CHARTING NEURODEVELOPMENT ALONG A SENSORIMOTOR-ASSOCIATION CORTICAL AXIS: PATTERNS OF PLASTICITY, ENVIRONMENTAL SUSCEPTIBILITY, AND PSYCHIATRIC VULNERABILITY

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ABSTRACT

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Human cortical development is protracted, heterochronous, sculpted by the environment, and associated with the emergence of diverse psychiatric conditions. Elucidating how developmental plasticity asynchronously progresses across the cortex is vital for understanding which cortical regions will be impacted by positive and negative environments and psychiatric insults and interventions at distinct developmental stages. Prior research has provided consistent evidence that cortical maturation occurs earlier in sensory and motor cortices and later in association cortices. However, beyond this coarse division in developmental timing between these two domains of cortex, there is marked variability in cortical development that remains undercharacterized—and therefore unaccounted for by contemporary accounts of human brain development. This thesis seeks to put forth a model of child and adolescent cortical maturation that accounts for our species' rich spatiotemporal developmental variability and psychiatric vulnerability. It first reviews existing knowledge concerning human brain development and brain organization and hypothesizes that maturation unfolds along an evolutionarily-rooted, hierarchical, and graded sensorimotor-to-associative axis of cortical organization. It discusses how the unfolding of development along this axis endows transmodal association cortices with both unique neurobiological properties and heightened inter-individual developmental variability and vulnerability. The thesis next leverages a proposed functional signature of plasticity illuminated by animal models to empirically evaluate the hypothesized developmental model. It provides evidence that human cortical development indeed progresses along a sensorimotor-association axis from ages 8 to 18 years and demonstrates how

environmental influences on the maturating brain are shaped by this developmental program. Finally, the thesis explores neural correlates of diminished reward responsiveness, a psychiatric risk factor, in a transdiagnostic sample of adolescents and young adults. It shows that this risk factor is dimensionally and selectively associated with lower levels of glutamate within transmodal association cortices and subcortical areas that comprise the brain's reward network. Together, the work presented here may help to inform environmental and psychiatric interventions for youth that incorporate basic principles of developmental plasticity and are delivered while the brain is undergoing demarcated periods of malleability.

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CHAPTER 1: INTRODUCTION

The human cerebral cortex undergoes a uniquely protracted course of neurodevelopment that extends into the third decade of life. This prolonged developmental program is critical for shaping many of the neurobiological and functional properties that allow the human brain to support advanced cognitive, social, and emotional processes. However, prolonged development also increases the time frame during which the cortex is malleable, and therefore the time frame during which it is vulnerable to developmental and environmental insults. The protracted nature of human cortical development thus puts our species at risk for developmental psychopathology, with many psychiatric disorders first manifesting during the adolescent period. Understanding which regions of the brain are most plastic during adolescence as well as the biological mechanisms giving rise to this plasticity can therefore provide insight into where and how the brain is developing during the primary window of psychiatric symptom emergence. This thesis explores two overarching and interrelated hypotheses concerning the patterning of developmental plasticity and youth risk. The first hypothesis proposes that transmodal association cortices exhibit heightened malleability during the adolescent period due to the sequential maturation of plasticity-regulating events along a sensorimotor-association axis of cortical organization. The second posits that differences in the unfolding of association cortex plasticity in youth from disadvantaged environments increases the risk for adolescent-onset psychiatric conditions.

The introduction of this thesis begins by describing the human brain's association cortices in terms of their anatomical location, functions, phylogenetic expansion, and distinguishing features. It puts forth evidence that there is an evolutionarily-rooted, dominant axis of cortical feature variability that spans between transmodal association cortices and primary sensory and motor cortices; furthermore, it explains how this axis of feature heterogeneity may emerge from developmental heterochronicity. The introduction next synthesizes the current knowledge on human developmental heterochronicity—which is maximal between sensorimotor and association cortices—while emphasizing limitations in the field's understanding of developmental variability. It discusses the need for a comprehensive model of the progression of developmental plasticity and proposes that such a model could be tested by translating biological insights from animal studies of plasticity to human neuroimaging. Last, the introduction explores how a socioeconomic gradient of environmental deprivation to enrichment may account for individual variation in the capacity for, or protractedness of, association cortex developmental plasticity. Reductions in association cortex plasticity may contribute to the emergence of deficits in executive functioning and reward responsiveness during adolescence, increasing the risk for diverse forms of youth-onset psychiatric symptomatology.

