereas cortical areas mid and high in the hierarchy are association cortices that enable integrative, perceptually decoupled, and abstract mental functions. In other words, the anatomically defined hierarchy is spatially coupled with a second, functional cortical hierarchy that is arranged from lower-order to higher-order faculties, with faculties that have progressed most in humans occupying the apex of this hierarchy (Burt et al., 2018; Margulies et al., 2016; Mesulam, 1998, 2008).

Remarkably, these anatomical and functional hierarchies map onto a third, evolution-based cortical hierarchy. The evolutionary hierarchy is indexed by patterns of cortical expansion observed between humans and other species in the mammalian evolutionary tree. Lower-order sensory and motor cortical regions were present and cortically dominant in the earliest of mammals (i.e., those falling lowest in the evolutionary tree). In many ensuing mammalian species, sensory brain regions underwent additional functional specialization, accompanied by sensory cortex enlargement or cortical magnification (Krubitzer, 2007). In the primate lineage, however, the proportion of the cortical surface dedicated to sensory and motor regions declined, whereas the proportion occupied by phylogenetically new association cortices subserving higher-order functions grew significantly larger (Buckner and Krienen, 2013; Halley and Krubitzer, 2019; Krubitzer, 2007; Krubitzer and Kahn, 2003). Humans, in particular, have frontal, temporal, and parietal association cortices that are more expanded than those of both macaques and chimpanzees—and substantially more expanded than expected from increases in brain size alone (Buckner and Krienen, 2013; Donahue et al., 2018; Hill et al., 2010a; Wei et al., 2019; Xu et al., 2020). The human cortical evolutionary hierarchy can therefore be uncovered by quantifying patterns of areal emergence and expansion across the human cortex. Of note, different conceptualizations of an evolutionary hierarchy could then be invoked. For example, sensory and motor regions could be considered the peak of an evolutionary hierarchy, as they are phylogenetically oldest and thus arguably the most evolutionarily honed or refined. Here, however, we operationalize position in the cortical evolutionary hierarchy by the degree to which an area has expanded in humans compared with other mammalian species, including other primates. Regions with the least expansion, which are nearly universally sensory and motor cortices, fall lowest in the hierarchy. In contrast, regions with the greatest expansion, which localize to lateral prefrontal, temporal, and parietal transmodal association cortices, are positioned highest in the hierarchy. Although defined by distinct measures, anatomical, functional, and evolutionary hierarchies exhibit *convergent spatial embedding* across the human cortical mantle, suggesting the existence of an overarching, hierarchy-related topography in the brain (Figure 1).

Work examining spatial variation across heterogeneous brain properties strongly supports the presence of a hierarchical axis of cortical topographical organization. The study of cortical organization is frequently approached via characterizing regional properties, for example, regional cytoarchitecture, connectivity, genetic composition, cell type distribution, or functional features. A complementary approach is to understand how such properties are distributed across the cortical landscape, by identifying axes of maximum feature variance and their spatial embedding in the brain. For univariate measures such as cortical thickness or neuron density, an axis is determined by ordering regions based directly on the univariate measure of interest. For multivariate measures such as functional connectivity profiles or gene sets, an axis is defined by applying linear (e.g., principal component analysis) or non-linear (e.g., spectral embedding) dimensionality reduction techniques and analyzing the resulting low-dimensional representation; this low-dimensional representation is often referred to as a gradient when feature variation along the dimension is continuous. Efforts focused on defining axes of cortical organization, although historically grounded, have accelerated substantially in recent years. These data-driven efforts have demonstrated that although multiple large-scale organizational axes exist (such as anterior-posterior and dorsal-ventral axes), the principal axis for diverse cortical features spatially aligns with the three canonical hierarchies described by anatomy, function, and evolution.

This principal axis is evident when examining neuroimaging-derived measures of cortical thickness (Burt et al., 2018; Wagstyl et al., 2015), intracortical myelination (Burt et al., 2018; Huntenburg et al., 2017; Paquola et al., 2019a), areal allometric scaling (Reardon et al., 2018), cerebral metabolism (Satterthwaite et al., 2014; Vaishnavi et al., 2010), cortico-cortical connectivity distance (Bazinet et al., 2020; Oligschläger et al., 2017; Sepulcre et al., 2010), functional connectivity patterns (Margulies et al., 2016), functional timescale length (Ito et al., 2020; Raut et al., 2020), and structure-function coupling (Baum et al., 2020; Preti and Van De Ville, 2019). Moreover, this principal axis is apparent when examining histology-derived measures of cellular microstructure (Goulas et al., 2018; Paquola et al., 2019a, 2020a), neuron density (Beul and Hilgetag, 2019; Cahalane et al., 2012), and excitatory neuron spine density (van den Heuvel et al., 2016a). Finally, this principal axis manifests in spatial maps of transcriptomics-derived measures of cortical gene expression (Burt et al., 2018) as well as autoradiography-derived measures of neurotransmitter receptor densities (Froudist-Walsh et al., 2021; Goulas et al., 2021). The concerted patterning of such diverse neurobiological properties across the cortical sheet provides strikingly convergent evidence for a unifying, hierarchical axis of organization that spans from primary sensory and motor areas to transmodal association areas: the S-A axis of cortical organization (; ; , Figure 2).

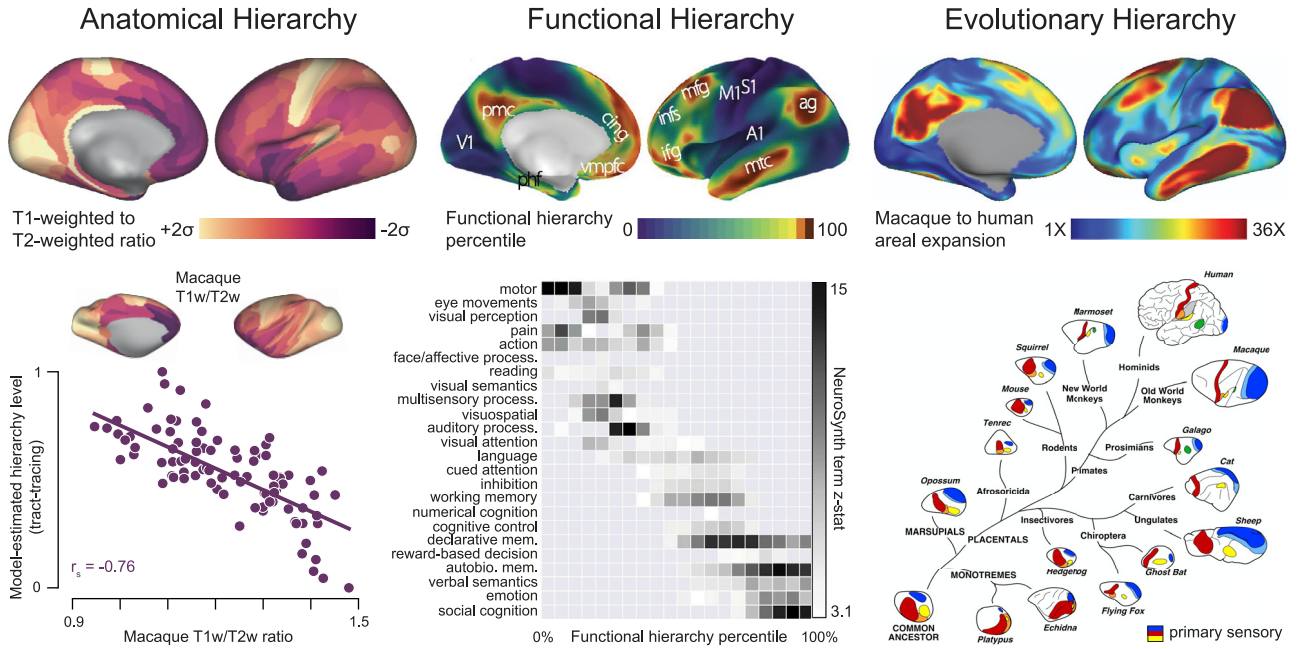


Figure 1. Anatomical, Functional, and Evolutionary Cortical Hierarchies

Anatomical Hierarchy: the human cortical anatomical hierarchy is revealed by inter-regional variation in the neuroimaging-derived T1-weighted to T2-weighted (T1w/T2w) ratio. The T1w/T2w ratio strongly negatively correlates with hierarchy level as estimated from the laminar origins of tract-traced cortical connections in the macaque, validating it as a robust *in vivo* measure of anatomical hierarchy. Lower hierarchical ranking, pale yellow; higher hierarchical ranking, dark purple. r_s, Spearman's rank correlation coefficient. Functional Hierarchy: the spatial embedding of the human cortical functional hierarchy—which captures a spectrum of faculties ranging from motor and visual functions to executive, emotional, and social functions—depicted across the cortical mantle. A NeuroSynth-based meta-analysis of 24 terms was conducted to map functions to cortical regions that are ranked along the hierarchy. Lower hierarchical ranking, dark blue; higher hierarchical ranking, dark red. Evolutionary Hierarchy: quantification of vertex-wise macaque to human surface area expansion captures the human cortical evolutionary hierarchy. Regions low in this hierarchy are predominantly sensory and motor cortices that are cortically dominant in mammals lower in the evolutionary tree and that have expanded less in primate evolution. Regions high in this hierarchy are transmodal association cortices that are cortically dominant in the primate lineage and that underwent marked cortical expansion in humans. Lower hierarchical ranking, blue; higher hierarchical ranking, red. Anatomical Hierarchy adapted from Burt et al. (2018), copyright 2018 with permission from Springer Nature, *Nature Neuroscience*. Functional Hierarchy adapted with permission from Margulies et al. (2016), copyright 2016 via the PNAS License to Publish. Evolutionary Hierarchy reprinted from Xu et al. (2020) with permission (https://creativecommons.org/licenses/by-nc-nd/4.0/) (top) and adapted from Krubitzer (2007), copyright 2007 and Krubitzer and Kahn (2003), copyright 2003 with permission from Elsevier (bottom).

The S-A axis thus represents a major axis of brain organization that captures systematic, correlated shifts in macrostructural, microstructural, and molecular features across the human cortex. It must be noted that feature changes along this axis can be continuous or abrupt between cortically adjacent regions (capturing both gradual cortical changes and sharp areal boundaries), that non-uniformities in axis hierarchical ordering are evident, and that additional prominent axes of cortical organization exist (Box 1). Although intrinsic and emergent characteristics of the S-A axis have been elaborated upon in recent years, this axis remains rooted in fundamental principles of both functional and structural cortical organization. Functionally, the S-A axis extends spatially outward from primary regions to the most cortically distant transmodal regions, traversing unimodal and multimodal cortices along the way, thus it is a cortex-wide embodiment of the principle of spatial continuity of function (Aflalo and Graziano, 2011). This principle proposes that the high-dimensional information space composed of all functions relevant to an organism's behavior is low-dimensionally embedded in cortical arrangement in a manner that optimizes continuity of function between adjacent areas (Aflalo and Graziano, 2011). This principle of functional continuity, which parallels the notion of gradients of cognitive function introduced by Elkhonon Goldberg (Goldberg, 1989), seemingly applies at the microscale (e.g., orientation columns in V1), at the regional level (e.g., somatotopic maps in S1), and at the whole-brain level, as revealed by the functional topography of the S-A axis (Aflalo and Graziano, 2011; Graziano and Aflalo, 2007). Structurally, the S-A axis coheres well with our understanding of systematic changes in the laminar structure of the cortex. Laminar differentiation tends to decrease from the sensorimotor to the association pole of the axis. Thus, the S-A axis accords with early observations of graded variation in architectonic differentiation (Sanides, 1962), with the Structural Model linking architectonic to connectivity variation (Barbas, 1986; García-Cabezas et al., 2019), and with Mesulam's seminal theory on sensory-fugal processing (Mesulam, 1998, 2008). Mesulam divided the cortex into ordered, spatially continuous zones of decreasing cytoarchitectonic differentiation and increasing level in a sensory-fugal processing hierarchy. The resulting cortical zones, referred to as primary sensory and motor zones, unimodal (or modality-selective) association zones, and transmodal association zones, align along the S-A axis. Importantly, Mesulam further differentiated between two broad types of transmodal association cortices on the basis

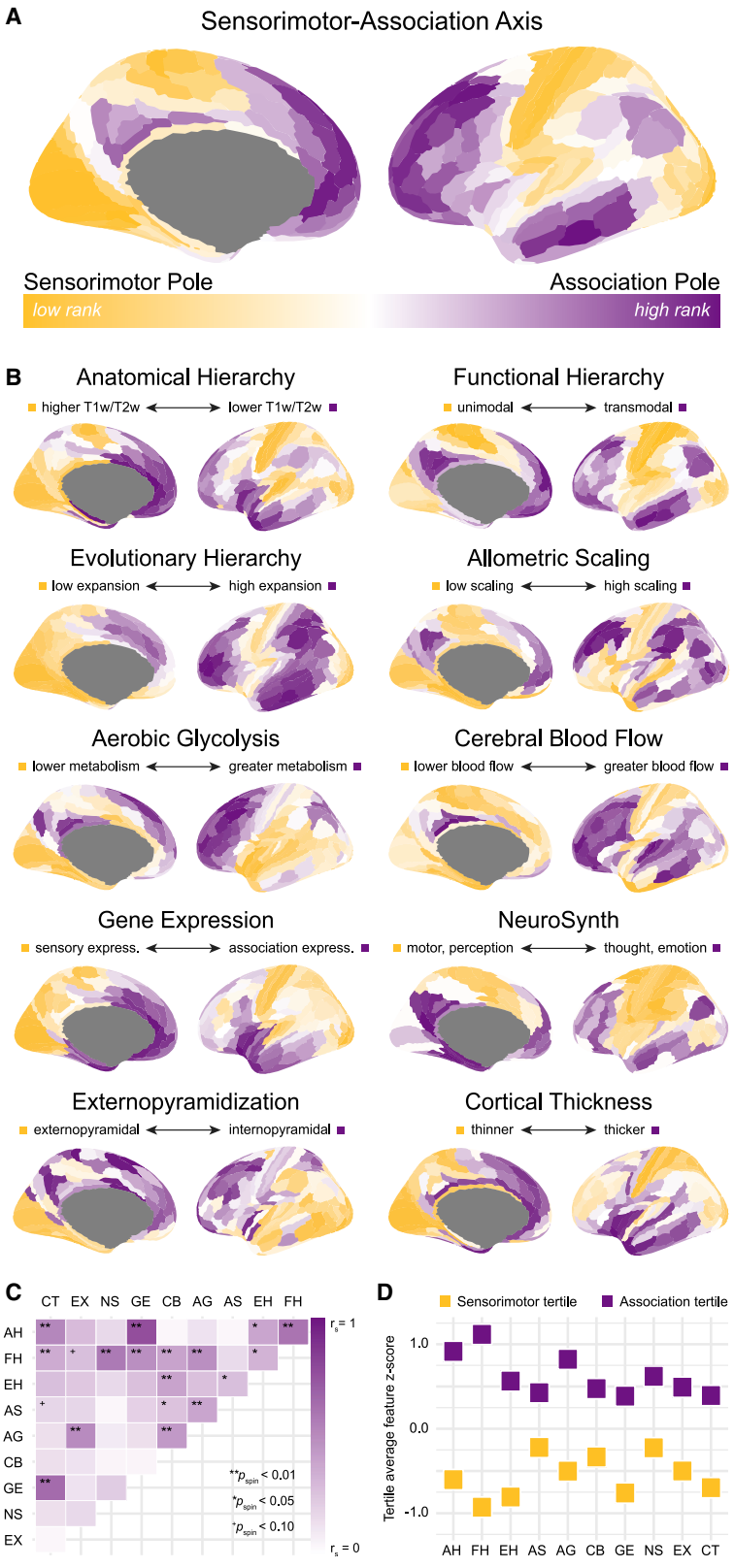


Figure 2. The sensorimotor-association axis of cortical organization

Diverse neurobiological properties reveal a principal S-A axis of topographical feature variation and organization. Cortical measures derived from ten different data types were independently averaged within 180 left hemisphere parcels (Glasser et al., 2016), and parcels were rank-ordered on the basis of value from 1 (low rank; yellow; sensorimotor-like) to 180 (high rank; purple; association-like).

(A) Individual parcel rankings from the ten cortical maps displayed in (B) were averaged to derive an archetypal S-A axis.

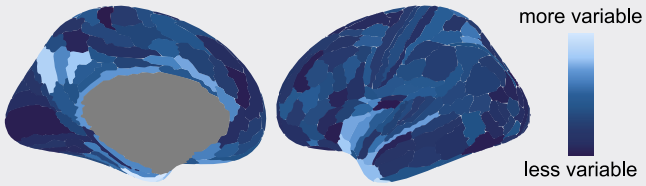
(B) Cortical maps for ten fundamental brain features are colored by parcel rankings. These macrostructural, microstructural, functional, metabolic, transcriptomic, and evolutionary features exhibit systematic variation between lower-order primary sensorimotor regions and higher-order transmodal association regions along the S-A cortical axis. Cortical maps (and data sources) displayed include Anatomical Hierarchy (AH), quantified by the T1-weighted to T2-weighted ratio (data from Glasser and Van Essen, 2011); Functional Hierarchy (FH), quantified by the principal gradient of functional connectivity (data from Margulies et al., 2016); Evolutionary Hierarchy (EH), quantified by macaque-to-human cortical expansion (data from Hill et al., 2010a); Allometric Scaling (AS), quantified as the relative extent of areal scaling with scaling of overall brain size (data from Reardon et al., 2018); Aerobic Glycolysis (AG), quantified from positron emission tomography measures of oxygen consumption and glucose use (data from Vaishnavi et al., 2010); Cerebral Blood Flow (CB), quantified via arterial spin labeling (data from Satterthwaite et al., 2014); Gene Expression (GE), quantified by the first principal component of brain-expressed genes (analysis conducted as in Burt et al., 2018); NeuroSynth (NS), quantified by the first principal component of NeuroSynth meta-analytic decodings (Yarkoni et al., 2011); Externopyramidization (EX), quantified as the ratio of supragranular pyramidal neuron soma size to infragranular pyramidal neuron soma size (data from Paquola et al., 2020a); and Cortical Thickness (CT), quantified from structural MRI (Human Connectome Project S1200 data).

(C) A Spearman's rank correlation matrix for the ten cortical features is displayed. The color bar indexes the absolute value of the Spearman's correlation coefficient (r_s) derived from each pair of features. Correlation significance (p_{spin}) was assessed using a conservative parcel-based spatial permutation spin test that preserves spatial covariance structure, as implemented by Váša et al. (2018).

(D) The archetypical S-A axis shown in (A) captures divergence between sensorimotor and association cortices across all ten cortical features, as revealed by average sensorimotor tertile versus association tertile feature *Z* scores. Sensorimotor and association tertiles included 60 cortical parcels with the lowest and the highest average ranks, respectively, based onthe multimodal map computed in (A).

Box 1. Boundaries and non-uniformities in the sensorimotor-association axis and additional axes of organization

The S-A axis—arranged from primary sensory and motor regions to unimodal, multimodal, and finally to transmodal association regions with human-advanced cognitive, socioemotional, and mentalizing functions—offers an important framework for understanding cortical heterogeneity and the patterning of features across the cortical landscape. The delineation of this axis in diversified data types has helped integrate organizational trends observed across studies, spatial scales, and species. Furthermore, it is now apparent that the systematic ordering of cortical regions along this axis on the basis of feature variation largely parallels their ordering in anatomical, functional, and evolutionary hierarchies, suggesting alignment along a common spatial dimension. Importantly, feature changes along this spatial dimension can be continuously graded between cortical regions, yielding smooth cortical transitions, or sharp and noncontinuous, as in the case of well-established anatomical and functional cortical boundaries (Bajada et al., 2020). Consequently, depending on the data type examined, both continuous (gradient-like) and discrete (edge-like) transitions will be embedded within the larger S-A axis of feature variation. In addition, depending on the data type examined, the exact sequence of regions along the axis will marginally differ, as non-uniformities in regional ordering can be identified; this is perhaps most evident when considering whether paralimbic or heteromodal association cortices define the associative end of the axis. For example, the paralimbic ventromedial prefrontal cortex frequently occupies the apex of the associative end of the S-A axis (e.g., when quantified fromintracortical myelination, intrinsic timescale length, and laminar differentiation). However, it occasionally sits below heteromodal cortices near the upper third of the axis, rather than near the apex (e.g., when quantified fromdiversity of interregional structural connections, distance of functional connections, and evolutionary expansion). Furthermore, when comparing across axes derived from ten fundamental cortical features (Figure 2B), the temporal pole, anterior insula, peri-entorhinal cortex, precuneus, and portions of the cingulate (representing primarily paralimbic regions) exhibit substantially variable axis positions, as quantified by the median absolute deviation of parcel rankings and displayed below.



These non-uniformities demonstrate that though the S-A axis provides a concise and powerful way to appreciate the immense complexity of the cortex, it does not explain nor capture the entire spectrum of cortical variability. It represents a simplified, low-dimensional representation of variability along one primary axis (i.e., along one data-driven vector, component, gradient, or embedding). Critically, alternative axes of organization exist that can both inform our understanding of cortical form and function and provide new insight into cortical development. The anterior-posterior axis of cortical variation is, for example, a prominent organizational axis that has been developmentally linked to differences in the length of neurogenesis across the cortex, as well as to early rostral and caudal morphogenic patterning centers (Charvet and Finlay, 2014; Chen et al., 2011; O'Leary et al., 2007; Valk et al., 2020). The anterior-posterior axis runs perpendicular to an observed dorsal-ventral organizational axis; it is hypothesized that the dorsal-ventral axis may emerge from early neurodevelopmental gradients that emanate out from the paleocortex and the archicortex (Huntenburg et al., 2021; Valk et al., 2020). Additional secondary organizational axes with more poorly understood developmental origins have been identified, including an axis characterized by visual versus somatomotor poles (Margulies et al., 2016) and an axis that captures divergence between cortices involved in perceptual versus affective processing (Hansen et al., 2021). Future work should pursue deeper knowledge regarding alternate axes of organization, and prioritize the study of when and how they are formed and refined throughout neurodevelopment.

of layer architecture. These include heteromodal association cortices involved in cognitive elaboration and control (including prefrontal, posterior parietal, lateral temporal, and medial temporal cortices with six layers) and paralimbic association cortices involved in mentalizing, motivation, and socioemotional processing (including orbitofrontal, ventromedial prefrontal, insular, temporopolar, and cingulate cortices with fewer apparent layers).

The S-A axis thus represents a continuum, not a dichotomous classification, as feature and function variation are apparent both between and within sensorimotor and association cortices. Features that vary along this dimension of organization will therefore exhibit both a marked degree of differentiation between sensorimotor and association cortex (Figure 2D), as well as subtler differences within sensorimotor and within association cortices (Figure 2B), providing nuanced insight into brain-wide differences in cortical functioning. Intracortical myelination, for example, is highest in primary cortex and progressively declines from primary to unimodal sensorimotor regions, from unimodal to multimodal and heteromodal association cortices, and from heteromodal to paralimbic association cortices (Burt et al., 2018; Paquola et al., 2019a, 2019b), suggesting that potential for ongoing plasticity is greatest in paralimbic cortices. Excitatory and inhibitory neural features additionally exhibit continuous variation along the entirety of the S-A axis, with functional implications. The density of parvalbumin (PV) inhibitory interneurons decreases between primary sensory cortices, heteromodal association cortices, and paralimbic association cortices

(Anderson et al., 2020a; Burt et al., 2018), whereas excitatory neuron size and spine density increase from primary to paralimbic (Elston and Fujita, 2014; Hilgetag et al., 2019). Correspondingly, the ratio of excitatory to inhibitory neurotransmitter receptors steadily increases along this principal axis of variation (Goulas et al., 2021), with consequences for regional excitation: inhibition (E:I) balance and electrophysiological information processing.

Neurodevelopment as a fourth hierarchy

The intrinsic co-variation of manifold properties across the cortical mantle underscores that the S-A axis represents a natural dimension of brain organization (García-Cabezas et al., 2019; Hilgetag et al., 2019; Huntenburg et al., 2018; Mesulam, 1998) that emerged with evolution (Buckner and Krienen, 2013). In addition, existing data suggest that feature variation along this principal axis is refined during brain development as cortical maturation proceeds from lower-order sensory and motor cortices to higher-order association cortices, in other words, as developmental programs advance along the hierarchical S-A axis. Thus, in addition to the three canonical hierarchies of anatomy, function, and evolution, it is increasingly evident that there exists a fourth hierarchy—*a neurodevelopmental hierarchy*—that describes the temporal sequence of brain development and aligns with the principal S-A axis. This neurodevelopmental hierarchy captures the progression of brain development from early to late maturation and thus from primary cortex to transmodal association cortex. In what follows, we review evidence of a neurodevelopmental hierarchy derived from both neuroimaging and complementary histological, electrophysiological, and transcriptomics studies, and we discuss how the unfolding of this developmental hierarchy shapes cortical function and complex human behaviors throughout childhood and adolescence.

NEURODEVELOPMENT OF THE ASSOCIATION CORTICES

Overarching patterns and temporal extension of human cortical development

In neurodevelopment the brain grows, organizes, and matures into an adult-like architecture, shaped by intrinsic biological factors as well as by extrinsic environments and experiences. Beginning in the third week of gestation, neurodevelopment continues until at least the third decade of life. By 2 years of age, the macroscale layout of the brain, patterns of cortical gyrification, major white matter connections, and identifiable functional networks have been established, forming the brain's basic structural and functional blueprint (Gilmore et al., 2018). This blueprint, however, is continuously refined throughout the next decades of life. Continuous refinement enables increasingly complex cognitive and behavioral repertoires to emerge, yet it also confers susceptibility to aberrant maturational processes, thereby heightening vulnerability to developmental psychiatric symptomatology (Kessler et al., 2005; Paus et al., 2008).

In this review, we focus specifically on refinement of the cortex in childhood and adolescence; a discussion of subcortical development is thus outside the scope of this work but is of clear neurobiological and clinical interest for future investigations. During childhood and adolescence, the temporal sequence of cortical refinement tends to progress in a spatially ordered manner along the S-A axis. Sensory and motor regions are predominantly modified during the first decade of life, in accordance with early development of vision, audition, and motor control. In contrast, transmodal association regions display a more protracted developmental course, remaining comparatively immature throughout childhood and the beginning of adolescence. Indeed, neurodevelopment of higher-order prefrontal, cingulate, middle temporal, and parietal association regions is so extended that it lengthens the total time course of human brain development. A multi-decade period of brain change, attributable to markedly late association cortex maturation, distinguishes human neurodevelopment from that of other primate species (Miller et al., 2012; Petanjek et al., 2011).

Comparative anatomy studies have shown that species with smaller brains and fast, synchronous cortical maturation exhibit minimal feature variation across the cortical sheet (Charvet and Finlay, 2014). As brains enlarge and overall developmental schedules lengthen, differences in both the timing of development and regional characteristics emerge across the cortex (Charvet and Finlay, 2014). These observations link temporal neurodevelopmental variability to spatial feature variability and highlight how the extension of association cortex development in humans may endow the growing human brain with evolutionarily novel structural, circuit, and electrophysiological properties (Buckner and Krienen, 2013). In the following section, we present *in vivo* studies of cortical macrostructure, intracortical myelination, structural connectivity, and functional systems that clearly reveal the pattern of neurodevelopmental variability across the human cortical mantle. This pattern is in large part temporally governed by the S-A axis and thus defines a development-related hierarchy that parallels the brain's anatomical, functional, and evolutionary hierarchies.

Neuroimaging of macroscale neurodevelopment

Cortical macrostructure

In vivo MRI enables quantification of macroscopic properties of cortical structure, including cortical thickness and surface area; together, these determine cortical volume. These properties, derived from a signal intensity-based segmentation of gray matter, reflect the thickness or area of brain tissue occupied by neurons and surrounding glia, vasculature, free water, and extracellular space. Imaging-derived measures of cortical thickness and evolutionary surface area expansion tend to increase from the sensorimotor pole to the associative pole of the S-A axis (Fischl and Dale, 2000; Hill et al., 2010a; Sotiras et al., 2017; Wagstyl et al., 2015, 2020) (though motor cortex is thick; Wagstyl et al., 2020). Imaging-derived measures of cortical macrostructure additionally display robust and reliable nonlinear changes from birth into adulthood. As measures of cortical macrostructure change developmentally, the macrostructural S-A axis, which is present to some extent at birth (Ball et al., 2020a), becomes increasingly pronounced (Li et al., 2015).

Global cortical thickness increases from birth to early childhood (Gilmore et al., 2020; Li et al., 2015; Lyall et al., 2015; Wang et al., 2019), followed by a protracted decline;

consequently, most of childhood and adolescence are typified by macrostructural cortical thinning. Although earlier neuroimaging efforts did report localized thickness increases until approximately mid to late childhood within temporal, parietal, and frontal association cortices (e.g., Shaw et al., 2008; Sowell et al., 2004)—possibly because of unmitigated motion artifact in younger children—more recent studies provide substantial evidence of widespread cortical thinning from as early as 2–4 years of age (Amlien et al., 2016; Ball et al., 2020b; LeWinn et al., 2017; Teeuw et al., 2019; Wang et al., 2019; Wierenga et al., 2014; Zhou et al., 2015; Zielinski et al., 2014). Cortical thinning in childhood and adolescence is extensive at the depths of sulci and less prominent at the gyral surface (Vandekar et al., 2015). This depth-dependent pattern of thinning is driven largely by preferential increases in myelin within deeper cortical layers (Paquola et al., 2019b; Whitaker et al., 2016), as myelination near sulcal cortex shifts the gray-white boundary outward, producing thinner gray matter (Natu et al., 2019; Vandekar et al., 2015; Whitaker et al., 2016). Myelination does not explain the full extent of age-related thickness decreases, however; macrostructural changes in cortical curvature and surface area (Natu et al., 2019) and changes in microstructure (Whitaker et al., 2016) are additionally understood to contribute to thinning.

The time frame and rate of cortical thinning are heterogeneous across the cortical sheet. Primary and unimodal cortical areas supporting sensory and motor functions (including occipital, precentral, postcentral, and medial temporal cortices) undergo a period of early, more rapid thinning prior to middle childhood (Amlien et al., 2016; Gilmore et al., 2018), followed by more minimal thinning in adolescence (Ball et al., 2020b; Sotiras et al., 2017; Vandekar et al., 2015; Whitaker et al., 2016). Despite this deceleration in thinning in sensorimotor cortex, near the onset of adolescence the overall rate of cortical thinning increases (Teeuw et al., 2019; Zhou et al., 2015), driven by enhanced thinning across transmodal association cortices (Ball et al., 2020b; Sotiras et al., 2017; Vandekar et al., 2015; Whitaker et al., 2016). In fact, heteromodal and paralimbic association regions that occupy the furthest end of the S-A axis continue to thin substantially from early childhood into the early twenties (Ball et al., 2020b; Sotiras et al., 2017; Vandekar et al., 2015; Whitaker et al., 2016). Available structural MRI findings thereby suggest a relationship between a region's temporal window of maximal thinning and its position in anatomical, functional, and evolutionary cortical hierarchies. Indeed, regions displaying the largest thickness-related changes in adolescence are also those that have expanded the most in evolution (Amlien et al., 2016; Sotiras et al., 2017). This observation suggests that the protracted timeline of macroanatomical cortical maturation observed in humans compared with other primates is largely carried by areally expanded association cortices.

Whereas cortical thickness increases in infancy and then undergoes a progressive developmental decline, cortical surface area increases throughout a longer period of brain development. Surface area begins to dramatically expand near the start of the third trimester of pregnancy (Clouchoux et al., 2012) as gyrification occurs and cells continue to migrate to their laminar position and extend new processes. Surface area further increases approximately 3-fold after birth (Hill et al., 2010a, 2010b; Raznahan et al., 2011; Wierenga et al., 2014), reaching a global peak at about 9–12 years of age and subsequently plateauing or modestly declining (Amlien et al., 2016; LeWinn et al., 2017; Raznahan et al., 2011; Wierenga et al., 2014). Surface area expansion early in childhood is driven largely by additional folding of secondary and tertiary sulci and by increasing sulcal depth (Hill et al., 2010a, 2010b; Li et al., 2013), although sensory regions with low between-subject gyral variability already show adult-like folding at birth (Hill et al., 2010a). Surface area enlargement in later childhood, on the other hand, reflects steady growth at the gyral surface (Raznahan et al., 2011), potentially related to changes in cortical layer microstructure, gliogenesis, or expansion of underlying white matter.

Critically, the overall topography of the cortex shifts throughout development, with lateral temporal, lateral parietal, and dorsal and medial prefrontal association cortices expanding 4-fold so as to occupy a larger percentage of the cortex (Hill et al., 2010a). In contrast, insular, medial temporal, and occipital cortices exhibit less (~2-fold) expansion. Thus, sensory and paralimbic cortices generally make up a smaller proportion of the cortical surface in mature individuals than in young children (Hill et al., 2010a). Healthy cortical development thereby involves areal redistribution (a shift in the allocation of cortical real estate) with heteromodal association regions supporting flexible and conceptual cognitive functions scaling most to occupy relatively larger territories. Interestingly, Reardon et al. (2018) demonstrated that, controlling for the effects of age, individuals with larger brains exhibit disproportionately greatest expansion (positive allometric scaling) of the same heteromodal associative regions. Moreover, in recent primate evolution, heteromodal association cortices expanded most on the cortical mantle (Hill et al., 2010a; Reardon et al., 2018). Such evidence supports that there are areal scaling principles that differ in extent across the principal S-A axis and that govern multifaceted cortical organizational shifts across timescales and individuals. Accordingly, shared mechanisms may drive the changes in cortical patterning seen throughout evolution, during brain development, and when examining inter-individual differences in neuroanatomy.

Collectively, studies examining cortical thickness and surface area reveal a progression of cortical maturation along the S-A axis. This progression begins in primary and unimodal visual, auditory, somatosensory, and motor cortices; transitions to intermediate, multimodal integration areas; and ends in transmodal areas with emotional, social, and executive functions. Significantly, association areas that continue to develop in adolescence and young adulthood ultimately show the greatest inter-individual variability in cortical thickness, surface area, and sulcal depth (Fischl and Dale, 2000; Mueller et al., 2013; Reardon et al., 2018). In addition, bulk tissue samples collected from late-developing association areas show elevated expression of genes implicated in schizophrenia, bipolar disorder, and major depression (Ball et al., 2020b; Whitaker et al., 2016). Together, these findings identify cortical regions that undergo significant adolescent structural development as sources of neurobiological heterogeneity in health and psychiatric illness.

Intracortical myelination

Cortical areas exhibit distinct myeloarchitectures, determined by the density, thickness, and organization of myelinated fibers.

Intracortical myelin content can be indirectly quantified with multiple *in vivo* imaging measures that are sensitive to myeloarchitecture, including magnetization transfer (MT) imaging, the T1-weighted to T2-weighted (T1w/T2w) ratio, and the R1 (1/T1) signal. In newborns, variability in myelin-sensitive imaging measures does not strongly follow the S-A axis (Ball et al., 2020a; Larivière et al., 2020). By adulthood, however, non-invasive measures of myelin content are highest in auditory, visual, somatosensory, and motor cortices, and they decline along the S-A axis, decreasing from multimodal to heteromodal to paralimbic cortices (Burt et al., 2018; Glasser and Van Essen, 2011; Grydeland et al., 2019; Huntenburg et al., 2017; Paquola et al., 2019a). This axis of cortical myelination is heavily influenced by variation in myelin content across cortical layers. In particular, whereas primary cortices are heavily myelinated across all cortical layers, most paralimbic association areas are only lightly myelinated in superficial layers; the continuum between these two myeloarchitectural patterns comprises the observed S-A myelin axis (Paquola et al., 2019b). This myeloarchitectural continuum may originate in part due to differences in the laminar origins (supragranular versus infragranular) of myelinated structural connections. Furthermore, it may signify that anatomical plasticity is less constrained by myelin-related proteins in superficial cortical layers within regions falling higher in the cortical hierarchy.

Whereas reductions in thickness are seen across the cortex from early childhood, both myelin-sensitive imaging and postmortem histology reveal that cortical myelin continuously increases with age (Grydeland et al., 2019; Miller et al., 2012; Natu et al., 2019; Norbom et al., 2019; Paquola et al., 2019b; Shafee et al., 2015; Whitaker et al., 2016). Increases in intracortical myelin are substantial within the first decade of life and continue until at least the middle of the third decade, with a second prominent wave of myelination beginning around 18–20 years of age (Grydeland et al., 2013, 2019; Miller et al., 2012; Shafee et al., 2015; Whitaker et al., 2016). Such a protracted second wave of cortical myelination is unique to humans (Miller et al., 2012) and is predominantly a consequence of late myelination of association cortices (Grydeland et al., 2019; Paquola et al., 2019b; Váša et al., 2018; Whitaker et al., 2016; Ziegler et al., 2019). Using a lifespan approach and the myelin-sensitive T1w/T2w ratio, Grydeland et al. (2019) characterized the early and late waves of human intracortical myelination. The first wave was distinguished by substantial and rapid myelin growth before age 13 years; this wave occurred primarily within brain regions that support motor and somatosensory functions. The second wave of myelin growth occurred more gradually after 13 years of age (peak growth rate at 19.5 years) in cortical areas that are robustly activated by language, comprehension, theory of mind, and mentalizing-related tasks in functional MRI studies. Additional work conducted with more restricted age ranges and MT imaging has replicated the finding of late myelination in association cortices (Paquola et al., 2019b; Whitaker et al., 2016; Ziegler et al., 2019), while also reporting that adolescent increases in myelin are larger within heteromodal than paralimbic cortices (Paquola et al., 2019b).

Knowledge regarding myeloarchitecture maturation has been further advanced by studies revealing that during adolescence and young adulthood, the process of myelination extends to superficial cortical layers within sensorimotor cortices, while it occurs primarily in deeper cortical layers in higher-order association cortices (Paquola et al., 2019b; Shafee et al., 2015). This distinction highlights fairly late developmental shaping of the layer-dependent adult S-A myelination axis. Interestingly, variable layer-specific (superficial versus deep) myelination during development further segregates sensorimotor and transmodal areas along the S-A axis. Specifically, during late adolescence, unimodal and heteromodal association cortices that occupy the middle of the S-A axis in childhood are drawn outward toward the poles of the axis (Paquola et al., 2019b). As a consequence, the myelin-defined axis expands into an increasingly bimodal distribution, indicative of greater differentiation across the principal axis in young adults than in both children (Paquola et al., 2019b) and infants (Ball et al., 2020a).

White matter microstructure and connectivity

The volume of the brain's white matter continually increases from birth to adulthood (Lebel and Beaulieu, 2011; Westlye et al., 2010). Furthermore, though most of the brain's major white matter pathways (also called tracts or bundles) are identifiable at birth, white matter microstructural tissue properties (e.g., axonal density, caliber, myelination) evolve throughout brain maturation. The development of cortico-cortical white matter pathways occurs in coordination with local patterns of gray matter change (Moura et al., 2017), suggesting interdependent refinement of cortical macrostructure and connectivity. Moreover, the development of cortico-cortical white matter pathways follows a sequential progression that is largely determined by the hierarchical position of the cortical areas connected by each pathway.

White matter microstructural development has been most frequently studied using diffusion tensor imaging (DTI), a single-compartment modeling approach that fits one diffusion tensor per voxel. DTI studies have consistently reported global developmental increases in white matter fractional anisotropy (FA; a normalized measure of diffusion anisotropy) and decreases in mean diffusivity (MD; a direction-independent measure of overall diffusivity) (Tamnes et al., 2018). Global white matter FA reaches a peak in the early thirties (Kochunov et al., 2012; Westlye et al., 2010); however, there are differences in maturational periods across white matter pathways. Projection tracts, occipital and parietal commissural tracts, and white matter pathways connecting sensory and motor brain regions develop significantly in early and middle childhood (Lebel and Beaulieu, 2011; Simmonds et al., 2014). This early microstructural development is both accompanied and followed by the maturation of pathways that connect lower- and higher-order brain regions, including the inferior fronto-occipital fasciculi (connecting occipital and frontal regions), the inferior longitudinal fasciculi (connecting temporal and occipital regions), and the superior longitudinal fasciculi (connecting occipital, temporal, and parietal lobes to frontal regions). Finally, pathways connecting paralimbic cortices involved in emotional and executive functions, such as the uncinate fasciculi and the cingulum bundles, exhibit their largest increases in FA and decreases in MD from adolescence until approximately the mid-thirties (Kochunov et al., 2012; Lebel and Beaulieu, 2011; Simmonds et al., 2014; Slater et al., 2019). Overall, tract-specific maturational windows illustrate that white

matter development is influenced by dual macroscale temporal axes—posterior-to-anterior and S-A axes—aligning with temporal patterns of white matter myelinogenesis documented by post-mortem histology (Yakovlev and Lecours, 1967).

The precise neurobiology underlying age-related increases in FA and decreases in MD remains somewhat unclear. This pattern of results could reflect increases in axon diameter, myelination, or packing density; proliferation of astrocytes; or decreases in membrane permeability or tissue free water content. Additional work has therefore harnessed multi-compartment diffusion modeling approaches (Pasternak et al., 2018) and myelin-sensitive imaging techniques in an effort to provide a deeper understanding of white matter diffusion maturation. Two advanced diffusion modeling approaches that have been applied to neurodevelopment are neurite orientation dispersion and density imaging (NODDI) (Zhang et al., 2012), a three-compartment diffusion model, and constrained spherical deconvolution (CSD), a method capable of modeling complex fiber architectures (Tournier et al., 2007). Both methods produce a measure related to restricted diffusion within the intra-axonal space, referred to as neurite density for NODDI and fiber density for CSD. Significant changes in both neurite density (Chang et al., 2015; Geeraert et al., 2019; Pines et al., 2020) and fiber density (Dimond et al., 2020; Genc et al., 2020) have been reported in early to late childhood, providing indirect support for increases in axon packing or diameter during these developmental stages (Genc et al., 2020). Select studies have also demonstrated that MT, R1, and R2* (transverse relaxation rate) signals increase within higher-order association bundles through childhood and adolescence, suggestive of increases in myelination (Bartzokis et al., 2012; Slater et al., 2019; Vanes et al., 2020; Yeatman et al., 2014; but see Moura et al., 2016). For example, a lifespan study of individuals 7 years of age and older reported significant increases in myelin-sensitive R1 into the thirties, with a clear hierarchical pattern of white matter tract R1 refinement (Yeatman et al., 2014).