Human association cortices: functions, phylogeny, and features

The brain's association cortices, composed of prefrontal, cingulate, inferior parietal, precuneus, and middle temporal regions, occupy expansive areas of the human cerebral cortex. While functionally heterogeneous, the association cortices collectively subserve human-elaborated psychological functions such as long-term planning, flexible decision making, social learning, reward processing, mentalizing, and imagination. The association cortices are thereby understood to be multi- or trans-modal, functionally flexible, and recruited for information integration, perceptually decoupled cognition, socioemotional processing, and internal thought (Margulies et al., 2016; Mesulam, 1998; Murphy et al., 2018; Yeo et al., 2015). Given the functions they subserve, the association cortices are also thought to account for humans' unique vulnerability to psychiatric symptomatology.

The association cortices can be principally contrasted against the brain's primary sensory and motor cortices, including visual, auditory, somatosensory, and motor cortices, which are unimodal, functionally specific, and involved in segregated perceptual processing and stimulus-dependent cognition. The capacity for the human brain to support advanced or "higher-order" executive, emotional, and social functions is predominantly attributed to the phylogenetic expansion of the association cortices—which far outpaced the expansion of sensory cortex during primate evolution (Hill et al., 2010; Krubitzer, 2007; Xu et al., 2020). Lower-order sensory and motor cortical regions were present and cortically dominant even in the earliest of mammals. In many ensuing mammalian species, sensory brain regions underwent additional functional specialization, accompanied by sensory cortex expansion or cortical magnification (e.g., expansion of S1 in platypuses; expansion of A1 in bats) (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 newer association cortices subserving higher-order functions grew significantly larger (Halley and Krubitzer, 2019; Krubitzer, 2007). 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 (Donahue et al., 2018; Hill et al., 2010; Wei et al., 2019; Xu et al., 2020). As a result, humans have diverged from both the evolutionarily-older common mammalian ancestor and evolutionarily-newer primate species through extensive cortical magnification of the association cortices.

The regions of the association cortex that underwent the most marked cortical expansion in humans are transmodal regions that occupy territories most distant on the cortical mantle from primary regions, and that are thus spatially untethered from idiotypic sensory and motor cortices. As a result of this spatial untethering, human association cortices have diverged from primary cortices in terms of their neural circuitry and neurobiological properties; this divergence enabled the emergence of unique association cortex capacities. Transmodal association cortices, for example, exhibit more long-distant and spatially distributed functional and structural connections than primary cortices (Goldman-Rakic, 1988; Krienen and Buckner, 2020; Oligschläger et al., 2017; Sepulcre et al., 2010), allowing them to communicate with more functionally diverse cortical areas. Transmodal association cortices have larger pyramidal neurons with a greater number of dendrites, spines, and synapses than primary cortices (Beul and Hilgetag, 2019; Elston, 2003, 2000); this ensures that pyramidal neurons in association cortex make more connections, enabling an enhanced functional range and higher-dimensional neural activity (Rigotti et al., 2013). Transmodal association cortices also have a higher ratio of excitatory-to-inhibitory neurotransmitter receptors (Goulas et al., 2021) and excitatory receptors with slower dynamics (Wang, 2020), facilitating greater recurrent excitation (Wang, 2020), longer timescales of excitatory neural activity (Gao et al., 2020; Murray et al., 2014; Raut et al., 2020), and temporally prolonged information accumulation and integration (Hasson et al., 2015, 2008; Honey et al., 2012; Lerner et al., 2011). Finally, compared to primary cortices, transmodal association cortices have lower levels of intracortical myelination (Glasser and Van Essen, 2011; John et al., 2022), a lower expression of parvalbumin interneurons (Anderson et al., 2020), and higher rates of glucose metabolism (Goyal et al., 2014; Luppi et al., 2022; Vaishnavi et al., 2010), which collectively suggest that these regions may be endowed with a greater capacity for ongoing circuit plasticity (Bufill et al., 2011; García-Cabezas et al., 2017). Hence, as association cortices expanded in evolution, they additionally acquired a set of modified features that cooperatively allowed them to subserve a qualitatively different set of psychological functions and behaviors. As association cortices expanded in evolution, they became not only spatially but also functionally untethered from sensory and motor cortices.

A unifying axis of cortical feature variability grounded in developmental variability

Dissimilarities in cortical properties between sensorimotor regions and higher-order association regions do not represent a simple dichotomy nor present as a sharp division on the cerebral cortex. Rather, there are graded axes of cortical feature variation that span continuously between primary sensory and motor cortices and the most cortically-distant, evolutionarily-expanded, and human-elaborated transmodal association cortices. Comparing axes of feature variation across remarkably diverse data types has revealed that many independently derived axes exhibit convergent spatial embedding in the cortex, pointing to the existence of a unifying motif of cortical organization.