Diffusion MRI measures are highly correlated across major white matter pathways at birth (Lee et al., 2017). Yet during development, individual bundles differentiate, concurrent with cortical feature differentiation across the S-A axis. This process of differentiation modifies central properties of the macroscale structural connectome, including its modular organization. A module is a densely interconnected group of cortical areas with sparse external connections; modularity enables efficient within-module communication and functional specialization. Throughout childhood and adolescence, structural connectivity-based modules become more segregated, driven by greater strengthening (defined as a greater increase in FA) of within-module white matter connections than between-module connections (Baum et al., 2017). Strengthening of within-module connectivity occurs for modules composed of regions located across the S-A axis but appears strongest for modules that fall at the extremes of the axis, within primary visual cortex, heteromodal cortex, and paralimbic cortex (Baum et al., 2017; Park et al., 2021). The pattern of strengthening modularity ultimately causes the structural connectivity architectures specific to prefrontal, temporal, and lateral parietal transmodal association cortices to further diverge from the connectivity profiles displayed by the rest of the cortex (Park et al., 2021). The result is enhanced differentiation of cortico-cortical connectivity across the S-A organizational axis (Park et al., 2021). Yet even while white matter modules become increasingly segregated and structural connectivity profiles diverge, there is an overall increase in global structural connectome integration (Baum et al., 2017). These seemingly paradoxical findings can be understood in light of the specific and substantial strengthening of white matter pathways connected to a small set of higher-order, interconnected cortical hubs: regions of association cortex with a large density of long-range, spatially distributed, between-module connections (Baker et al., 2015; Baum et al., 2017; Wierenga et al., 2018). Thus, as the properties of the structural connectome diversify along the S-A axis during youth, modular segregation allows for increasing circuit efficiency, and strengthening association hub connectivity allows for improved cortical synchronization (Baum et al., 2020) and information integration.

Functional systems

Functional MRI measures time-dependent changes in the blood oxygen level-dependent (BOLD) signal. As a result, functional MRI enables quantification of inter-regional functional connectivity, which indexes the degree to which BOLD signal fluctuations are correlated between regions of cortex. Studies characterizing widespread patterns of cortico-cortical functional connectivity have identified multiple discrete, reproducible, large-scale functional systems in the brain. These dissociable systems cover distributed areas of cortex and consist of groups of regions that exhibit synchronized BOLD activity at rest (Power et al., 2011; Yeo et al., 2011). Functional systems exhibit greater structural connectivity (Hermundstad et al., 2013) and more correlated gene expression within than between systems (Anderson et al., 2018; Krienen et al., 2016). They furthermore recapitulate coordinated activity changes evoked during task-based functional MRI (Smith et al., 2009). Functional systems thus provide a powerful, data-driven way of understanding intrinsic cortical organization in a manner that interpretably maps onto brain function.

Individual functional systems are composed of cortical regions that are concentrated in similar positions along the S-A axis (Margulies et al., 2016). Lower-order functional systems, including visual, auditory, and somatomotor systems, are defined by the primary and unimodal end of the axis, whereas dorsal attention, ventral attention, and salience systems are formed from cortical regions occupying more intermediate positions along the S-A axis. Frontoparietal, cingulo-opercular, and default mode systems predominantly consist of transmodal association cortices and thus fall near the association end of the axis (Margulies et al., 2016). Just as regional structure and connectivity vary along the S-A axis, so too do properties of these spatially distributed systems. Lower-order systems display shorter connections, canonical feedforward-feedback circuit architecture, and minimal inter-individual topographical variability. Higher-order systems exhibit distributed long-range connections, non-canonical circuit organization, and substantial spatial variability across individuals (Buckner and Krienen, 2013; Cui et al., 2020; Kong et al., 2019; Mueller et al., 2013; Oligschläger et al., 2017; Sepulcre et al., 2010).

Visual, auditory, and somatomotor systems display an adult-like topography in newborns (Gilmore et al., 2018). In contrast,

association functional systems become identifiable in the first few years of life and undergo considerable reconfiguration during both childhood and adolescence, with attention and frontoparietal systems maturing before the default mode system (Dong et al., 2020). Mirroring the development of the structural connectome, functional systems of the association cortex become increasingly modular and segregated during brain maturation, driven by the strengthening of within-system functional connections as well as the weakening of between-system functional connections (Bassett et al., 2018; Dosenbach et al., 2010; Fair et al., 2008; Satterthwaite et al., 2013). For example, whereas the default mode system is only weakly connected at about 7–9 years of age, its within-system connections strengthen considerably into adulthood (Fair et al., 2008). Furthermore, whereas the heteromodal frontoparietal system and paralimbic cingulo-opercular system are more strongly functionally connected in children, these two systems gradually segregate over time, enabling a clearer demarcation of functional systems that occupy different zones of transmodal cortex (Fair et al., 2007). Together, concordant patterns of structural and functional segregation within associative brain systems lead to a strengthening of structure-function coupling (i.e., to a stronger correspondence between white matter architecture and patterns of coordinated functional system activity). The magnitude of age-related coupling increases is predicted by cortical hierarchy: developmental enhancements in coupling between structural connectivity and functional communication progressively increase as regions rank higher in functional and evolutionary hierarchies, and thus tend to increase with greater distance from primary cortex (Baum et al., 2020).

The restructuring of functional system connections as youth progress toward adulthood leads to the modification of overall functional system topography, a clearer delineation of functional system boundaries, and greater between-individual functional connectome distinctiveness (Cui et al., 2020; Fair et al., 2007; Kaufmann et al., 2017). In addition, the maturation of functional connections appears to enhance connectivity differences between lower-order and higher-order functional systems, further embedding the S-A axis as a primary functional organizational axis over time (Dong et al., 2020; Nenning et al., 2020). It has in fact been shown that the S-A axis explains a lesser degree of variation in regional functional connectivity profiles in neonates (Larivière et al., 2020) and young children (Dong et al., 2020) than in adolescents. Accordingly, during infancy and early childhood, alternative functional connectivity-derived spatial axes are dominant, including visual-somatomotor and anterior-posterior axes (Dong et al., 2020; Larivière et al., 2020). Interestingly, a visual-somatomotor axis presents as a prominent axis of connectivity variability in both mice and macaques (Huntenburg et al., 2021; Xu et al., 2020). These collective findings suggest that throughout the course of cortical development, the functional organization of the human brain becomes increasingly sensorimotor-to-associative, and increasingly differentiable from the organization characteristic of other mammals. In sum, phylogenetically older, lower-order functional systems are refined in childhood, whereas evolutionarily newer systems subserving higher-order faculties continue to mature throughout adolescence. The spatiotemporal maturation of functional system properties, cortical macrostructure, intracortical myelination, and white matter connectivity thus progresses heterochronously along the S-A organizational axis, conforming to the three canonical hierarchies of anatomy, function, and evolution, and defining a *hierarchical neurodevelopmental axis in youth* (Figure 3).

Microscale mechanisms driving macroscale developmental changes

Evidence that the brain exhibits both a hierarchical spatial feature axis and temporal neurodevelopmental axis that correspond to a principal S-A axis arises not just from macroscale neuroimaging data but also from microscale cellular and molecular data. In this section, we introduce important cellular and molecular features that systematically vary along the S-A axis in adulthood, and review foundational human and animal studies examining how these features change throughout child and adolescent (or juvenile and peripubertal) development. Notably, major neurodevelopmental events including neurogenesis, cell migration, laminar allocation, and initial wiring are largely complete prenatally or in the first years of life (Lim et al., 2018). Childhood and adolescence are therefore characterized predominantly by cellular and circuit refinement processes. Here we focus on developmental refinement of cortical excitation, cortical inhibition, and glial function, while calling attention to spatiotemporal variability in refinement processes along the S-A axis. Although our understanding of regional differences in microscale maturational processes is incomplete, existing work provides insight as to how developmental findings are linked across scales. Specifically, available data indicate that the hierarchical pattern of cortical maturation observed with neuroimaging at the macroscale is driven in part by developmental plasticity associated with excitatory, inhibitory, and glial cell types at the microscale (Larsen and Luna, 2018; Toyoizumi et al., 2013).

Cortical excitation

An axis of excitation exists within the adult cerebral cortex, with numerous excitatory features progressively increasing in brain regions that fall higher in anatomical, functional, and evolutionary hierarchies (Chaudhuri et al., 2015; Elston et al., 2011; Goulas et al., 2021; van den Heuvel et al., 2016b; Hoftman et al., 2018; Wang, 2020). These features include markers of glutamatergic neurotransmission (Froudist-Walsh et al., 2021; van den Heuvel et al., 2016b; Hoftman et al., 2018), the ratio of excitatory to inhibitory neurotransmitter receptors (Goulas et al., 2021), and excitatory neuron spine counts (Elston et al., 2009). The adult axis of cortical excitation emerges largely from areal variability in the architecture and receptor expression of pyramidal neurons, the predominant type of excitatory neuron in the mammalian cortex. Adult pyramidal neurons exhibit pronounced microstructural differences between sensory and association cortical areas, as well as finer alterations between heteromodal and paralimbic association areas. As laminar differentiation decreases along the S-A axis from primary to unimodal, heteromodal, and paralimbic cortices, pyramidal neurons display increasingly larger soma cross-section, greater dendritic tree size, and a higher spine and synapse count (Beul and Hilgetag, 2019; Cahalane et al., 2012; Elston and Fujita, 2014; Hilgetag et al., 2019). As a result, association cortex excitatory neurons occupy a

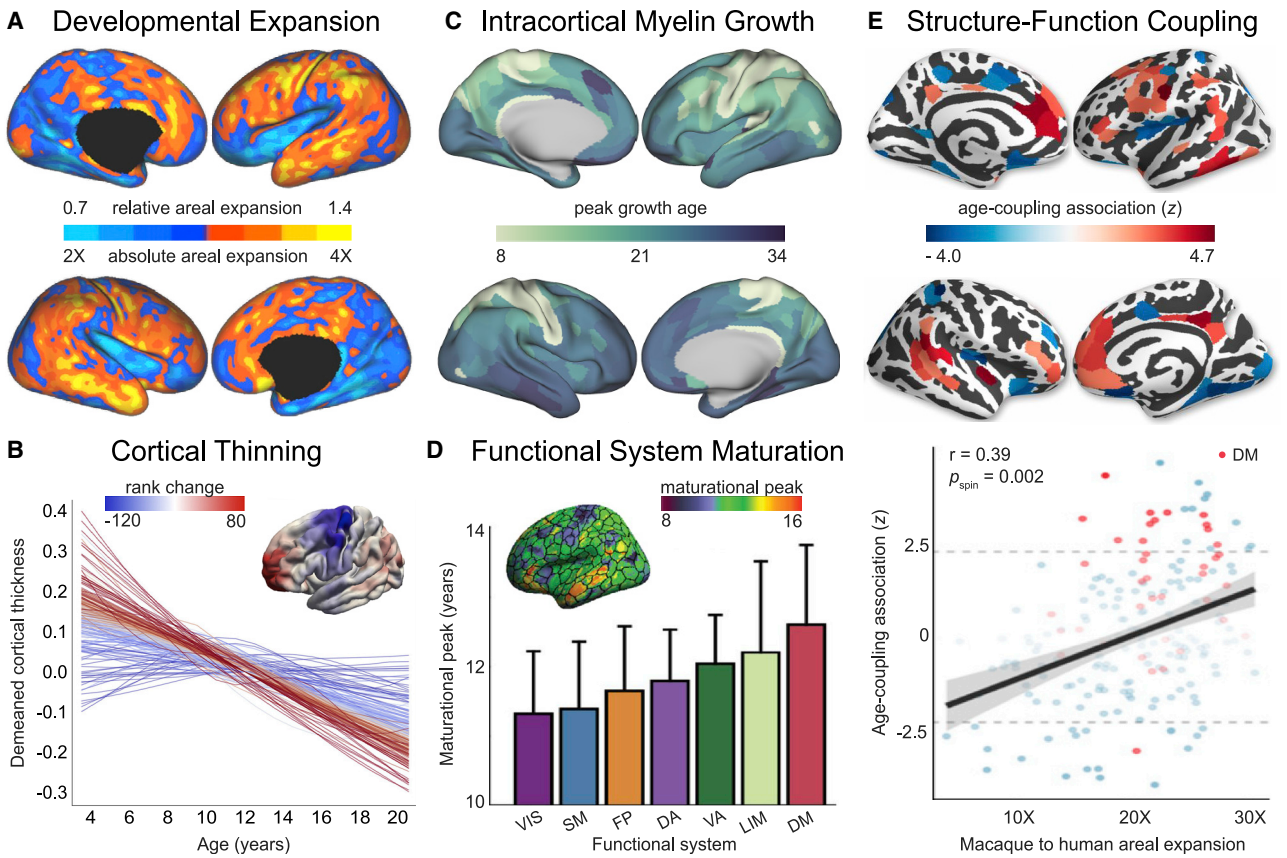


Figure 3. Hierarchical neurodevelopment in youth

(A–E) The magnitude and timing of development-related changes varies across the cortical mantle during childhood and adolescence and is linked to anatomical, functional, and evolutionary hierarchies. Consequently, compared with primary and unimodal visual, auditory, somatosensory, and motor cortices, transmodal association cortices tend to exhibit greater total surface area expansion (A), enhanced adolescent cortical thinning (B), a later age of peak intracortical myelin growth (C), temporally delayed functional system maturation (D), and a larger increase in structure-function coupling (E), with continuous variation being evident along the S-A axis. VIS, visual; SM, somatomotor; FP, frontoparietal; DA, dorsal attention; VA, ventral attention; LIM, limbic; DM, default mode; r, Pearson's correlation coefficient.

substantially larger cortical volume and area, in line with neuroimaging findings that thickest association cortices have greatest expression of excitatory neuron marker genes (Patel et al., 2020; Seidlitz et al., 2020). The expression of excitatory N-methyl-D-aspartate (NMDA) receptor subunits also varies along the S-A axis. NMDA receptors are glutamate-gated receptors that exhibit variable biophysical properties determined by their subunit composition. Significantly, the density of NMDA subunit NR2B, which lengthens the time course of excitatory synaptic activity and facilitates synaptic plasticity, also continuously increases from primary to transmodal cortices (Burt et al., 2018; Wang et al., 2008). Increased dendritic tree size, spine and synapse density, and NMDA NR2B expression allow transmodal associative pyramidal cells to achieve greater input integration and regulation, more sustained excitatory activity, and an enhanced functional range (Elston, 2003; Hilgetag et al., 2019; Wang, 2020).

Differences in pyramidal cell properties across the S-A axis are far more pronounced in adulthood than in infancy, suggesting that the axis of cortical excitation unfolds throughout child or adolescent development (Elston and Fujita, 2014; Elston et al., 2009). Supporting this view, in the first few years of life, excitatory pyramidal cells in prefrontal association cortices exhibit substantially larger increases in basal dendritic tree size, spine density, and synapse number than cells located in primary visual and unimodal visual association cortices (Elston and Fujita, 2014; Elston et al., 2009). Lower-order sensory and higher-order association cortices additionally display differences not only in the extent but also in the timing of spinogenesis and synaptogenesis, as well as in the timing of spine and synaptic pruning. Prefrontal association regions reach peak synaptic density later than auditory and visual sensory regions (in late rather than early childhood) and undergo pruning throughout adolescence, long beyond when synaptic stability is reached in sensory cortices

(Elston et al., 2009; Glantz et al., 2007; Huttenlocher, 1979; Petanjek et al., 2011). Delayed attainment of synaptic stability in association cortices allows forcontinued experience-dependent refinement of neural connections (Holtmaat et al., 2006), thus prolonging the window during which association circuit-subserved functions can be updated and enhanced (Holtmaat et al., 2006)—or potentially disrupted by early life stress (Lupien et al., 2009). For example, experience-dependent synaptic pruning is regulated by glucocorticoid stress hormones, yet prolonged glucocorticoid exposure during development can cause excessive and irreversible synapse loss (Liston and Gan, 2011; Liston et al., 2013). Finally, as demonstrated by rodent studies, association regions also display an increase in NMDA NR2B-dependent neurotransmission during the peripubertal (quasi-adolescent) period, which facilitates continued plasticity within higher-order cortex (Flores-Barrera et al., 2014). Microscale studies of cortical excitation thus corroborate the prolonged period of association cortex maturation identified by neuroimaging data and reveal that excitatory plasticity-related events may be important drivers of how structural and functional imaging measures change during hierarchical neurodevelopment.

Cortical inhibition

Cortical association regions express lower levels of GABA synthetic enzymes and $GABA_A$ receptors than sensory regions (Froudist-Walsh et al., 2021; Hoftman et al., 2018). There is thus evidence for an intrinsic axis of cortical inhibitory strength that is the inverse of, and may to a degree facilitate, the axis of excitation described above (Wang, 2020). Studies conducted with rodents, macaques, and humans have characterized regional differences in the expression of interneurons that inhibit excitatory pyramidal cells, including perisomatic-targeting, output-gating PV interneurons and dendrite-targeting, input-gating somatostatin (SST) interneurons (Anderson et al., 2020a). PV interneurons, in particular, decrease in expression from primary and unimodal sensory and motor cortices to transmodal association cortices, hence variability in the expression of PV cells may serve as a cellular basis for variation in GABAergic function across the S-A axis.

During brain development, levels of GABA and the strength of GABAergic neurotransmission increase (Larsen et al., 2021), as revealed by both *in vivo* human magnetic resonance spectroscopy (Ghisleni et al., 2015; Silveri et al., 2013) and animal model studies (Piekarski et al., 2017; Zhang et al., 2011). This increase in cortical inhibition arises largely from the maturation of PV interneurons (Fung et al., 2010) and the strengthening of PV inputs onto pyramidal neurons (Caballero et al., 2014; Hensch, 2005; Takesian and Hensch, 2013). Significantly, developmental increases in PV interneuron signaling have been shown to initiate the onset of critical period plasticity in sensory cortices, as increasing or decreasing inhibitory interneuron activity alone can accelerate or delay the timing of a critical period (Fagiolini and Hensch, 2000; Hensch, 2005; Larsen and Luna, 2018; Reh et al., 2020; Takesian and Hensch, 2013; Toyoizumi et al., 2013). Moreover, developmental increases in PV signaling follow the temporal neurodevelopmental hierarchy. PV interneurons reach adult levels relatively quickly in sensory cortices, whereas gradual increases in PV interneuron cell counts, mRNA expression, and protein expression occur until the adolescent period in association cortices (Caballero et al., 2014; Condé et al., 1996; Fung et al., 2010; Larsen and Luna, 2018; Toyoizumi et al., 2013). Given that the maturation of PV interneurons is largely experience-dependent, heterochronous PV development may arise because of temporal differences in exposure to key lower-order sensory experiences versus higher-order cognitive experiences (Reh et al., 2020; Takesian and Hensch, 2013). Overall, the spatiotemporal pattern of PV signaling enhancement indicates that delayed maturation of plasticity-regulating cortical inhibition within association cortices may be causally linked to their late periods of development documented with neuroimaging.

Glia

Glia are non-neuronal cells that are at least as populous in the brain as neurons. Glia are subdivided into three major cell classes with distinctive functional roles. Broadly, oligodendrocytes are responsible for myelin production, astrocytes regulate synapse formation and neurotransmission, and microglia function as immune cells. Whereas the density of microglia appears relatively constant across the cortex (Dos Santos et al., 2020), the density of astrocytes (Carlo and Stevens, 2013) and oligodendrocytes (Kamholz et al., 1988) varies along the S-A axis. Astrocytes, which facilitate synaptic plasticity, increase in density along the S-A axis, resulting in a greater number of these cells in the association cortex during development (Carlo and Stevens, 2013; Patel et al., 2020). In contrast, oligodendrocytes, which help suppress synaptic plasticity, decrease in density along the S-A axis and are thus expressed at a lower density in transmodal association regions when the brain is maturing (Burt et al., 2018; Glasser and Van Essen, 2011; Huntenburg et al., 2017; Paquola et al., 2019a).

Oligodendrocytes produce the early and late waves of myelination observed with myelin-sensitive imaging techniques in somatomotor (early wave) and association (late wave) cortices (Grydeland et al., 2019; Miller et al., 2012). Myelination of the cortex restrains further axonal and dendritic plasticity (McGee et al., 2005), as myelin-associated proteins inhibit neurite outgrowth. Consequently, myelin is understood to be one of two main structural brakes on plasticity, with the second being perineuronal nets: extracellular matrix structures that ensheath dendrites (preferentially PV interneuron dendrites) and control their plasticity (Carulli et al., 2010; Hensch, 2005; Mauney et al., 2013; Takesian and Hensch, 2013). Myelin and perineuronal nets thereby help stabilize the architecture of developing neural circuits, yet they do not reach adult levels until relatively late in association cortices, after the second decade of life. The hierarchical development of myelin and extracellular limiters of plasticity indicates that transmodal association cortices display not only a late increase in plasticity-inducing cortical inhibition and plasticity-facilitating excitatory mechanisms, but additionally a markedly slow and protracted increase in plasticity-stabilizing features (Larsen and Luna, 2018; Toyoizumi et al., 2013).

Functional significance of multi-scale development

Developmental changes in cortical excitation, cortical inhibition, and glia coincide with, and likely partly underlie, the hierarchical refinement of macroscale cortical features observed with neuroimaging from early childhood to early adulthood (Figure 4). As discussed below, this multi-scale maturation has fundamental

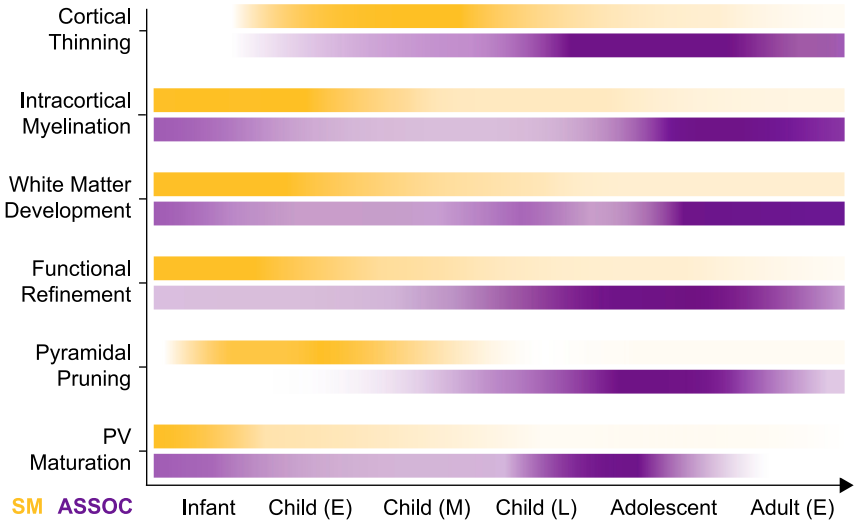


Figure 4. Multi-scale temporal neurodevelopment in sensorimotor and association cortex

The time course and tempo of major developmental changes in sensorimotor cortex (SM; yellow) and association cortex (ASSOC; purple) are illustrated; darker shading indicates larger magnitude changes. This qualitative synthesis of the reviewed literature underscores how the temporal neurodevelopmental axis indexes heterochronous changes between lower-order versus higher-order cortical regions. This synthesis further reveals prolonged association cortex neurodevelopment marked by substantial changes in late childhood and adolescence. Convergent data arise from neuroimaging-derived measures and plasticity-related cellular changes. E, early; M, middle; L, late; PV, parvalbumin.

consequences for cortical functioning, as it modifies microcircuit activity, macrocircuit connectivity, and cortical information processing. Furthermore, because the maturation of multi-scale features is asynchronous and hierarchical, it strengthens and expands the brain's S-A spatial feature axis, such that it explains a greater degree of cortical variability in young adulthood than in childhood and infancy. The result, as emphasized here, is the emergence of essential properties of higher-order, transmodal association cortices—properties that enable uniquely human cognitive and mentalizing functions.

Microcircuit activity

As excitatory neurons are pruned and GABAergic interneurons mature—early in sensory cortices and later in association cortices—the cortical E:I ratio decreases (Larsen et al., 2021). This decline in the local E:I ratio, a hallmark of neurodevelopmental plasticity, reduces baseline pyramidal neuron firing rates and shifts the balance of circuit activity from spontaneous to evoked (Toyoizumi et al., 2013). The result is an enhanced microcircuit signal-to-noise ratio, more reliable stimulus-evoked population responses, and a greater synchronization of neural communication; temporal development of these properties parallels hierarchical functional system maturation. Notably, once pruning ceases and inhibitory circuitry fully develops, the E:I ratio appears to stabilize at a higher level near the associative pole of the S-A axis, which encompasses primarily frontoparietal and default mode system regions (Chaudhuri et al., 2015; van den Heuvel et al., 2016b; Hoftman et al., 2018; Margulies et al., 2016; Wang, 2020). A higher E:I ratio could allow for an overall greater level of spontaneous (rather than evoked) activity and thus for heightened internally driven (rather than extrinsically driven) signaling (Yizhar et al., 2011). This property of greater stimulus-independent signaling may be central to perceptually decoupled cognition, internal mentation, and self-referential processing, core executive and default mode system-supported processes (Murphy et al., 2018, 2019).

Cortico-cortical connectivity

Cortico-cortical structural connections are microstructurally modified and myelinated in youth, as revealed by multi-compartment diffusion MRI, myelin-sensitive imaging, and post-mortem histology. The maturation of cortico-cortical white matter facilitates faster, more reliable long-range axonal signal transduction and more efficient communication between cortical modules. Cortico-cortical white matter maturation additionally enhances the capacity for association cortex hubs to integrate signals from diverse brain regions, leading to more complex functional dynamics that support advanced computations in association cortex. Notably, pyramidal neurons largely constitute the cellular basis of long-distance cortico-cortical connections. Age-dependent changes in macroscale cortico-cortical connectivity are thus intrinsically linked to changes in this major class of excitatory neurons. Cortical areas with more complex pyramidal neuron dendritic trees and greater spine density (i.e., heteromodal and paralimbic association cortices) connect to more extensive areas of cortex, as evinced by the integration of histology with tract tracing (Beul and Hilgetag, 2019) and diffusion MRI (van den Heuvel et al., 2016a; Scholtens et al., 2014). The environment in which association cortex pyramidal neurons develop thus engenders both greater local connectivity and more distributed, long-range connectivity, yielding a highly interconnected circuit architecture. This circuit architecture, designed to enhance integration of local inputs as well as communication with wide-spanning, functionally heterogeneous cortical areas, appears to be phylogenetically newer and optimized for exerting top-down cognitive control over ongoing neural processes (Buckner and Krienen, 2013).

Electrophysiological information processing

Although variation in areal properties exists to some degree along the S-A axis at birth (Ball et al., 2020a), the temporal and topographical sequence of neurodevelopment serves to enhance feature divergence between lower-order and higher-order brain regions, widening and strengthening the S-A axis. As a result, in adulthood, transmodal association cortices that define the upper end of the axis are commonly characterized by greater cortical thickness, expanded surface area, larger excitatory pyramidal cell arbors, denser cortico-cortical inputs, higher expression of NMDA NR2B subunits, lower PV interneuron density, and reduced intracortical myelination. The confluence of these macro- and micro-scale features gives rise to electrophysiological and circuit differences that yield two emergent

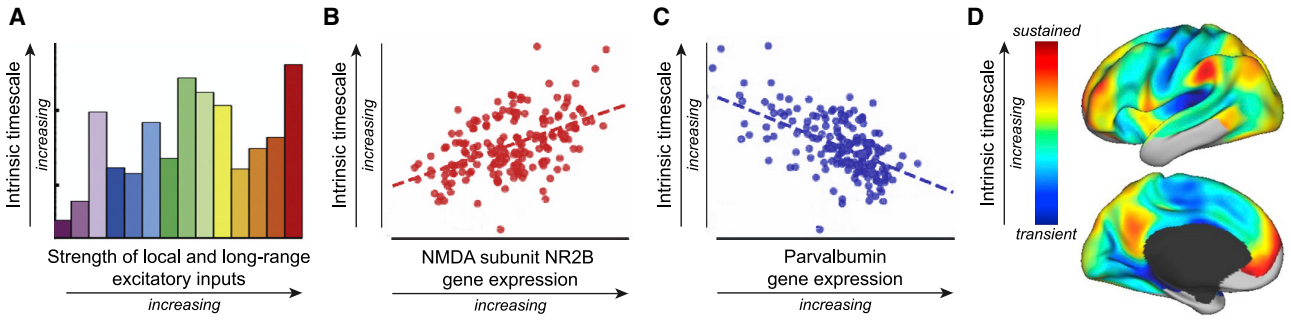


Figure 5. Excitatory and inhibitory feature variability produces a gradient of information processing timescales

(A) Results from an anatomically informed computational model of the macaque cortex support a link between longer intrinsic timescales and stronger local and long-range excitatory inputs. Each bar represents a cortical region that was modeled. The strength of local and long-range excitatory inputs varied by region (excitatory strength increasing from purple to red) and was informed by pyramidal neuron dendritic spine count data and tract tracing data. The cortical regions modeled include (from purple to red) V1, V4, 8m, 8l, TEO, 2, 7A, 10, 9/46v, 9/46d, TEpd, 7m, 7B, 24c. Adapted from Chaudhuri et al. (2015), copyright 2015 with permission from Elsevier.

(B and C) The integration of human electrocorticography recordings and post-mortem human brain gene expression data uncovers an association between longer intrinsic timescales and both higher expression of the excitatory NMDA receptor subunit NR2B (B) and lower expression of parvalbumin inhibitory interneurons (C). Adapted from Gao et al. (2020) copyright 2020 with permission (https://creativecommons.org/licenses/by/4.0/).

(D) Patterned variability in these excitatory and inhibitory features along the S-A axis facilitates a hierarchical gradient of intrinsic timescales characterized by transient responding in early sensory and motor cortices and sustained responding in transmodal association cortices. Adapted with permission from Raut et al. (2020) copyright 2020 via the PNAS License to Publish.

properties of association cortex neurons: longer intrinsic timescales and mixed selectivity.

Intrinsic timescale reflects how long neural activity persists above a given threshold following activity onset, either at the level of single neurons (duration of spiking) or cortical regions (duration of autocorrelated neural-related signal, quantified from local field potential recordings or the BOLD signal). Numerous structural and neurochemical features are understood to promote persistent, tonic firing over transient, phasic firing, and to thereby lengthen cortical timescales. These features include increased number and strength of local excitatory inputs, higher expression of the NMDA NR2B subunit, lower expression of PV interneurons, and a greater number of long-range, cortico-cortical projections (Chaudhuri et al., 2015; Gao et al., 2020; Murray et al., 2014; Raut et al., 2020; Wang, 2020). Critically, these neurobiological features are characteristic of transmodal association cortices in adulthood, and they gradually evolve throughout neurodevelopment, suggesting maturational calibration of cortical timescales. Ultimately, by early adulthood, topographical variability in these features across the cortex results in a gradient of neural timescales that aligns to the S-A axis (Figure 5). At one end of this gradient, sensory and motor brain regions exhibit short intrinsic timescales characterized by rapid-onset, high-frequency, adaptable responses. At the other end, transmodal frontal, parietal, and medial temporal association cortices manifest long intrinsic timescales characterized by slow fluctuations, sustained activity, and prolonged information processing. This continuous spectrum of timescales is evident in macaque single neuron spike train data (Murray et al., 2014), human electrocorticography recordings (Gao et al., 2020; Honey et al., 2012), and human functional MRI data (Ito et al., 2020; Raut et al., 2020), and it in part enables functional diversity across the cortex. The short timescales observed in sensory and motor regions are critical for detecting momentary changes in the external environment, and thus for fast perception and action. The longer timescales observed in transmodal association regions are linked to temporally extensive information accumulation and modulation (Honey et al., 2012), and thus to physiological features that support flexible, abstract, and cumulative cognitive functions such as problem solving, learning, and decision making (Gao et al., 2020; Murray et al., 2014; Wang, 2020).

In addition to variance in intrinsic timescales across the cortical sheet, areas also systematically differ in their level of stimulus selectivity. Primary sensory regions have a higher prevalence of pure selectivity neurons, which exclusively and linearly encode single stimulus features or stimulus categories via low-dimensional activity patterns. Higher-order frontal and parietal association cortices, conversely, appear to have a relatively higher proportion of mixed selectivity neurons. Mixed selectivity neurons encode combinations of stimulus features and task-relevant variables. They behave differently (yet reproducibly) depending on the context, thereby enabling adaptable, non-linear, and high-dimensional neural encoding (Fusi et al., 2016; Rigotti et al., 2013).

Mixed selectivity may have ontogenic origins in the spatiotemporal maturation of cortical inhibition. Previous work has established that developmental increases in inhibition are coupled to the emergence of stimulus selectivity within sensory cortices, and that higher levels of inhibition lead to narrower tuning of neural responses (Li et al., 2012; Sadagopan and Wang, 2010). These findings suggest that the delayed maturational increase in cortical inhibition and higher E:I ratio within association cortex may facilitate the emergence of mixed selectivity neurons, simultaneously enabling more complex computations. Pure selectivity allows for localized and invariant responses to very specific features and thus for cortical specialization. Mixed selectivity, however, produces multifaceted population responses that expand the functional range and computational capacity of a cortical region, thus supporting more diverse and dynamic forms of cognition and associated behaviors (Fusi et al., 2016; Rigotti et al., 2013).

Although mixed selectivity describes patterns of encoding at the neuronal level, an inherent relationship between increasing degrees of mixed selectivity and greater dimensionality of neural representations ensures that selectivity can be estimated at the macroscale with functional neuroimaging. Indeed, the approach originally used to infer dimensionality from single neuron recordings (Rigotti et al., 2013) has been adapted to quantify the dimensionality of functional MRI activity, revealing that higher dimensional stimulus representations are associated with faster learning (Tang et al., 2019). In this approach, dimensionality is indexed by the number of linear classifiers that can be trained on BOLD activity to reliably distinguish between binary task or stimulus conditions, with linear classifications increasing exponentially with the dimensionality of local neural responses. Moving forward, the selectivity of neural encoding could be mapped across the S-A axis during neurodevelopment by evaluating areal dimensionality of stimulus representations, in particular for stimuli that are both diverse and represented across most of the cortex (e.g., natural language and semantic representations; Huth et al., 2016).

Hierarchical multi-scale development gives rise to an extended window of association cortex plasticity

Taken together, convergent evidence from multiple data types and scales of analysis supports that human neurodevelopment progresses across the cortical landscape in a spatially ordered manner, in accordance with canonical anatomical, functional, and evolutionary hierarchies. This sequence of brain development ensures that transmodal association cortices undergo sustained development through childhood and adolescence and into young adulthood, allowing these areas of cortex to continuously diverge in form and function from primary and unimodal cortices. Such prolonged malleability indicates that higher-order association cortices remain plastic throughout later developmental epochs. Their increased duration of plasticity is facilitated by the late maturation of inhibitory circuitry, by a slower reduction in local E:I ratio, and by adolescent enhancement of plasticity-facilitating NMDA N2RB subunits. Moreover, it is enabled by the temporally prolonged development of plasticity-stabilizing features such as intracortical myelination and perineuronal nets, which do not reach adult-like levels in higher-order cortices until after multiple decades of life. This temporal patterning of cortical plasticity underlies hypotheses that late childhood and adolescence represent a *sensitive* or *critical period* for refinement of association cortices and the functions that they subserve (Fuhrmann et al., 2015; Gabard-Durnam and McLaughlin, 2020; Larsen and Luna, 2018; Larsen et al., 2021). A prolonged plastic period, although a vital and unique component of human neurodevelopment, leads to heightened inter-individual developmental variability and vulnerability within association cortex.

CAUSES AND CONSEQUENCES OF INTER-INDIVIDUAL VARIABILITY IN THE DEVELOPMENT OF ASSOCIATION CORTICES

Individualization across the sensorimotor-association axis

Existing work suggests that the hierarchy of the S-A axis serves as the foundation for human brain development. Each individual's unique combination of biology and experience differentially interacts with this foundation, giving rise to inter-individual cortical variability. Although marked inter-individual cortical variability is embedded within the first few years of life (Gilmore et al., 2020; Stoecklein et al., 2020), variability is believed to increase over the course of development, particularly within phylogenetically expanded association cortices (Stoecklein et al., 2020). Here, we first briefly consider putative intrinsic and extrinsic causes of developmental variability. Although establishing causal determinants of neurobiological variability is quite difficult, convergent data from humans and animals point to the impact of genes, molecular signals, the environment, and experience. We also consider how proposed underpinnings of neurobiological variability differ to an extent across time and across the S-A axis, in a manner that ultimately amplifies individual differences in association areas supporting human-enhanced psychological faculties. Finally, we end by discussing ramifications of cortical variability, describing how transdiagnostic symptoms of mental illness can be conceptualized as an important potential consequence of variable association cortex development.

Intrinsic and extrinsic causes of association cortex maturational variability

Genes

A wealth of *in vivo* imaging work has established that cortical features are heritable and polygenic, with evidence for heritability of both brain structure (cortical thickness, surface area, sulcal width, intracortical myelination) and function (functional connectivity, signal amplitude) (Alexander-Bloch et al., 2020; Anderson et al., 2020a; Chen et al., 2011; Elliott et al., 2018; Schmitt et al., 2020; Valk et al., 2020). The aggregate effects of many genetic variants thereby exert a substantial influence on the organization and physiology of an individual's cortex, with some evidence for lower heritability in paralimbic and heteromodal association cortices than in unimodal and primary cortices (Vainik et al., 2020). The genes that affect cortical properties vary across the brain, yet regions that share more similar positions in the S-A axis are more likely to share genetic determinants (Chen et al., 2011; Rimol et al., 2010; Valk et al., 2020). A critical outcome of this topographical pattern of genetic influence is that certain genetic variants underlying cortical variability will have concentrated effects within transmodal association cortices, and thus on advanced mental faculties. Of interest, select studies have shown that genetic influence on association cortex macrostructure is greater in adolescence than in childhood, paralleling reports that the heritability of IQ and prosocial behavior increases in later development (Lenroot et al., 2009; Schmitt et al., 2014). Finally, it has been hypothesized that genetic diversity within the population is greater for genes that determine association cortex compared with sensorimotor cortex properties, as genes that shape evolutionarily newer regions may have had less time to reach allelic fixation (Schmitt et al., 2014). This hypothesis is well supported by evidence that evolution-linked, human-accelerated genes (genes that display elevated divergence in humans compared with other primates) are most highly expressed in association cortices near the apex of the cortical hierarchy (Wei et al., 2019). Cortex-related genetic variability, and

the inter-individual neurobiological variability it engenders, may thus map onto the brain's organizational S-A axis.

Molecular signals

Just as the genes governing cortical maturation differ across the cortex, so too do development-related molecular signals. During prenatal development, gradients of evolutionarily conserved signaling molecules associated with primary patterning centers (e.g., fibroblast growth factor family 8, sonic hedgehog, bone morphogenetic proteins, Wnts) determine the location and arealization of sensory and motor cortical areas (O'Leary et al., 2007). Yet these patterning molecules are proposed to be more highly expressed near primary cortex and to thus exert less control over the development of cortically distant association regions, especially within the context of the expanded human cortex (Buckner and Krienen, 2013). Lower expression of phylogenetically old molecular developmental determinants within association cortex would ensure that other classes of signaling molecules, ones that we speculate may be more variable across individuals, have a larger impact on association cortex specification and molding. Candidate molecules include prenatally expressed signals thought to influence the size and connectivity of prefrontal cortex in primates (e.g., retinoic acid) (Shibata et al., 2019), as well as signals expressed later in development shown to affect association cortex structural refinement.

Indeed, during late childhood and adolescence, a different class of molecular signals appears to substantially influence association cortex development: pubertal hormones. Preliminary neuroimaging studies have shown that levels of testosterone and estrogen in developing youth are associated with individual differences in cortical macrostructure and white matter microstructure (Herting et al., 2012; Koolschijn et al., 2014; Vijayakumar et al., 2021). Associations between hormone levels and cortical variability have been observed almost exclusively in association cortex, underlying white matter, and subcortical structures, suggesting a degree of spatial specificity for the influence of adolescent pubertal hormones. Rodent studies provide consistent evidence, revealing that during adolescence, pubertal hormones affect pyramidal neuron pruning (Delevich et al., 2020), the expression of NMDA NR2B subunits (Smith and McMahon, 2006), and increases in cortical inhibition (Piekarski et al., 2017). Piekarski et al. (2017) found that estrogen facilitates increases in cortical inhibition within medial frontal but not somatosensory cortex, supporting spatially localized effects in associative but not primary cortices. Prior work thus suggests that molecular mechanisms of cortical modeling are both temporally and spatially differentiable, with variability in pubertal hormone levels contributing to further individualization of the association cortices during adolescence.

Environment and experience

Abundant evidence suggests that the environments and experiences encountered during youth affect brain development. However, the specific impact of a given environmental stimulus is critically dependent upon the neurotemporal context or upon how plasticity is distributed along the S-A axis at the time (Cooper and Mackey, 2016). Cortical maturation is putatively most affected when there is temporal alignment between a cortical region's peak period of maturational plasticity and exposure (or lack thereof) to experiences that effectively engage that region. Sensory and motor experiences disproportionately affect the developing brain early in life, when primary regions are most plastic. For example, in early infancy, deprivation of auditory, visual, and tactile stimuli greatly affects the organization and maturation of sensorimotor regions (Hubel and Wiesel, 1970; Kanjlia et al., 2019; Simons and Land, 1987). Deprivation of these stimuli during later developmental periods has comparably minimal effects, although notably abnormal development of sensory regions early in life may affect later development of connected association regions (Rosen et al., 2019). Remarkably, cognitive, social, and emotional experiences significantly affect cortical development not only during infancy (McLaughlin et al., 2014) but additionally during childhood, adolescence, and early adulthood—attributable to the elevated level of plasticity maintained in higher-order cortices throughout these developmental periods (Mackey et al., 2013). Indeed, variability in peer social exposure (Hinton et al., 2019), cognitive training (Huber et al., 2018; Iuculano et al., 2015), stress (Lupien et al., 2009; Sheth et al., 2017), and enrichment versus deprivation of one's socioemotional, educational, and neighborhood environments (Alnæs et al., 2020; Leonard et al., 2019; Llera et al., 2019; Modabbernia et al., 2021; Smith et al., 2015; Tooley et al., 2020) is thought to affect association cortex maturation in middle and late periods of development. Collectively, these data underscore how the nature of brain-environment associations may change as brain development unfolds along the hierarchical S-A axis.

Linking genetic, molecular, and experiential variability to neurobiological variability

Neurobiological variability is not equal across the cortex; rather, it systematically varies. Neurobiological variability is predicted to be higher in cortical regions with more genetic diversity, higher human-accelerated gene expression, weaker constraints from phylogenetically older patterning centers, and greater individual differences in developmental signaling molecules. Furthermore, variability is predicted to be higher in regions that are sculpted by diverse experiences and that remain malleable by experience for a longer period of time. Critically, genetic diversity, human-accelerated gene expression, distance from primary patterning centers, effects of adolescent hormonal signals, experiential variability, and the time frame of plasticity all increase along the S-A axis. Accordingly, *inter-individual neurobiological variability increases along the S-A axis* as well, with most marked individual differences found in evolutionarily expanded heteromodal association cortices (Cui et al., 2020; Mueller et al., 2013; Reardon et al., 2018; Figure 6). Heightened neurobiological variability within transmodal associative compared with unimodal sensorimotor cortices is apparent when examining both macroscale and microscale features, including cortical structure (Fischl and Dale, 2000; Hill et al., 2010a; Mueller et al., 2013; Reardon et al., 2018), connectivity architecture (Gratton et al., 2018; Mueller et al., 2013; Xu et al., 2019), the topographical organization of functional systems (Cui et al., 2020; Kong et al., 2019), and the total number of pyramidal neuron dendritic spines (Elston et al., 2011). As discussed below, such pronounced individual differences within the brain's higher-order, evolutionarily newer, enduringly plastic association cortices produce a wide spectrum of psychological functioning in both health and mental illness.

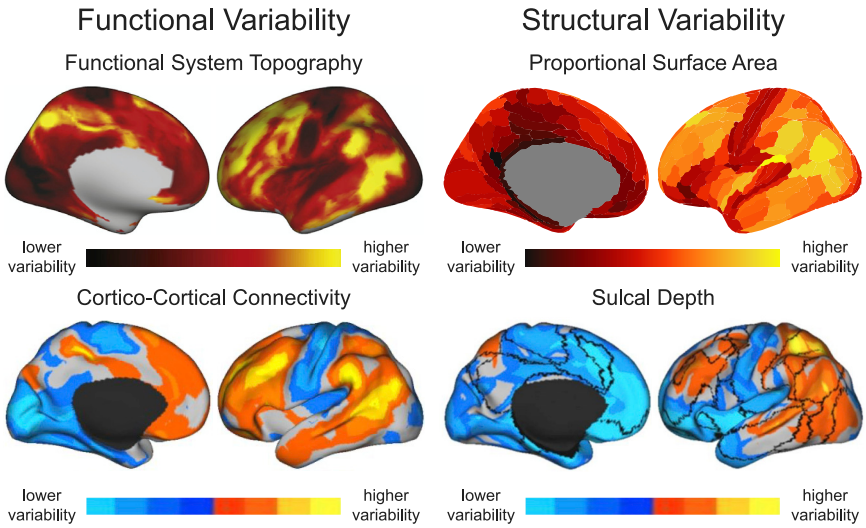


Figure 6. Inter-individual variability in functional and structural properties across the cortical mantle

Inter-individual variability in functional system topography, cortico-cortical functional connectivity architecture, proportional surface area, and sulcal depth varies by the S-A organizational axis and is generally highest in transmodal heteromodal association regions. Functional system topography adapted from Cui et al. (2020), copyright 2020 with permission from Elsevier. Cortico-cortical connectivity and sulcal depth adapted from Mueller et al. (2013), copyright 2013 with permission from Elsevier. Proportional surface area data from Reardon et al. (2018).

Consequences of association cortex maturational variability: Transdiagnostic developmental psychopathology

Symptoms of mental illness often emerge in mid to late childhood (e.g., anxiety symptoms) or in adolescence and early adulthood (e.g., mood and psychosis-spectrum symptoms), during prominent periods of plasticity for cortices subserving cognitive, mentalizing, and socioemotional functions (Caspi et al., 2020; Kessler et al., 2005; Merikangas et al., 2010; Paus et al., 2008). Although the canonical psychiatric diagnostic system (the *Diagnostic and Statistical Manual of Mental Disorders*) defines mental illnesses as discrete disorders, epidemiological data underscore the fact that most individuals experience comorbid symptoms not adequately captured by a single diagnosis (Caspi et al., 2020; Merikangas et al., 2010). Moreover, common and important symptom domains (e.g., anhedonia, emotion dysregulation, anxiety, irritability, executive dysfunction) are transdiagnostic features of many disorders. Given the comorbid and transdiagnostic nature of psychiatric symptomatology, it has been proposed that there is a latent factor that predicts a generalized vulnerability to diverse psychopathology (the "p-factor") (Caspi et al., 2014, 2020; Michelini et al., 2019). Significantly, the comorbid symptoms captured by the p-factor all tend to emerge relatively later in the brain's hierarchical developmental program, strongly implicating non-normative maturation of transmodal association cortices in transdiagnostic psychopathology.

Multiple lines of evidence support the claim that maturational variability within higher-order association cortices is causally related to inter-individual variability in psychological functioning and psychiatric illness. First, genes influencing variability in association cortex features confer overlapping genetic liability to multiple psychiatric conditions (Anttila et al., 2018; Grasby et al., 2020; Hofer et al., 2020). Second, an earlier increase in pubertal hormones that affect association cortex maturation, driven by younger pubertal onset, confers heightened risk for developing all forms of psychopathology (Ullsperger and Nikolas, 2017). Third, environmental and experiential factors that affect association cortex development, including low social support, neighborhood deprivation, and stress, are risk factors for mental illness (Modabbernia et al., 2021). Fourth, differences in cortical structure and function shared across many forms of psychopathology occur within the association cortices, with larger effects detectable as regions progress up the S-A axis (McTeague et al., 2017; Romer et al., 2021; Figure 7A). Specifically, symptoms of depression, anxiety, fear, mania, compulsivity, psychosis, and generalized psychopathology are associated with reduced volume and thickness of the association cortices (Goodkind et al., 2015; Kaczkurkin et al., 2019; Romer et al., 2021). Moreover, these diverse symptoms are associated with microstructural modifications in white matter pathways projecting from higher-order frontal cortices (Alnæs et al., 2018), and with altered activity and connectivity of cingulo-opercular, frontoparietal, and default mode systems (McTeague et al., 2017; Shanmugan et al., 2016; Xia et al., 2018).

The enrichment of phenotypes associated with psychopathology within the association cortices suggests that evolutionarily newer brain regions that undergo prolonged neurodevelopment play a central role in diverse psychiatric symptoms. Overlap in neuroimaging signatures of developmental psychopathology does not, however, necessarily indicate shared microscale mechanisms; it is likely that disparate mechanisms lead to similar macroscale cortical phenotypes. Still, studies combining *in vivo* imaging with histology and transcriptomics collectively point to alterations in *plasticity-related cellular features* as potentially critical for developmental psychopathology. In particular, recent work bridging the macroscale and the microscale suggests that psychopathology-related dysfunction involves deviations in plasticity mechanisms related to cortical excitation, cortical inhibition, and glia. For example, psychosis-linked alterations in macroscale structural connectivity are largest in regions that exhibit the greatest psychosis-linked reductions in pyramidal spine density; this observation potentially relates disordered cortico-cortical connectivity to alterations in cortical excitatory plasticity and pruning (van den Heuvel et al., 2016a; Figure 7B). In addition, the cortical distribution of altered resting state signal amplitude observed in depression corresponds to the expression of SST inhibitory interneurons (Anderson et al., 2020b), implicating irregularities in inhibition or inhibition-associated plasticity in affective symptoms (Larsen et al., 2021; Figure 7C). Extending

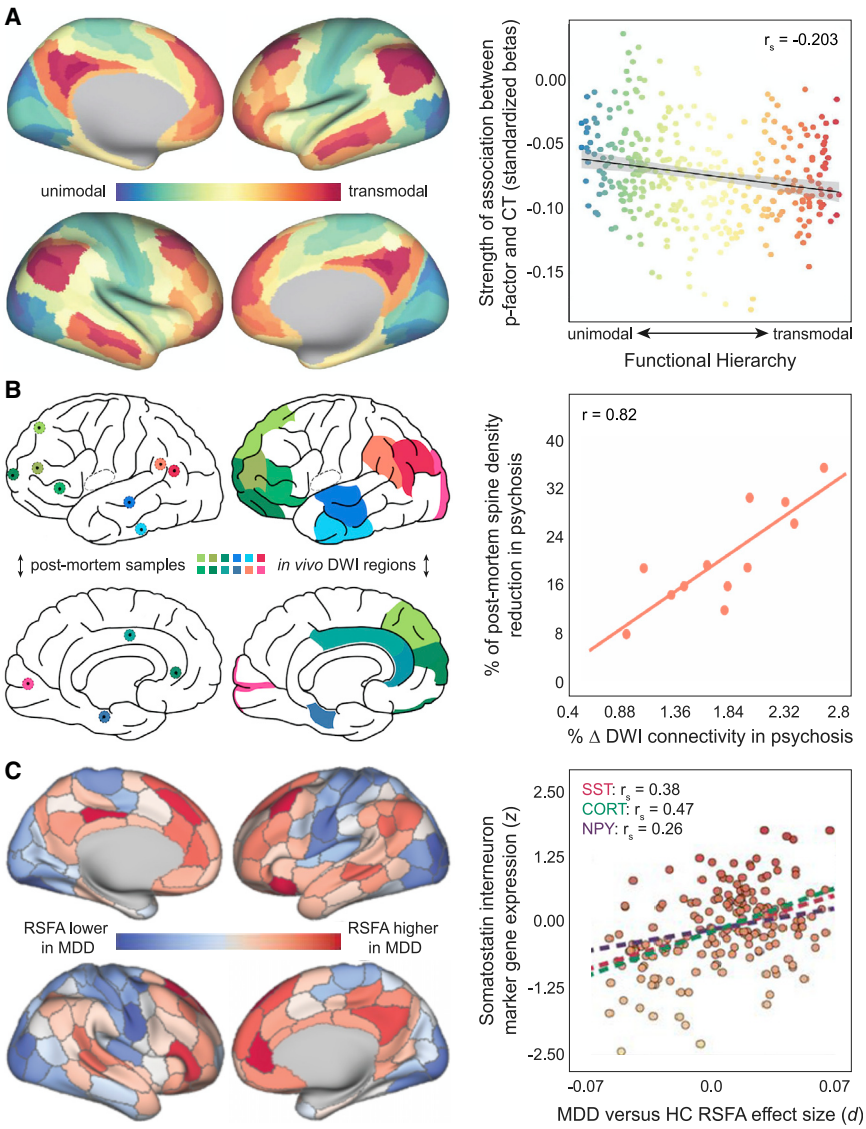


Figure 7. Psychopathology-linked cortical phenotypes and potential cellular correlates

(A) The strength of the association between more severe generalized psychopathology (p-factor) and reduced cortical thickness (CT) increases along the cortical functional hierarchy, with stronger effects in transmodal (orange/red) than in unimodal (blue/green) cortices.

(B) Cortical regions that exhibit larger alterations in macroscale structural connectivity in individuals with psychosis (*in vivo* diffusion-weighted imaging [DWI] data) additionally display greater reductions in neuron spine density in psychotic individuals (post-mortem data).

(C) The across-cortex pattern of resting state functional amplitude (RSFA) differences between individuals with a history of major depressive disorder (MDD) and healthy controls (HC) (indexed by Cohen's *d*) corresponds to the spatial distribution of three somatostatin inhibitory interneuron markers, somatostatin (SST), cortistatin (CORT), and neuropeptide Y (NPY). r_s, Spearman's rank correlation coefficient; r, Pearson's correlation coefficient.

(A) adapted from Romer et al. (2021) with permission from the *American Journal of Psychiatry*, (copyright 2021). American Psychiatric Association. All rights reserved. (B) adapted from van den Heuvel et al. (2016a) copyright 2016 with permission from Elsevier. (C) Adapted from Anderson et al. (2020b) copyright 2020 with permission (https://creativecommons.org/licenses/by-nc-nd/4.0/).

this pattern, individuals with greater symptoms of anxiety, impulsivity, thought disorder, and generalized psychopathology exhibit non-normative development of association cortex intracortical myelin, a critical feature for stabilizing developmental plasticity (Norbom et al., 2019; Ziegler et al., 2019).

The complex relationship between association cortex maturation, plasticity-regulating mechanisms, and transdiagnostic developmental psychopathology has profound implications for mental health interventions and treatment. First, this relationship suggests that initiatives that support healthy development of the association cortices may decrease risk for many forms of psychopathology. Initiatives could include school-based programs that train individuals to alleviate stress, regulate emotions, improve social skills, explore rewarding activities, enhance reasoning and planning capabilities, and engage in flexible and critical thinking (Durlak et al., 2011; Robinson, 2004; Zenner et al., 2014), as well as community-based programs that focus on environmental enrichment and the reduction of socioeconomic and racial disparities (Mackey et al., 2013; Modabbernia et al., 2021; Reiss, 2013). Links among association cortex maturation, plasticity, and diverse psychiatric symptoms additionally suggest that psychotropics that target plasticity-related neurobiological mechanisms and transdiagnostic therapies for youth may prove to be particularly effective interventions (Caspi and Moffitt, 2018; Dalgleish et al., 2020). Importantly, late childhood and adolescence may represent an optimal period for implementing these interventions, as this developmental period is characterized by programmed plasticity within association cortices at the apex of anatomical, functional, evolutionary, and neurodevelopmental hierarchies. Interventions in this uniquely human sensitive period may hold great potential for preventing psychopathology-related developmental insults from becoming permanently embedded in cortical organization.

FUTURE EXPLORATION OF THE SENSORIMOTOR-ASSOCIATION AXIS OF HUMAN NEURODEVELOPMENT: INTRINSIC DRIVERS, INDIVIDUALIZATION, AND INTERVENTIONS

Although the human cortex exhibits nearly unparalleled complexity, the S-A axis represents one important large-scale

Box 2. Outstanding questions to be explored in future work

How is the S-A axis established during early brain development, and when does it become a principal axis of cortical organization? Does the S-A axis emerge because of interactions among multiple early morphogenic and transcriptional gradients?
How does subcortical development interact with hierarchical cortical development? Can the neurodevelopmental hierarchy be extended to maturation of subcortical structures?
When in life do alternative prominent axes of organization (Box 1) emerge, and how can they inform our understanding of cortical maturation? How does their development interact with development of the S-A axis?
What factors influence individual differences in the topographical maturation and developmental strengthening of the S-A axis?
To what extent does altered development of sensorimotor cortices early in life affect subsequent maturation of cortical properties across the entire S-A axis?
How do structural, neurochemical, and electrophysiological changes jointly govern hierarchical cortical development, and can temporal precedence be identified?
Do the genes governing cortical maturation change throughout brain development, as development unfolds along the S-A axis? How do epigenetic mechanisms contribute?
How do pubertal hormones affect the timing and the nature of human developmental plasticity? Are hormonal effects spatially localized, sex specific, or variable among individuals with different gender identities?
What environments and experiences have the largest impact on the association cortices, and when? Can sensitive periods be demarcated? Can experience modulate the onset and temporal trajectory of association cortex development?
What neurobiological mechanisms underlie transdiagnostic differences in association cortex structure and function?
When is developmental programming of the association cortices most amenable to interventions aimed at preventing or treating psychiatric symptomatology?

organizational motif. The S-A axis describes the hierarchical patterning of cortical variability and provides insight into the origins of functional diversity across the brain. Furthermore, the S-A axis in part encapsulates the evolution of the primate cortex, as well as its non-linear expansion in humans. Finally, as revealed by extensive human neuroimaging investigations and complementary studies conducted at the microscale, the temporal sequence of human cortical maturation progresses along the S-A axis, culminating in a late period of plasticity within transmodal association cortices supporting advanced faculties. This maturational program modifies, strengthens, and expands the S-A feature axis, facilitating the development of higher-order brain functions that are both unique to the human species and markedly variable between individuals within our species.

The work reviewed here has begun to elegantly characterize patterns of human cortical maturation, underlying mechanisms, and complex links to transdiagnostic psychopathology. Although only cortical maturation was considered, subcortical regions that execute heterogeneous, multi-order functions, including the striatum, thalamus, hippocampus, and cerebellum, display regional S-A axes; these axes capture variation both in local function and in patterns of cortical connectivity (Guell et al., 2018; Haber, 2003; Müller et al., 2020; Paquola et al., 2020b; Raut et al., 2020; Yang et al., 2020). Moreover, subcortical regions develop in tandem with functionally similar cortex, with subcortical structural and functional connections to transmodal association cortices continuing to change in strength throughout adolescence (Larsen et al., 2018; Park et al., 2021; Váša et al., 2020). Given such evidence supporting hierarchical organization and development of subcortical regions—and the profound impact these regions have on cortical arealization, whole-brain functional dynamics, and psychopathology-relevant behaviors—it is clearly of interest to determine whether the conceptual framework put forth in this review extends to the subcortex. This represents one major avenue to be explored in future work (see also Box 2). Continued investigation of these outstanding questions will provide rich information on intrinsic drivers of hierarchical human brain development in cortex and subcortex, will identify additional spatiotemporal axes of maturation, will delineate factors influencing individualized maturational trajectories, and will further uncover how inter-individual variation in neurobiological properties produces a spectrum of cognitive and psychological functioning. Ultimately, such insights may yield interventions that align with the developmental context described by the hierarchical neurodevelopmental axis, and that are thus capable of mitigating risk for the development of diverse and disabling psychopathologies in youth.

ACKNOWLEDGMENTS

This work was supported by a National Science Foundation Graduate Research Fellowship (DGE-1845298 to V.J.S.) and by the National Institute of Mental Health (R01 MH112847 to T.D.S., R01 MH113550 and RF1 MH116920 to T.D.S. and D.S.B., R01 MH120482 to T.D.S. and M.P.M., T32 MH014654 to B.L., K08 MH120564 to A.A.-B., F31 MH123063 to A.P., R01 MH120174 and R01 MH119185 to D.R., T32 MH19112-29 to J.S., and R01 MH111439 to T.X.).

AUTHOR CONTRIBUTIONS

Conceptualization, V.J.S. and T.D.S.; Writing – Original Draft, V.J.S., B.L., and T.D.S.; Writing – Review & Editing, V.J.S., B.L., D.S.B., A.A.-B., D.A.F., C.L., A.P.M., M.P.M., A.P., D.R.R., J.S., T.X., A.R., and T.D.S.; Visualization, V.J.S. and J.S.; Supervision, T.D.S.

DECLARATION OF INTERESTS

The authors declare no competing interests.

REFERENCES

Aflalo, T.N., and Graziano, M.S.A. (2011). Organization of the macaque extrastriate visual cortex re-examined using the principle of spatial continuity of function. J. Neurophysiol. *105*, 305–320.

Alexander-Bloch, A.F., Raznahan, A., Vandekar, S.N., Seidlitz, J., Lu, Z., Mathias, S.R., Knowles, E., Mollon, J., Rodrigue, A., Curran, J.E., et al. (2020). Imaging local genetic influences on cortical folding. Proc. Natl. Acad. Sci. U S A *117*, 7430–7436.

Alnæs, D., Kaufmann, T., Doan, N.T., Córdova-Palomera, A., Wang, Y., Bettella, F., Moberget, T., Andreassen, O.A., and Westlye, L.T. (2018). Association of heritable cognitive ability and psychopathology with white matter properties in children and adolescents. JAMA Psychiatry *75*, 287–295.

Alnæs, D., Kaufmann, T., Marquand, A.F., Smith, S.M., and Westlye, L.T. (2020). Patterns of sociocognitive stratification and perinatal risk in the child brain. Proc. Natl. Acad. Sci. U S A *117*, 12419–12427.

Amlien, I.K., Fjell, A.M., Tamnes, C.K., Grydeland, H., Krogsrud, S.K., Chaplin, T.A., Rosa, M.G.P., and Walhovd, K.B. (2016). Organizing principles of human cortical development—thickness and area from 4 to 30 years: insights from comparative primate neuroanatomy. Cereb. Cortex *26*, 257–267.

Anderson, K.M., Krienen, F.M., Choi, E.Y., Reinen, J.M., Yeo, B.T.T., and Holmes, A.J. (2018). Gene expression links functional networks across cortex and striatum. Nat. Commun. *9*, 1428.

Anderson, K.M., Collins, M.A., Chin, R., Ge, T., Rosenberg, M.D., and Holmes, A.J. (2020a). Transcriptional and imaging-genetic association of cortical interneurons, brain function, and schizophrenia risk. Nat. Commun. *11*, 2889.

Anderson, K.M., Collins, M.A., Kong, R., Fang, K., Li, J., He, T., Chekroud, A.M., Yeo, B.T.T., and Holmes, A.J. (2020b). Convergent molecular, cellular, and cortical neuroimaging signatures of major depressive disorder. Proc. Natl. Acad. Sci. U S A *117*, 25138–25149.

Anttila, V., Bulik-Sullivan, B., Finucane, H.K., Walters, R.K., Bras, J., Duncan, L., Escott-Price, V., Falcone, G.J., Gormley, P., Malik, R., et al.; Brainstorm Consortium (2018). Analysis of shared heritability in common disorders of the brain. Science *360*, eaap8757.

Bajada, C.J., Costa Campos, L.Q., Caspers, S., Muscat, R., Parker, G.J.M., Lambon Ralph, M.A., Cloutman, L.L., and Trujillo-Barreto, N.J. (2020). A tutorial and tool for exploring feature similarity gradients with MRI data. Neuroimage *221*, 117140.

Baker, S.T.E., Lubman, D.I., Yücel, M., Allen, N.B., Whittle, S., Fulcher, B.D., Zalesky, A., and Fornito, A. (2015). Developmental changes in brain network hub connectivity in late adolescence. J. Neurosci. *35*, 9078–9087.

Ball, G., Seidlitz, J., O'Muircheartaigh, J., Dimitrova, R., Fenchel, D., Makropoulos, A., Christiaens, D., Schuh, A., Passerat-Palmbach, J., Hutter, J., et al. (2020a). Cortical morphology at birth reflects spatiotemporal patterns of gene expression in the fetal human brain. PLoS Biol. *18*, e3000976.

Ball, G., Seidlitz, J., Beare, R., and Seal, M.L. (2020b). Cortical remodelling in childhood is associated with genes enriched for neurodevelopmental disorders. Neuroimage *215*, 116803.

Barbas, H. (1986). Pattern in the laminar origin of corticocortical connections. J. Comp. Neurol. *252*, 415–422.

Bartzokis, G., Lu, P.H., Heydari, P., Couvrette, A., Lee, G.J., Kalashyan, G., Freeman, F., Grinstead, J.W., Villablanca, P., Finn, J.P., et al. (2012). Multimodal magnetic resonance imaging assessment of white matter aging trajectories over the lifespan of healthy individuals. Biol. Psychiatry *72*, 1026–1034.

Bassett, D.S., Xia, C.H., and Satterthwaite, T.D. (2018). Understanding the emergence of neuropsychiatric disorders with network neuroscience. Biol. Psychiatry Cogn. Neurosci. Neuroimaging *3*, 742–753.

Baum, G.L., Ciric, R., Roalf, D.R., Betzel, R.F., Moore, T.M., Shinohara, R.T., Kahn, A.E., Vandekar, S.N., Rupert, P.E., Quarmley, M., et al. (2017). Modular segregation of structural brain networks supports the development of executive function in youth. Curr. Biol. *27*, 1561–1572.e8.

Baum, G.L., Cui, Z., Roalf, D.R., Ciric, R., Betzel, R.F., Larsen, B., Cieslak, M., Cook, P.A., Xia, C.H., Moore, T.M., et al. (2020). Development of structure-function coupling in human brain networks during youth. Proc. Natl. Acad. Sci. U S A *117*, 771–778.

Bazinet, V., de Wael, R.V., Hagmann, P., Bernhardt, B.C., and Misic, B. (2020). Multiscale communication in cortico-cortical networks. bioRxiv. https://doi.org/10.1101/2020.10.02.323030.

Beul, S.F., and Hilgetag, C.C. (2019). Neuron density fundamentally relates to architecture and connectivity of the primate cerebral cortex. Neuroimage *189*, 777–792.

Buckner, R.L., and Krienen, F.M. (2013). The evolution of distributed association networks in the human brain. Trends Cogn. Sci. *17*, 648–665.

Burt, J.B., Demirtaş, M., Eckner, W.J., Navejar, N.M., Ji, J.L., Martin, W.J., Bernacchia, A., Anticevic, A., and Murray, J.D. (2018). Hierarchy of transcriptomic specialization across human cortex captured by structural neuroimaging topography. Nat. Neurosci. *21*, 1251–1259.

Caballero, A., Flores-Barrera, E., Cass, D.K., and Tseng, K.Y. (2014). Differential regulation of parvalbumin and calretinin interneurons in the prefrontal cortex during adolescence. Brain Struct. Funct. *219*, 395–406.

Cahalane, D.J., Charvet, C.J., and Finlay, B.L. (2012). Systematic, balancing gradients in neuron density and number across the primate isocortex. Front. Neuroanat. *6*, 28.

Carlo, C.N., and Stevens, C.F. (2013). Structural uniformity of neocortex, revisited. Proc. Natl. Acad. Sci. U S A *110*, 1488–1493.

Carulli, D., Pizzorusso, T., Kwok, J.C.F., Putignano, E., Poli, A., Forostyak, S., Andrews, M.R., Deepa, S.S., Glant, T.T., and Fawcett, J.W. (2010). Animals lacking link protein have attenuated perineuronal nets and persistent plasticity. Brain *133*, 2331–2347.

Caspi, A., and Moffitt, T.E. (2018). All for one and one for all: mental disorders in one dimension. Am. J. Psychiatry *175*, 831–844.

Caspi, A., Houts, R.M., Belsky, D.W., Goldman-Mellor, S.J., Harrington, H., Israel, S., Meier, M.H., Ramrakha, S., Shalev, I., Poulton, R., and Moffitt, T.E. (2014). The p factor: one general psychopathology factor in the structure of psychiatric disorders? Clin. Psychol. Sci. *2*, 119–137.

Caspi, A., Houts, R.M., Ambler, A., Danese, A., Elliott, M.L., Hariri, A., Harrington, H., Hogan, S., Poulton, R., Ramrakha, S., et al. (2020). Longitudinal assessment of mental health disorders and comorbidities across 4 decades among participants in the Dunedin Birth Cohort Study. JAMA Netw. Open *3*, e203221.

Chang, Y.S., Owen, J.P., Pojman, N.J., Thieu, T., Bukshpun, P., Wakahiro, M.L.J., Berman, J.I., Roberts, T.P.L., Nagarajan, S.S., Sherr, E.H., and Mukherjee, P. (2015). White matter changes of neurite density and fiber orientation dispersion during human brain maturation. PLoS ONE *10*, e0123656.

Charvet, C.J., and Finlay, B.L. (2014). Evo-devo and the primate isocortex: the central organizing role of intrinsic gradients of neurogenesis. Brain Behav. Evol. *84*, 81–92.

Chaudhuri, R., Knoblauch, K., Gariel, M.-A., Kennedy, H., and Wang, X.-J. (2015). A large-scale circuit mechanism for hierarchical dynamical processing in the primate cortex. Neuron *88*, 419–431.

Chen, C.-H., Panizzon, M.S., Eyler, L.T., Jernigan, T.L., Thompson, W., Fennema-Notestine, C., Jak, A.J., Neale, M.C., Franz, C.E., Hamza, S., et al. (2011). Genetic influences on cortical regionalization in the human brain. Neuron *72*, 537–544.

Clouchoux, C., Kudelski, D., Gholipour, A., Warfield, S.K., Viseur, S., Bouyssi-Kobar, M., Mari, J.-L., Evans, A.C., du Plessis, A.J., and Limperopoulos, C. (2012). Quantitative in vivo MRI measurement of cortical development in the fetus. Brain Struct. Funct. *217*, 127–139.

Condé, F., Lund, J.S., and Lewis, D.A. (1996). The hierarchical development of monkey visual cortical regions as revealed by the maturation of parvalbumin-immunoreactive neurons. Brain Res. Dev. Brain Res. *96*, 261–276.

Cooper, E.A., and Mackey, A.P. (2016). Sensory and cognitive plasticity: implications for academic interventions. Curr. Opin. Behav. Sci. *10*, 21–27.

Cui, Z., Li, H., Xia, C.H., Larsen, B., Adebimpe, A., Baum, G.L., Cieslak, M., Gur, R.E., Gur, R.C., Moore, T.M., et al. (2020). Individual variation in functional topography of association networks in youth. Neuron *106*, 340–353.e8.

Dalgleish, T., Black, M., Johnston, D., and Bevan, A. (2020). Transdiagnostic approaches to mental health problems: Current status and future directions. J. Consult. Clin. Psychol. *88*, 179–195.

Delevich, K., Okada, N.J., Rahane, A., Zhang, Z., Hall, C.D., and Wilbrecht, L. (2020). Sex and pubertal status influence dendritic spine density on frontal corticostriatal projection neurons in mice. Cereb. Cortex *30*, 3543–3557.

Dimond, D., Rohr, C.S., Smith, R.E., Dhollander, T., Cho, I., Lebel, C., Dewey, D., Connelly, A., and Bray, S. (2020). Early childhood development of white matter fiber density and morphology. Neuroimage *210*, 116552.

Donahue, C.J., Glasser, M.F., Preuss, T.M., Rilling, J.K., and Van Essen, D.C. (2018). Quantitative assessment of prefrontal cortex in humans relative to nonhuman primates. Proc. Natl. Acad. Sci. U S A *115*, E5183–E5192.

Dong, H.-M., Margulies, D.S., Zuo, X.-N., and Holmes, A.J. (2020). Shifting gradients of macroscale cortical organization mark the transition from childhood to adolescence. bioRxiv. https://doi.org/10.1101/2020.11.17.385260.

Dos Santos, S.E., Medeiros, M., Porfirio, J., Tavares, W., Pessôa, L., Grinberg, L., Leite, R.E.P., Ferretti-Rebustini, R.E.L., Suemoto, C.K., Filho, W.J., et al. (2020). Similar microglial cell densities across brain structures and mammalian species: implications for brain tissue function. J. Neurosci. *40*, 4622–4643.

Dosenbach, N.U.F., Nardos, B., Cohen, A.L., Fair, D.A., Power, J.D., Church, J.A., Nelson, S.M., Wig, G.S., Vogel, A.C., Lessov-Schlaggar, C.N., et al. (2010). Prediction of individual brain maturity using fMRI. Science *329*, 1358–1361.

Durlak, J.A., Weissberg, R.P., Dymnicki, A.B., Taylor, R.D., and Schellinger, K.B. (2011). The impact of enhancing students' social and emotional learning: a meta-analysis of school-based universal interventions. Child Dev. *82*, 405–432.

Elliott, L.T., Sharp, K., Alfaro-Almagro, F., Shi, S., Miller, K.L., Douaud, G., Marchini, J., and Smith, S.M. (2018). Genome-wide association studies of brain imaging phenotypes in UK Biobank. Nature *562*, 210–216.

Elston, G.N. (2003). Cortex, cognition and the cell: new insights into the pyramidal neuron and prefrontal function. Cereb. Cortex *13*, 1124–1138.

Elston, G.N., and Fujita, I. (2014). Pyramidal cell development: postnatal spinogenesis, dendritic growth, axon growth, and electrophysiology. Front. Neuroanat. *8*, 78.

Elston, G.N., Oga, T., and Fujita, I. (2009). Spinogenesis and pruning scales across functional hierarchies. J. Neurosci. *29*, 3271–3275.

Elston, G.N., Benavides-Piccione, R., Elston, A., Manger, P.R., and Defelipe, J. (2011). Pyramidal cells in prefrontal cortex of primates: marked differences in neuronal structure among species. Front. Neuroanat. *5*, 2.

Fagiolini, M., and Hensch, T.K. (2000). Inhibitory threshold for critical-period activation in primary visual cortex. Nature *404*, 183–186.

Fair, D.A., Dosenbach, N.U.F., Church, J.A., Cohen, A.L., Brahmbhatt, S., Miezin, F.M., Barch, D.M., Raichle, M.E., Petersen, S.E., and Schlaggar, B.L. (2007). Development of distinct control networks through segregation and integration. Proc. Natl. Acad. Sci. U S A *104*, 13507–13512.

Fair, D.A., Cohen, A.L., Dosenbach, N.U.F., Church, J.A., Miezin, F.M., Barch, D.M., Raichle, M.E., Petersen, S.E., and Schlaggar, B.L. (2008). The maturing architecture of the brain's default network. Proc. Natl. Acad. Sci. U S A *105*, 4028–4032.

Felleman, D.J., and Van Essen, D.C. (1991). Distributed hierarchical processing in the primate cerebral cortex. Cereb. Cortex *1*, 1–47.

Fischl, B., and Dale, A.M. (2000). Measuring the thickness of the human cerebral cortex from magnetic resonance images. Proc. Natl. Acad. Sci. U S A *97*, 11050–11055.

Flores-Barrera, E., Thomases, D.R., Heng, L.-J., Cass, D.K., Caballero, A., and Tseng, K.Y. (2014). Late adolescent expression of GluN2B transmission in the prefrontal cortex is input-specific and requires postsynaptic protein kinase A and D1 dopamine receptor signaling. Biol. Psychiatry *75*, 508–516.

Froudist-Walsh, S., Xu, T., Niu, M., Rapan, L., Margulies, D.S., Zilles, K., Wang, X.-J., and Palomero-Gallagher, N. (2021). Gradients of receptor expression in the macaque cortex. bioRxiv. https://doi.org/10.1101/2021.02.22.432173.

Fuhrmann, D., Knoll, L.J., and Blakemore, S.-J. (2015). Adolescence as a sensitive period of brain development. Trends Cogn. Sci. *19*, 558–566.

Fung, S.J., Webster, M.J., Sivagnanasundaram, S., Duncan, C., Elashoff, M., and Weickert, C.S. (2010). Expression of interneuron markers in the dorsolateral prefrontal cortex of the developing human and in schizophrenia. Am. J. Psychiatry *167*, 1479–1488.

Fusi, S., Miller, E.K., and Rigotti, M. (2016). Why neurons mix: high dimensionality for higher cognition. Curr. Opin. Neurobiol. *37*, 66–74.

Gabard-Durnam, L., and McLaughlin, K.A. (2020). Sensitive periods in human development: charting a course for the future. Curr. Opin. Behav. Sci. *36*, 120–128.

Gao, R., van den Brink, R.L., Pfeffer, T., and Voytek, B. (2020). Neuronal timescales are functionally dynamic and shaped by cortical microarchitecture. eLife *9*, e61277.

García-Cabezas, M.Á., Zikopoulos, B., and Barbas, H. (2019). The structural model: a theory linking connections, plasticity, pathology, development and evolution of the cerebral cortex. Brain Struct. Funct. *224*, 985–1008.

Geeraert, B.L., Lebel, R.M., and Lebel, C. (2019). A multiparametric analysis of white matter maturation during late childhood and adolescence. Hum. Brain Mapp. *40*, 4345–4356.

Genc, S., Malpas, C.B., Gulenc, A., Sciberras, E., Efron, D., Silk, T.J., and Seal, M.L. (2020). Longitudinal patterns of white matter fibre density and morphology in children are associated with age and pubertal stage. Dev. Cogn. Neurosci. *45*, 100853.

Ghisleni, C., Bollmann, S., Poil, S.-S., Brandeis, D., Martin, E., Michels, L., O'Gorman, R.L., and Klaver, P. (2015). Subcortical glutamate mediates the reduction of short-range functional connectivity with age in a developmental cohort. J. Neurosci. *35*, 8433–8441.

Gilmore, J.H., Knickmeyer, R.C., and Gao, W. (2018). Imaging structural and functional brain development in early childhood. Nat. Rev. Neurosci. *19*, 123–137.

Gilmore, J.H., Langworthy, B., Girault, J.B., Fine, J., Jha, S.C., Kim, S.H., Cornea, E., and Styner, M. (2020). Individual variation of human cortical structure is established in the first year of life. Biol. Psychiatry Cogn. Neurosci. Neuroimaging *5*, 971–980.

Glantz, L.A., Gilmore, J.H., Hamer, R.M., Lieberman, J.A., and Jarskog, L.F. (2007). Synaptophysin and postsynaptic density protein 95 in the human prefrontal cortex from mid-gestation into early adulthood. Neuroscience *149*, 582–591.

Glasser, M.F., and Van Essen, D.C. (2011). Mapping human cortical areas in vivo based on myelin content as revealed by T1- and T2-weighted MRI. J. Neurosci. *31*, 11597–11616.

Glasser, M.F., Coalson, T.S., Robinson, E.C., Hacker, C.D., Harwell, J., Yacoub, E., Ugurbil, K., Andersson, J., Beckmann, C.F., Jenkinson, M., et al. (2016). A multi-modal parcellation of human cerebral cortex. Nature *536*, 171–178.

Goldberg, E. (1989). Gradiental approach to neocortical functional organization. J. Clin. Exp. Neuropsychol. *11*, 489–517.

Goodkind, M., Eickhoff, S.B., Oathes, D.J., Jiang, Y., Chang, A., Jones-Hagata, L.B., Ortega, B.N., Zaiko, Y.V., Roach, E.L., Korgaonkar, M.S., et al. (2015). Identification of a common neurobiological substrate for mental illness. JAMA Psychiatry *72*, 305–315.

Goulas, A., Zilles, K., and Hilgetag, C.C. (2018). Cortical gradients and laminar projections in mammals. Trends Neurosci. *41*, 775–788.

Goulas, A., Changeux, J.-P., Wagstyl, K., Amunts, K., Palomero-Gallagher, N., and Hilgetag, C.C. (2021). The natural axis of transmitter receptor distribution in the human cerebral cortex. Proc. Natl. Acad. Sci. U S A *118*, e2020574118.

Grasby, K.L., Jahanshad, N., Painter, J.N., Colodro-Conde, L., Bralten, J., Hibar, D.P., Lind, P.A., Pizzagalli, F., Ching, C.R.K., McMahon, M.A.B., et al.; Alzheimer's Disease Neuroimaging Initiative; CHARGE Consortium; EPIGEN Consortium; IMAGEN Consortium; SYS Consortium; Parkinson's Progression Markers Initiative; Enhancing NeuroImaging Genetics Through Meta-Analysis Consortium (ENIGMA)—Genetics Working Group (2020). The genetic architecture of the human cerebral cortex. Science *367*, eaay6690.

Gratton, C., Laumann, T.O., Nielsen, A.N., Greene, D.J., Gordon, E.M., Gilmore, A.W., Nelson, S.M., Coalson, R.S., Snyder, A.Z., Schlaggar, B.L., et al. (2018). Functional brain networks are dominated by stable group and individual factors, not cognitive or daily variation. Neuron *98*, 439–452.e5.

Graziano, M.S.A., and Aflalo, T.N. (2007). Rethinking cortical organization: moving away from discrete areas arranged in hierarchies. Neuroscientist *13*, 138–147.

Grydeland, H., Walhovd, K.B., Tamnes, C.K., Westlye, L.T., and Fjell, A.M. (2013). Intracortical myelin links with performance variability across the human lifespan: results from T1- and T2-weighted MRI myelin mapping and diffusion tensor imaging. J. Neurosci. *33*, 18618–18630.

Grydeland, H., Vértes, P.E., Váša, F., Romero-Garcia, R., Whitaker, K., Alexander-Bloch, A.F., Bjørnerud, A., Patel, A.X., Sederevičius, D., Tamnes, C.K., et al. (2019). Waves of maturation and senescence in micro-structural MRI markers of human cortical myelination over the lifespan. Cereb. Cortex *29*, 1369–1381.

Guell, X., Schmahmann, J.D., Gabrieli, J., and Ghosh, S.S. (2018). Functional gradients of the cerebellum. eLife *7*, e36652.

Haber, S.N. (2003). The primate basal ganglia: parallel and integrative networks. J. Chem. Neuroanat. *26*, 317–330.

Halley, A.C., and Krubitzer, L. (2019). Not all cortical expansions are the same: the coevolution of the neocortex and the dorsal thalamus in mammals. Curr. Opin. Neurobiol. *56*, 78–86.

Hansen, J.Y., Markello, R.D., Vogel, J.W., Seidlitz, J., Bzdok, D., and Misic, B. (2021). Mapping gene transcription and neurocognition across human neocortex. Nat. Hum. Behav. Published online March 25, 2021. https://doi.org/10.1038/s41562-021-01082-z.

Hensch, T.K. (2005). Critical period plasticity in local cortical circuits. Nat. Rev. Neurosci. *6*, 877–888.

Hermundstad, A.M., Bassett, D.S., Brown, K.S., Aminoff, E.M., Clewett, D., Freeman, S., Frithsen, A., Johnson, A., Tipper, C.M., Miller, M.B., et al. (2013). Structural foundations of resting-state and task-based functional connectivity in the human brain. Proc. Natl. Acad. Sci. U S A *110*, 6169–6174.

Herting, M.M., Maxwell, E.C., Irvine, C., and Nagel, B.J. (2012). The impact of sex, puberty, and hormones on white matter microstructure in adolescents. Cereb. Cortex *22*, 1979–1992.

Hilgetag, C.C., and Goulas, A. (2020). 'Hierarchy' in the organization of brain networks. Philos. Trans. R. Soc. Lond. B Biol. Sci. *375*, 20190319.

Hilgetag, C.C., Beul, S.F., van Albada, S.J., and Goulas, A. (2019). An architectonic type principle integrates macroscopic cortico-cortical connections with intrinsic cortical circuits of the primate brain. Netw. Neurosci. *3*, 905–923.

Hill, J., Inder, T., Neil, J., Dierker, D., Harwell, J., and Van Essen, D. (2010a). Similar patterns of cortical expansion during human development and evolution. Proc. Natl. Acad. Sci. U S A *107*, 13135–13140.

Hill, J., Dierker, D., Neil, J., Inder, T., Knutsen, A., Harwell, J., Coalson, T., and Van Essen, D. (2010b). A surface-based analysis of hemispheric asymmetries and folding of cerebral cortex in term-born human infants. J. Neurosci. *30*, 2268–2276.

Hinton, E.A., Li, D.C., Allen, A.G., and Gourley, S.L. (2019). Social isolation in adolescence disrupts cortical development and goal-dependent decision-making in adulthood, despite social reintegration. eNeuro *6*, ENEURO.0318-19.2019.

Hofer, E., Roshchupkin, G.V., Adams, H.H.H., Knol, M.J., Lin, H., Li, S., Zare, H., Ahmad, S., Armstrong, N.J., Satizabal, C.L., et al.; ENIGMA consortium (2020). Genetic correlations and genome-wide associations of cortical structure in general population samples of 22,824 adults. Nat. Commun. *11*, 4796.

Hoftman, G.D., Dienel, S.J., Bazmi, H.H., Zhang, Y., Chen, K., and Lewis, D.A. (2018). Altered gradients of glutamate and gamma-aminobutyric acid transcripts in the cortical visuospatial working memory network in schizophrenia. Biol. Psychiatry *83*, 670–679.

Holtmaat, A., Wilbrecht, L., Knott, G.W., Welker, E., and Svoboda, K. (2006). Experience-dependent and cell-type-specific spine growth in the neocortex. Nature *441*, 979–983.

Honey, C.J., Thesen, T., Donner, T.H., Silbert, L.J., Carlson, C.E., Devinsky, O., Doyle, W.K., Rubin, N., Heeger, D.J., and Hasson, U. (2012). Slow cortical dynamics and the accumulation of information over long timescales. Neuron *76*, 423–434.

Hubel, D.H., and Wiesel, T.N. (1970). The period of susceptibility to the physiological effects of unilateral eye closure in kittens. J. Physiol. *206*, 419–436.

Huber, E., Donnelly, P.M., Rokem, A., and Yeatman, J.D. (2018). Rapid and widespread white matter plasticity during an intensive reading intervention. Nat. Commun. *9*, 2260.

Huntenburg, J.M., Bazin, P.-L., Goulas, A., Tardif, C.L., Villringer, A., and Margulies, D.S. (2017). A systematic relationship between functional connectivity and intracortical myelin in the human cerebral cortex. Cereb. Cortex *27*, 981–997.

Huntenburg, J.M., Bazin, P.-L., and Margulies, D.S. (2018). Large-scale gradients in human cortical organization. Trends Cogn. Sci. *22*, 21–31.

Huntenburg, J.M., Yeow, L.Y., Mandino, F., and Grandjean, J. (2021). Gradients of functional connectivity in the mouse cortex reflect neocortical evolution. Neuroimage *225*, 117528.

Huth, A.G., de Heer, W.A., Griffiths, T.L., Theunissen, F.E., and Gallant, J.L. (2016). Natural speech reveals the semantic maps that tile human cerebral cortex. Nature *532*, 453–458.

Huttenlocher, P.R. (1979). Synaptic density in human frontal cortex—developmental changes and effects of aging. Brain Res. *163*, 195–205.

Ito, T., Hearne, L.J., and Cole, M.W. (2020). A cortical hierarchy of localized and distributed processes revealed via dissociation of task activations, connectivity changes, and intrinsic timescales. Neuroimage *221*, 117141.

Iuculano, T., Rosenberg-Lee, M., Richardson, J., Tenison, C., Fuchs, L., Supekar, K., and Menon, V. (2015). Cognitive tutoring induces widespread neuroplasticity and remediates brain function in children with mathematical learning disabilities. Nat. Commun. *6*, 8453.

Kaczkurkin, A.N., Park, S.S., Sotiras, A., Moore, T.M., Calkins, M.E., Cieslak, M., Rosen, A.F.G., Ciric, R., Xia, C.H., Cui, Z., et al. (2019). Evidence for dissociable linkage of dimensions of psychopathology to brain structure in youths. Am. J. Psychiatry *176*, 1000–1009.

Kamholz, J., Toffenetti, J., and Lazzarini, R.A. (1988). Organization and expression of the human myelin basic protein gene. J. Neurosci. Res. *21*, 62–70.

Kanjlia, S., Pant, R., and Bedny, M. (2019). Sensitive period for cognitive repurposing of human visual cortex. Cereb. Cortex *29*, 3993–4005.

Kaufmann, T., Alnæs, D., Doan, N.T., Brandt, C.L., Andreassen, O.A., and Westlye, L.T. (2017). Delayed stabilization and individualization in connectome development are related to psychiatric disorders. Nat. Neurosci. *20*, 513–515.

Kessler, R.C., Berglund, P., Demler, O., Jin, R., Merikangas, K.R., and Walters, E.E. (2005). Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch. Gen. Psychiatry *62*, 593–602.

Kochunov, P., Williamson, D.E., Lancaster, J., Fox, P., Cornell, J., Blangero, J., and Glahn, D.C. (2012). Fractional anisotropy of water diffusion in cerebral white matter across the lifespan. Neurobiol. Aging *33*, 9–20.

Kong, R., Li, J., Orban, C., Sabuncu, M.R., Liu, H., Schaefer, A., Sun, N., Zuo, X.-N., Holmes, A.J., Eickhoff, S.B., and Yeo, B.T.T. (2019). Spatial topography of individual-specific cortical networks predicts human cognition, personality, and emotion. Cereb. Cortex *29*, 2533–2551.

Koolschijn, P.C.M.P., Peper, J.S., and Crone, E.A. (2014). The influence of sex steroids on structural brain maturation in adolescence. PLoS ONE *9*, e83929.

Krienen, F.M., Yeo, B.T.T., Ge, T., Buckner, R.L., and Sherwood, C.C. (2016). Transcriptional profiles of supragranular-enriched genes associate with corticocortical network architecture in the human brain. Proc. Natl. Acad. Sci. U S A *113*, E469–E478.

Krubitzer, L. (2007). The magnificent compromise: cortical field evolution in mammals. Neuron *56*, 201–208.

Krubitzer, L., and Kahn, D.M. (2003). Nature versus nurture revisited: an old idea with a new twist. Prog. Neurobiol. *70*, 33–52.

Larivière, S., Vos de Wael, R., Hong, S.-J., Paquola, C., Tavakol, S., Lowe, A.J., Schrader, D.V., and Bernhardt, B.C. (2020). Multiscale structure-function gradients in the neonatal connectome. Cereb. Cortex *30*, 47–58.

Larsen, B., and Luna, B. (2018). Adolescence as a neurobiological critical period for the development of higher-order cognition. Neurosci. Biobehav. Rev. *94*, 179–195.

Larsen, B., Verstynen, T.D., Yeh, F.-C., and Luna, B. (2018). Developmental changes in the integration of affective and cognitive corticostriatal pathways are associated with reward-driven behavior. Cereb. Cortex *28*, 2834–2845.

Larsen, B., Cui, Z., Adebimpe, A., Pines, A.R., Alexander-Bloch, A., Bertolero, M., Calkins, M.E., Gur, R.E., Gur, R.C., Mahadevan, A.S., et al. (2021). A developmental reduction of the excitation:inhibition ratio in association cortex during adolescence. bioRxiv. https://doi.org/10.1101/2021.05.19.444703.

Lebel, C., and Beaulieu, C. (2011). Longitudinal development of human brain wiring continues from childhood into adulthood. J. Neurosci. *31*, 10937–10947.

Lee, S.J., Steiner, R.J., Yu, Y., Short, S.J., Neale, M.C., Styner, M.A., Zhu, H., and Gilmore, J.H. (2017). Common and heritable components of white matter microstructure predict cognitive function at 1 and 2 y. Proc. Natl. Acad. Sci. U S A *114*, 148–153.

Lenroot, R.K., Schmitt, J.E., Ordaz, S.J., Wallace, G.L., Neale, M.C., Lerch, J.P., Kendler, K.S., Evans, A.C., and Giedd, J.N. (2009). Differences in genetic and environmental influences on the human cerebral cortex associated with development during childhood and adolescence. Hum. Brain Mapp. *30*, 163–174.

Leonard, J.A., Romeo, R.R., Park, A.T., Takada, M.E., Robinson, S.T., Grotzinger, H., Last, B.S., Finn, A.S., Gabrieli, J.D.E., and Mackey, A.P. (2019). Associations between cortical thickness and reasoning differ by socioeconomic status in development. Dev. Cogn. Neurosci. *36*, 100641.

LeWinn, K.Z., Sheridan, M.A., Keyes, K.M., Hamilton, A., and McLaughlin, K.A. (2017). Sample composition alters associations between age and brain structure. Nat. Commun. *8*, 874.

Li, Y.-T., Ma, W.-P., Pan, C.-J., Zhang, L.I., and Tao, H.W. (2012). Broadening of cortical inhibition mediates developmental sharpening of orientation selectivity. J. Neurosci. *32*, 3981–3991.

Li, G., Nie, J., Wang, L., Shi, F., Lin, W., Gilmore, J.H., and Shen, D. (2013). Mapping region-specific longitudinal cortical surface expansion from birth to 2 years of age. Cereb. Cortex *23*, 2724–2733.

Li, G., Lin, W., Gilmore, J.H., and Shen, D. (2015). Spatial patterns, longitudinal development, and hemispheric asymmetries of cortical thickness in infants from birth to 2 years of age. J. Neurosci. *35*, 9150–9162.

Lim, L., Mi, D., Llorca, A., and Marín, O. (2018). Development and functional diversification of cortical interneurons. Neuron *100*, 294–313.

Liston, C., and Gan, W.-B. (2011). Glucocorticoids are critical regulators of dendritic spine development and plasticity in vivo. Proc. Natl. Acad. Sci. U S A *108*, 16074–16079.

Liston, C., Cichon, J.M., Jeanneteau, F., Jia, Z., Chao, M.V., and Gan, W.-B. (2013). Circadian glucocorticoid oscillations promote learning-dependent synapse formation and maintenance. Nat. Neurosci. *16*, 698–705.

Llera, A., Wolfers, T., Mulders, P., and Beckmann, C.F. (2019). Inter-individual differences in human brain structure and morphology link to variation in demographics and behavior. eLife *8*, e44443.

Lupien, S.J., McEwen, B.S., Gunnar, M.R., and Heim, C. (2009). Effects of stress throughout the lifespan on the brain, behaviour and cognition. Nat. Rev. Neurosci. *10*, 434–445.

Lyall, A.E., Shi, F., Geng, X., Woolson, S., Li, G., Wang, L., Hamer, R.M., Shen, D., and Gilmore, J.H. (2015). Dynamic development of regional cortical thickness and surface area in early childhood. Cereb. Cortex *25*, 2204–2212.

Mackey, A.P., Raizada, R.D.S., and Bunge, S.A. (2013). Environmental influences on prefrontal development. In Principles of Frontal Lobe Function, D.T. Stuss and R.T. Knight, eds. (Oxford University Press), pp. 145–163.

Margulies, D.S., Ghosh, S.S., Goulas, A., Falkiewicz, M., Huntenburg, J.M., Langs, G., Bezgin, G., Eickhoff, S.B., Castellanos, F.X., Petrides, M., et al. (2016). Situating the default-mode network along a principal gradient of macroscale cortical organization. Proc. Natl. Acad. Sci. U S A *113*, 12574–12579.

Markov, N.T., Vezoli, J., Chameau, P., Falchier, A., Quilodran, R., Huissoud, C., Lamy, C., Misery, P., Giroud, P., Ullman, S., et al. (2014). Anatomy of hierarchy: feedforward and feedback pathways in macaque visual cortex. J. Comp. Neurol. *522*, 225–259.

Mauney, S.A., Athanas, K.M., Pantazopoulos, H., Shaskan, N., Passeri, E., Berretta, S., and Woo, T.-U.W. (2013). Developmental pattern of perineuronal nets in the human prefrontal cortex and their deficit in schizophrenia. Biol. Psychiatry *74*, 427–435.

McGee, A.W., Yang, Y., Fischer, Q.S., Daw, N.W., and Strittmatter, S.M. (2005). Experience-driven plasticity of visual cortex limited by myelin and Nogo receptor. Science *309*, 2222–2226.

McLaughlin, K.A., Sheridan, M.A., Winter, W., Fox, N.A., Zeanah, C.H., and Nelson, C.A. (2014). Widespread reductions in cortical thickness following severe early-life deprivation: a neurodevelopmental pathway to ADHD. Biol. Psychiatry *76*, 629–638.

McTeague, L.M., Huemer, J., Carreon, D.M., Jiang, Y., Eickhoff, S.B., and Etkin, A. (2017). Identification of common neural circuit disruptions in cognitive control across psychiatric disorders. Am. J. Psychiatry *174*, 676–685.

Merikangas, K.R., He, J.P., Burstein, M., Swanson, S.A., Avenevoli, S., Cui, L., Benjet, C., Georgiades, K., and Swendsen, J. (2010). Lifetime prevalence of mental disorders in U.S. adolescents: results from the National Comorbidity Survey Replication–Adolescent Supplement (NCS-A). J. Am. Acad. Child Adolesc. Psychiatry *49*, 980–989.

Mesulam, M.M. (1998). From sensation to cognition. Brain *121*, 1013–1052.

Mesulam, M. (2008). Representation, inference, and transcendent encoding in neurocognitive networks of the human brain. Ann. Neurol. *64*, 367–378.

Michelini, G., Barch, D.M., Tian, Y., Watson, D., Klein, D.N., and Kotov, R. (2019). Delineating and validating higher-order dimensions of psychopathology in the Adolescent Brain Cognitive Development (ABCD) study. Transl. Psychiatry *9*, 261.

Miller, D.J., Duka, T., Stimpson, C.D., Schapiro, S.J., Baze, W.B., McArthur, M.J., Fobbs, A.J., Sousa, A.M.M., Šestan, N., Wildman, D.E., et al. (2012). Prolonged myelination in human neocortical evolution. Proc. Natl. Acad. Sci. U S A *109*, 16480–16485.

Modabbernia, A., Janiri, D., Doucet, G.E., Reichenberg, A., and Frangou, S. (2021). Multivariate patterns of brain-behavior-environment associations in the adolescent brain and cognitive development study. Biol. Psychiatry *89*, 510–520.

Moura, L.M., Kempton, M., Barker, G., Salum, G., Gadelha, A., Pan, P.M., Hoexter, M., Del Aquilla, M.A.G., Picon, F.A., Anés, M., et al. (2016). Age-effects in white matter using associated diffusion tensor imaging and magnetization transfer ratio during late childhood and early adolescence. Magn. Reson. Imaging *34*, 529–534.

Moura, L.M., Crossley, N.A., Zugman, A., Pan, P.M., Gadelha, A., Del Aquilla, M.A.G., Picon, F.A., Anés, M., Amaro, E., Jr., de Jesus Mari, J., et al. (2017). Coordinated brain development: exploring the synchrony between changes in grey and white matter during childhood maturation. Brain Imaging Behav. *11*, 808–817.

Mueller, S., Wang, D., Fox, M.D., Yeo, B.T.T., Sepulcre, J., Sabuncu, M.R., Shafee, R., Lu, J., and Liu, H. (2013). Individual variability in functional connectivity architecture of the human brain. Neuron *77*, 586–595.

Müller, E.J., Munn, B., Hearne, L.J., Smith, J.B., Fulcher, B., Arnatkevičiūtė, A., Lurie, D.J., Cocchi, L., and Shine, J.M. (2020). Core and matrix thalamic subpopulations relate to spatio-temporal cortical connectivity gradients. Neuroimage *222*, 117224.

Murphy, C., Jefferies, E., Rueschemeyer, S.-A., Sormaz, M., Wang, H.T., Margulies, D.S., and Smallwood, J. (2018). Distant from input: evidence of regions within the default mode network supporting perceptually-decoupled and conceptually-guided cognition. Neuroimage *171*, 393–401.

Murphy, C., Wang, H.-T., Konu, D., Lowndes, R., Margulies, D.S., Jefferies, E., and Smallwood, J. (2019). Modes of operation: a topographic neural gradient supporting stimulus dependent and independent cognition. Neuroimage *186*, 487–496.

Murray, J.D., Bernacchia, A., Freedman, D.J., Romo, R., Wallis, J.D., Cai, X., Padoa-Schioppa, C., Pasternak, T., Seo, H., Lee, D., and Wang, X.J. (2014). A hierarchy of intrinsic timescales across primate cortex. Nat. Neurosci. *17*, 1661–1663.

Natu, V.S., Gomez, J., Barnett, M., Jeska, B., Kirilina, E., Jaeger, C., Zhen, Z., Cox, S., Weiner, K.S., Weiskopf, N., and Grill-Spector, K. (2019). Apparent thinning of human visual cortex during childhood is associated with myelination. Proc. Natl. Acad. Sci. U S A *116*, 20750–20759.

Nenning, K.-H., Xu, T., Schwartz, E., Arroyo, J., Woehrer, A., Franco, A.R., Vogelstein, J.T., Margulies, D.S., Liu, H., Smallwood, J., et al. (2020). Joint embedding: a scalable alignment to compare individuals in a connectivity space. Neuroimage *222*, 117232.

Norbom, L.B., Doan, N.T., Alnæs, D., Kaufmann, T., Moberget, T., Rokicki, J., Andreassen, O.A., Westlye, L.T., and Tamnes, C.K. (2019). Probing brain developmental patterns of myelination and associations with psychopathology in youths using gray/white matter contrast. Biol. Psychiatry *85*, 389–398.

O'Leary, D.D.M., Chou, S.-J., and Sahara, S. (2007). Area patterning of the mammalian cortex. Neuron *56*, 252–269.

Oligschläger, S., Huntenburg, J.M., Golchert, J., Lauckner, M.E., Bonnen, T., and Margulies, D.S. (2017). Gradients of connectivity distance are anchored in primary cortex. Brain Struct. Funct. *222*, 2173–2182.

Paquola, C., Vos De Wael, R., Wagstyl, K., Bethlehem, R.A.I., Hong, S.-J., Seidlitz, J., Bullmore, E.T., Evans, A.C., Misic, B., Margulies, D.S., et al. (2019a). Microstructural and functional gradients are increasingly dissociated in transmodal cortices. PLoS Biol. *17*, e3000284.

Paquola, C., Bethlehem, R.A., Seidlitz, J., Wagstyl, K., Romero-Garcia, R., Whitaker, K.J., Vos de Wael, R., Williams, G.B., Vértes, P.E., Margulies, D.S., et al.; NSPN Consortium (2019b). Shifts in myeloarchitecture characterise adolescent development of cortical gradients. eLife *8*, e50482.

Paquola, C., Seidlitz, J., Benkarim, O., Royer, J., Klimes, P., Bethlehem, R.A.I., Larivière, S., Vos de Wael, R., Rodríguez-Cruces, R., Hall, J.A., et al. (2020a). A multi-scale cortical wiring space links cellular architecture and functional dynamics in the human brain. PLoS Biol. *18*, e3000979.

Paquola, C., Benkarim, O., DeKraker, J., Larivière, S., Frässle, S., Royer, J., Tavakol, S., Valk, S., Bernasconi, A., Bernasconi, N., et al. (2020b). Convergence of cortical types and functional motifs in the human mesiotemporal lobe. eLife *9*, e60673.

Park, B.Y., Bethlehem, R.A., Paquola, C., Larivière, S., Rodríguez-Cruces, R., Vos de Wael, R., Bullmore, E.T., and Bernhardt, B.C.; Neuroscience in Psychiatry Network (NSPN) Consortium (2021). An expanding manifold in transmodal regions characterizes adolescent reconfiguration of structural connectome organization. eLife *10*, e64694.

Pasternak, O., Kelly, S., Sydnor, V.J., and Shenton, M.E. (2018). Advances in microstructural diffusion neuroimaging for psychiatric disorders. Neuroimage *182*, 259–282.

Patel, Y., Shin, J., Drakesmith, M., Evans, J., Pausova, Z., and Paus, T. (2020). Virtual histology of multi-modal magnetic resonance imaging of cerebral cortex in young men. Neuroimage *218*, 116968.

Paus, T., Keshavan, M., and Giedd, J.N. (2008). Why do many psychiatric disorders emerge during adolescence? Nat. Rev. Neurosci. *9*, 947–957.

Petanjek, Z., Judaš, M., Šimic, G., Rašin, M.R., Uylings, H.B.M., Rakic, P., and Kostović, I. (2011). Extraordinary neoteny of synaptic spines in the human prefrontal cortex. Proc. Natl. Acad. Sci. U S A *108*, 13281–13286.

Piekarski, D.J., Boivin, J.R., and Wilbrecht, L. (2017). Ovarian hormones organize the maturation of inhibitory neurotransmission in the frontal cortex at puberty onset in female mice. Curr. Biol. *27*, 1735–1745.e3.

Pines, A.R., Cieslak, M., Larsen, B., Baum, G.L., Cook, P.A., Adebimpe, A., Dávila, D.G., Elliott, M.A., Jirsaraie, R., Murtha, K., et al. (2020). Leveraging multi-shell diffusion for studies of brain development in youth and young adulthood. Dev. Cogn. Neurosci. *43*, 100788.

Power, J.D., Cohen, A.L., Nelson, S.M., Wig, G.S., Barnes, K.A., Church, J.A., Vogel, A.C., Laumann, T.O., Miezin, F.M., Schlaggar, B.L., and Petersen, S.E. (2011). Functional network organization of the human brain. Neuron *72*, 665–678.

Preti, M.G., and Van De Ville, D. (2019). Decoupling of brain function from structure reveals regional behavioral specialization in humans. Nat. Commun. *10*, 4747.

Raut, R.V., Snyder, A.Z., and Raichle, M.E. (2020). Hierarchical dynamics as a macroscopic organizing principle of the human brain. Proc. Natl. Acad. Sci. U S A *117*, 20890–20897.

Raznahan, A., Shaw, P., Lalonde, F., Stockman, M., Wallace, G.L., Greenstein, D., Clasen, L., Gogtay, N., and Giedd, J.N. (2011). How does your cortex grow? J. Neurosci. *31*, 7174–7177.

Reardon, P.K., Seidlitz, J., Vandekar, S., Liu, S., Patel, R., Park, M.T.M., Alexander-Bloch, A., Clasen, L.S., Blumenthal, J.D., Lalonde, F.M., et al. (2018). Normative brain size variation and brain shape diversity in humans. Science *360*, 1222–1227.

Reh, R.K., Dias, B.G., Nelson, C.A., 3rd, Kaufer, D., Werker, J.F., Kolb, B., Levine, J.D., and Hensch, T.K. (2020). Critical period regulation across multiple timescales. Proc. Natl. Acad. Sci. U S A *117*, 23242–23251.

Reiss, F. (2013). Socioeconomic inequalities and mental health problems in children and adolescents: a systematic review. Soc. Sci. Med. *90*, 24–31.

Rigotti, M., Barak, O., Warden, M.R., Wang, X.-J., Daw, N.D., Miller, E.K., and Fusi, S. (2013). The importance of mixed selectivity in complex cognitive tasks. Nature *497*, 585–590.

Rimol, L.M., Panizzon, M.S., Fennema-Notestine, C., Eyler, L.T., Fischl, B., Franz, C.E., Hagler, D.J., Lyons, M.J., Neale, M.C., Pacheco, J., et al. (2010). Cortical thickness is influenced by regionally specific genetic factors. Biol. Psychiatry *67*, 493–499.

Robinson, K.E. (2004). Advances in School-Based Mental Health Interventions: Best Practices and Program Models (Civic Research Institute, Inc.).

Romer, A.L., Elliott, M.L., Knodt, A.R., Sison, M.L., Ireland, D., Houts, R., Ramrakha, S., Poulton, R., Keenan, R., Melzer, T.R., et al. (2021). Pervasively thinner neocortex as a transdiagnostic feature of general psychopathology. Am. J. Psychiatry *178*, 174–182.

Rosen, M.L., Amso, D., and McLaughlin, K.A. (2019). The role of the visual association cortex in scaffolding prefrontal cortex development: a novel mechanism linking socioeconomic status and executive function. Dev. Cogn. Neurosci. *39*, 100699.

Sadagopan, S., and Wang, X. (2010). Contribution of inhibition to stimulus selectivity in primary auditory cortex of awake primates. J. Neurosci. *30*, 7314–7325.

Sanides, F. (1962). Die Architektonik des Menschlichen Stirnhirns: Zugleich eine Darstellung der Prinzipien Seiner Gestaltung als Spiegel der Stammesgeschichtlichen Differenzierung der Grosshirnrinde (Springer-Verlag).

Satterthwaite, T.D., Wolf, D.H., Ruparel, K., Erus, G., Elliott, M.A., Eickhoff, S.B., Gennatas, E.D., Jackson, C., Prabhakaran, K., Smith, A., et al. (2013). Heterogeneous impact of motion on fundamental patterns of developmental changes in functional connectivity during youth. Neuroimage *83*, 45–57.

Satterthwaite, T.D., Shinohara, R.T., Wolf, D.H., Hopson, R.D., Elliott, M.A., Vandekar, S.N., Ruparel, K., Calkins, M.E., Roalf, D.R., Gennatas, E.D., et al. (2014). Impact of puberty on the evolution of cerebral perfusion during adolescence. Proc. Natl. Acad. Sci. U S A *111*, 8643–8648.

Schmitt, J.E., Neale, M.C., Fassassi, B., Perez, J., Lenroot, R.K., Wells, E.M., and Giedd, J.N. (2014). The dynamic role of genetics on cortical patterning during childhood and adolescence. Proc. Natl. Acad. Sci. U S A *111*, 6774–6779.

Schmitt, J.E., Raznahan, A., Liu, S., and Neale, M.C. (2020). The genetics of cortical myelination in young adults and its relationships to cerebral surface area, cortical thickness, and intelligence: A magnetic resonance imaging study of twins and families. Neuroimage *206*, 116319.

Scholtens, L.H., Schmidt, R., de Reus, M.A., and van den Heuvel, M.P. (2014). Linking macroscale graph analytical organization to microscale neuroarchitectonics in the macaque connectome. J. Neurosci. *34*, 12192–12205.

Seidlitz, J., Nadig, A., Liu, S., Bethlehem, R.A.I., Vértes, P.E., Morgan, S.E., Váša, F., Romero-Garcia, R., Lalonde, F.M., Clasen, L.S., et al. (2020). Transcriptomic and cellular decoding of regional brain vulnerability to neurogenetic disorders. Nat. Commun. *11*, 3358.

Sepulcre, J., Liu, H., Talukdar, T., Martincorena, I., Yeo, B.T.T., and Buckner, R.L. (2010). The organization of local and distant functional connectivity in the human brain. PLoS Comput. Biol. *6*, e1000808.

Shafee, R., Buckner, R.L., and Fischl, B. (2015). Gray matter myelination of 1555 human brains using partial volume corrected MRI images. Neuroimage *105*, 473–485.

Shanmugan, S., Wolf, D.H., Calkins, M.E., Moore, T.M., Ruparel, K., Hopson, R.D., Vandekar, S.N., Roalf, D.R., Elliott, M.A., Jackson, C., et al. (2016). Common and dissociable mechanisms of executive system dysfunction across psychiatric disorders in youth. Am. J. Psychiatry *173*, 517–526.

Shaw, P., Kabani, N.J., Lerch, J.P., Eckstrand, K., Lenroot, R., Gogtay, N., Greenstein, D., Clasen, L., Evans, A., Rapoport, J.L., et al. (2008). Neurodevelopmental trajectories of the human cerebral cortex. J. Neurosci. *28*, 3586–3594.

Sheth, C., McGlade, E., and Yurgelun-Todd, D. (2017). Chronic stress in adolescents and its neurobiological and psychopathological consequences: an RDoC perspective. Chronic Stress (Thousand Oaks) *1*, 2470547017715645.

Shibata, M., Pattabiraman, K., Lorente-Galdos, B., Andrijevic, D., Xing, X., Sousa, A.M.M., Santpere, G., and Sestan, N. (2019). Regulation of prefrontal patterning, connectivity and synaptogenesis by retinoic acid. bioRxiv. https://doi.org/10.1101/2019.12.31.891036.

Silveri, M.M., Sneider, J.T., Crowley, D.J., Covell, M.J., Acharya, D., Rosso, I.M., and Jensen, J.E. (2013). Frontal lobe γ-aminobutyric acid levels during adolescence: associations with impulsivity and response inhibition. Biol. Psychiatry *74*, 296–304.

Simmonds, D.J., Hallquist, M.N., Asato, M., and Luna, B. (2014). Developmental stages and sex differences of white matter and behavioral development through adolescence: a longitudinal diffusion tensor imaging (DTI) study. Neuroimage *92*, 356–368.

Simons, D.J., and Land, P.W. (1987). Early experience of tactile stimulation influences organization of somatic sensory cortex. Nature *326*, 694–697.

Slater, D.A., Melie-Garcia, L., Preisig, M., Kherif, F., Lutti, A., and Draganski, B. (2019). Evolution of white matter tract microstructure across the life span. Hum. Brain Mapp. *40*, 2252–2268.

Smith, C.C., and McMahon, L.L. (2006). Estradiol-induced increase in the magnitude of long-term potentiation is prevented by blocking NR2B-containing receptors. J. Neurosci. *26*, 8517–8522.

Smith, S.M., Fox, P.T., Miller, K.L., Glahn, D.C., Fox, P.M., Mackay, C.E., Filippini, N., Watkins, K.E., Toro, R., Laird, A.R., and Beckmann, C.F. (2009). Correspondence of the brain's functional architecture during activation and rest. Proc. Natl. Acad. Sci. U S A *106*, 13040–13045.

Smith, S.M., Nichols, T.E., Vidaurre, D., Winkler, A.M., Behrens, T.E.J., Glasser, M.F., Ugurbil, K., Barch, D.M., Van Essen, D.C., and Miller, K.L. (2015). A positive-negative mode of population covariation links brain connectivity, demographics and behavior. Nat. Neurosci. *18*, 1565–1567.

Sotiras, A., Toledo, J.B., Gur, R.E., Gur, R.C., Satterthwaite, T.D., and Davatzikos, C. (2017). Patterns of coordinated cortical remodeling during adolescence and their associations with functional specialization and evolutionary expansion. Proc. Natl. Acad. Sci. U S A *114*, 3527–3532.

Sowell, E.R., Thompson, P.M., Leonard, C.M., Welcome, S.E., Kan, E., and Toga, A.W. (2004). Longitudinal mapping of cortical thickness and brain growth in normal children. J. Neurosci. *24*, 8223–8231.

Stoecklein, S., Hilgendorff, A., Li, M., Förster, K., Flemmer, A.W., Galiè, F., Wunderlich, S., Wang, D., Stein, S., Ehrhardt, H., et al. (2020). Variable functional connectivity architecture of the preterm human brain: Impact of developmental cortical expansion and maturation. Proc. Natl. Acad. Sci. U S A *117*, 1201–1206.

Takesian, A.E., and Hensch, T.K. (2013). Balancing plasticity/stability across brain development. In Progress in Brain Research, M.M. Merzenich, M. Nahum, and T.M. Van Vleet, eds. (Elsevier), pp. 3–34.

Tamnes, C.K., Roalf, D.R., Goddings, A.-L., and Lebel, C. (2018). Diffusion MRI of white matter microstructure development in childhood and adolescence: methods, challenges and progress. Dev. Cogn. Neurosci. *33*, 161–175.

Tang, E., Mattar, M.G., Giusti, C., Lydon-Staley, D.M., Thompson-Schill, S.L., and Bassett, D.S. (2019). Effective learning is accompanied by high-dimensional and efficient representations of neural activity. Nat. Neurosci. *22*, 1000–1009.

Teeuw, J., Brouwer, R.M., Koenis, M.M.G., Swagerman, S.C., Boomsma, D.I., and Hulshoff Pol, H.E. (2019). Genetic influences on the development of cerebral cortical thickness during childhood and adolescence in a Dutch longitudinal twin sample: the Brainscale study. Cereb. Cortex *29*, 978–993.

Tooley, U.A., Mackey, A.P., Ciric, R., Ruparel, K., Moore, T.M., Gur, R.C., Gur, R.E., Satterthwaite, T.D., and Bassett, D.S. (2020). Associations between neighborhood SES and functional brain network development. Cereb. Cortex *30*, 1–19.

Tournier, J.-D., Calamante, F., and Connelly, A. (2007). Robust determination of the fibre orientation distribution in diffusion MRI: non-negativity constrained super-resolved spherical deconvolution. Neuroimage *35*, 1459–1472.

Toyoizumi, T., Miyamoto, H., Yazaki-Sugiyama, Y., Atapour, N., Hensch, T.K., and Miller, K.D. (2013). A theory of the transition to critical period plasticity: inhibition selectively suppresses spontaneous activity. Neuron *80*, 51–63.

Ullsperger, J.M., and Nikolas, M.A. (2017). A meta-analytic review of the association between pubertal timing and psychopathology in adolescence: are there sex differences in risk? Psychol. Bull. *143*, 903–938.

Vainik, U., Paquola, C., Wang, X., Zheng, Y., Bernhardt, B., Misic, B., and Dagher, A. (2020). Heritability of cortical morphology reflects a sensory-fugal plasticity gradient. bioRxiv. https://doi.org/10.1101/2020.11.03.366419.

Vaishnavi, S.N., Vlassenko, A.G., Rundle, M.M., Snyder, A.Z., Mintun, M.A., and Raichle, M.E. (2010). Regional aerobic glycolysis in the human brain. Proc. Natl. Acad. Sci. U S A *107*, 17757–17762.

Valk, S.L., Xu, T., Margulies, D.S., Masouleh, S.K., Paquola, C., Goulas, A., Kochunov, P., Smallwood, J., Yeo, B.T.T., Bernhardt, B.C., and Eickhoff, S.B. (2020). Shaping brain structure: genetic and phylogenetic axes of macroscale organization of cortical thickness. Sci. Adv. *6*, eabb3417.

van den Heuvel, M.P., Scholtens, L.H., de Reus, M.A., and Kahn, R.S. (2016a). Associated microscale spine density and macroscale connectivity disruptions in schizophrenia. Biol. Psychiatry *80*, 293–301.

van den Heuvel, M.P., Scholtens, L.H., Turk, E., Mantini, D., Vanduffel, W., and Feldman Barrett, L. (2016b). Multimodal analysis of cortical chemoarchitecture and macroscale fMRI resting-state functional connectivity. Hum. Brain Mapp. *37*, 3103–3113.

Vandekar, S.N., Shinohara, R.T., Raznahan, A., Roalf, D.R., Ross, M., DeLeo, N., Ruparel, K., Verma, R., Wolf, D.H., Gur, R.C., et al. (2015). Topologically dissociable patterns of development of the human cerebral cortex. J. Neurosci. *35*, 599–609.

Vanes, L.D., Moutoussis, M., Ziegler, G., Goodyer, I.M., Fonagy, P., Jones, P.B., Bullmore, E.T., and Dolan, R.J.; NSPN Consortium (2020). White matter tract myelin maturation and its association with general psychopathology in adolescence and early adulthood. Hum. Brain Mapp. *41*, 827–839.

Váša, F., Seidlitz, J., Romero-Garcia, R., Whitaker, K.J., Rosenthal, G., Vértes, P.E., Shinn, M., Alexander-Bloch, A., Fonagy, P., Dolan, R.J., et al.; NSPN consortium (2018). Adolescent tuning of association cortex in human structural brain networks. Cereb. Cortex *28*, 281–294.

Váša, F., Romero-Garcia, R., Kitzbichler, M.G., Seidlitz, J., Whitaker, K.J., Vaghi, M.M., Kundu, P., Patel, A.X., Fonagy, P., Dolan, R.J., et al.; NSPN Consortium (2020). Conservative and disruptive modes of adolescent change in human brain functional connectivity. Proc. Natl. Acad. Sci. U S A *117*, 3248–3253.

Vijayakumar, N., Youssef, G.J., Allen, N.B., Anderson, V., Efron, D., Hazell, P., Mundy, L., Nicholson, J.M., Patton, G., Seal, M.L., et al. (2021). A longitudinal analysis of puberty-related cortical development. Neuroimage *228*, 117684.

Wagstyl, K., Ronan, L., Goodyer, I.M., and Fletcher, P.C. (2015). Cortical thickness gradients in structural hierarchies. Neuroimage *111*, 241–250.

Wagstyl, K., Larocque, S., Cucurull, G., Lepage, C., Cohen, J.P., Bludau, S., Palomero-Gallagher, N., Lewis, L.B., Funck, T., Spitzer, H., et al. (2020). BigBrain 3D atlas of cortical layers: Cortical and laminar thickness gradients diverge in sensory and motor cortices. PLoS Biol. *18*, e3000678.

Wang, X.-J. (2020). Macroscopic gradients of synaptic excitation and inhibition in the neocortex. Nat. Rev. Neurosci. *21*, 169–178.

Wang, H., Stradtman, G.G., 3rd, Wang, X.-J., and Gao, W.-J. (2008). A specialized NMDA receptor function in layer 5 recurrent microcircuitry of the adult rat prefrontal cortex. Proc. Natl. Acad. Sci. U S A *105*, 16791–16796.

Wang, F., Lian, C., Wu, Z., Zhang, H., Li, T., Meng, Y., Wang, L., Lin, W., Shen, D., and Li, G. (2019). Developmental topography of cortical thickness during infancy. Proc. Natl. Acad. Sci. U S A *116*, 15855–15860.

Wei, Y., de Lange, S.C., Scholtens, L.H., Watanabe, K., Ardesch, D.J., Jansen, P.R., Savage, J.E., Li, L., Preuss, T.M., Rilling, J.K., et al. (2019). Genetic mapping and evolutionary analysis of human-expanded cognitive networks. Nat. Commun. *10*, 4839.

Westlye, L.T., Walhovd, K.B., Dale, A.M., Bjørnerud, A., Due-Tønnessen, P., Engvig, A., Grydeland, H., Tamnes, C.K., Østby, Y., and Fjell, A.M. (2010). Life-span changes of the human brain white matter: diffusion tensor imaging (DTI) and volumetry. Cereb. Cortex *20*, 2055–2068.

Whitaker, K.J., Vértes, P.E., Romero-Garcia, R., Váša, F., Moutoussis, M., Prabhu, G., Weiskopf, N., Callaghan, M.F., Wagstyl, K., Rittman, T., et al.; NSPN Consortium (2016). Adolescence is associated with genomically patterned consolidation of the hubs of the human brain connectome. Proc. Natl. Acad. Sci. U S A *113*, 9105–9110.

Wierenga, L.M., Langen, M., Oranje, B., and Durston, S. (2014). Unique developmental trajectories of cortical thickness and surface area. Neuroimage *87*, 120–126.

Wierenga, L.M., van den Heuvel, M.P., Oranje, B., Giedd, J.N., Durston, S., Peper, J.S., Brown, T.T., and Crone, E.A.; The Pediatric Longitudinal Imaging, Neurocognition, and Genetics Study (2018). A multisample study of longitudinal changes in brain network architecture in 4-13-year-old children. Hum. Brain Mapp. *39*, 157–170.

Xia, C.H., Ma, Z., Ciric, R., Gu, S., Betzel, R.F., Kaczkurkin, A.N., Calkins, M.E., Cook, P.A., García de la Garza, A., Vandekar, S.N., et al. (2018). Linked dimensions of psychopathology and connectivity in functional brain networks. Nat. Commun. *9*, 3003.

Xu, T., Sturgeon, D., Ramirez, J.S.B., Froudist-Walsh, S., Margulies, D.S., Schroeder, C.E., Fair, D.A., and Milham, M.P. (2019). Interindividual variability of functional connectivity in awake and anesthetized rhesus macaque monkeys. Biol. Psychiatry Cogn. Neurosci. Neuroimaging *4*, 543–553.

Xu, T., Nenning, K.-H., Schwartz, E., Hong, S.-J., Vogelstein, J.T., Goulas, A., Fair, D.A., Schroeder, C.E., Margulies, D.S., Smallwood, J., et al. (2020). Cross-species functional alignment reveals evolutionary hierarchy within the connectome. Neuroimage *223*, 117346.

Yakovlev, P., and Lecours, A. (1967). The myelogenetic cycles of regional maturation of the brain. In Regional Development of the Brain in Early Life, A. Minkowski, ed. (Blackwell), pp. 3–70.

Yang, S., Meng, Y., Li, J., Li, B., Fan, Y.-S., Chen, H., and Liao, W. (2020). The thalamic functional gradient and its relationship to structural basis and cognitive relevance. Neuroimage *218*, 116960.

Yarkoni, T., Poldrack, R.A., Nichols, T.E., Van Essen, D.C., and Wager, T.D. (2011). Large-scale automated synthesis of human functional neuroimaging data. Nat. Methods *8*, 665–670.

Yeatman, J.D., Wandell, B.A., and Mezer, A.A. (2014). Lifespan maturation and degeneration of human brain white matter. Nat. Commun. *5*, 4932.

Yeo, B.T.T., Krienen, F.M., Sepulcre, J., Sabuncu, M.R., Lashkari, D., Hollinshead, M., Roffman, J.L., Smoller, J.W., Zöllei, L., Polimeni, J.R., et al. (2011). The organization of the human cerebral cortex estimated by intrinsic functional connectivity. J. Neurophysiol. *106*, 1125–1165.

Yeo, B.T.T., Krienen, F.M., Eickhoff, S.B., Yaakub, S.N., Fox, P.T., Buckner, R.L., Asplund, C.L., and Chee, M.W.L. (2015). Functional specialization and flexibility in human association cortex. Cereb. Cortex *25*, 3654–3672.

Yizhar, O., Fenno, L.E., Prigge, M., Schneider, F., Davidson, T.J., O'Shea, D.J., Sohal, V.S., Goshen, I., Finkelstein, J., Paz, J.T., et al. (2011). Neocortical excitation/inhibition balance in information processing and social dysfunction. Nature *477*, 171–178.

Zenner, C., Herrnleben-Kurz, S., and Walach, H. (2014). Mindfulness-based interventions in schools-a systematic review and meta-analysis. Front. Psychol. *5*, 603.

Zhang, Z., Jiao, Y.-Y., and Sun, Q.-Q. (2011). Developmental maturation of excitation and inhibition balance in principal neurons across four layers of somatosensory cortex. Neuroscience *174*, 10–25.

Zhang, H., Schneider, T., Wheeler-Kingshott, C.A., and Alexander, D.C. (2012). NODDI: practical in vivo neurite orientation dispersion and density imaging of the human brain. Neuroimage *61*, 1000–1016.

Zhou, D., Lebel, C., Treit, S., Evans, A., and Beaulieu, C. (2015). Accelerated longitudinal cortical thinning in adolescence. Neuroimage *104*, 138–145.

Ziegler, G., Hauser, T.U., Moutoussis, M., Bullmore, E.T., Goodyer, I.M., Fonagy, P., Jones, P.B., Lindenberger, U., and Dolan, R.J.; NSPN Consortium (2019). Compulsivity and impulsivity traits linked to attenuated developmental frontostriatal myelination trajectories. Nat. Neurosci. *22*, 992–999.

Zielinski, B.A., Prigge, M.B.D., Nielsen, J.A., Froehlich, A.L., Abildskov, T.J., Anderson, J.S., Fletcher, P.T., Zygmunt, K.M., Travers, B.G., Lange, N., et al. (2014). Longitudinal changes in cortical thickness in autism and typical development. Brain *137*, 1799–1812.