An axis is a unidimensional ordering of all cortical regions that is 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, revealing large-scale organizational trends. Delineating axes of organization complements early efforts by Friedrich Sanides and Elkhonon Goldberg to delineate gradients of architectonic differentiation (Sanides, 1962) and functional organization (Elkhonon Goldberg, 1989). Critically, more recent efforts to delineate axes of feature variation have revealed that the principal axis of variation is commonly anchored by primary cortices at one end and transmodal cortices at the other, with unimodal and multimodal cortices involved in sensory integration, language, attention, and retention occupying the middle. There is thus a dominant spatial axis of large-scale feature organization that captures systematic and concerted shifts in many properties across the human cortex.

Properties that vary along a unifying axis anchored by primary and transmodal poles (but exhibiting structured variation between these poles) include cortico-cortical connectivity features as indexed by connectivity distance (Oligschläger et al., 2017; Sepulcre et al., 2010), layer originations (Burt et al., 2018), and functional connectivity profiles (Margulies et al., 2016) as well as structural features such as laminar architecture (Hilgetag et al., 2019), neuron density (Beul and Hilgetag, 2019) and intracortical myelin density (Glasser and Van Essen, 2011; Paquola et al., 2019b). Metabolic indicators such as cerebral blood flow (Satterthwaite et al., 2014) and aerobic glycolysis (Vaishnavi et al., 2010) also show natural differentiation along a primary-transmodal axis. This axis furthermore manifests when examining electrophysiological (Murray et al., 2014; Raut et al., 2020) and neurotransmitter receptor (Goulas et al., 2021) differences across the cortex. The concerted patterning of multifaceted features along a unifying spatial axis suggests that they may have cooperatively emerged in evolution as the cerebral cortex expanded out from primary cortical regions. Furthermore, it is likely that these spatially covarying features are sculpted through joint neurodevelopment as developmental processes are carried out along an expanding cortical mantle.

Indeed, comparative anatomy studies have shown that species with smaller brains and fast, synchronous cortical maturation exhibit minimal feature variation across the cortical sheet. As cortices expand and overall developmental schedules lengthen (Workman et al., 2013), differences in both the timing of development and regional characteristics emerge across the cortex (Charvet and Finlay, 2014), producing new phenotypic outcomes. In macaques, for example, the length of neurogenesis varies along a rostral-caudal cortical axis, with caudal regions undergoing more prolonged neurogenesis. As a direct result, there is a rostral-caudal gradient of cortical microstructure, with caudal regions containing both higher neuron density and neurons with smaller dendritic arbors and shorter processes (Cahalane et al., 2012). These observations suggest that the relationship between evolutionary cortical expansion and cortical feature heterogeneity may be strongly driven by neurodevelopmental heterochronicity (Suárez and Halley, 2022). More specifically, these observations link spatial feature variability and temporal neurodevelopmental variability and suggest that differences in cortical properties between primary and transmodal association cortices may arise due to differences in their developmental timescales.

Characterizing spatial and temporal variability in cortical development and plasticity

Humans undergo a uniquely protracted period of postnatal cortical development, experiencing neoteny (the retention of juvenile characteristics) for longer than other primate species (Bufill et al., 2011). The slow progression of human brain maturation does not unfold uniformly across the cortex; development is temporally heterogeneous. Extensive research harnessing *in vivo* neuroimaging in humans has shown that large-scale developmental changes occur earlier in sensory and motor cortices and later in association cortices. This temporal developmental trend has been shown for reductions in cortical volume

(Bethlehem et al., 2022; Gogtay et al., 2004) and thickness (Vandekar et al., 2015), changes in cortical microstructure (Paquola et al., 2019a), refinement of cortical functional connectivity (Dong et al., 2021), and reductions in cerebral blood flow (Satterthwaite et al., 2014). Accordingly, convergent findings reveal that association cortices mature later than the rest of the cortex, furthermore suggesting that they are developmentally plastic for longer (Larsen and Luna, 2018).

Delayed maturation and prolonged plasticity within association as compared to sensorimotor cortex is now thought to be a defining principle of human neurodevelopment. Nonetheless, beyond this coarse division in developmental timing between these two expansive domains of cortex, there is marked variability in cortical development that remains undercharacterized—and therefore unaccounted for by contemporary accounts of human brain development. The field has thus lacked an account of the precise spatiotemporal progression of cortical plasticity and the sequence of cortical maturation. Understanding how developmental processes unfold across the cortex is vital for identifying windows of developmental vulnerability and opportunity. In particular, understanding spatially-localized periods of enhanced and diminished malleability can provide insight into which cortical regions will be maximally impacted by both environmental insults and psychiatric interventions at distinct developmental stages. A comprehensive and mechanistic model that accounts for heterochronicity in developmental plasticity could accordingly have far-reaching implications for population-level policies and individual-level interventions. Developing such a model is challenging given that there is no direct or gold standard measure of plasticity in the living human brain. One approach to overcoming this challenge is to translate biological insights from animal studies of developmental plasticity to non-invasive human neuroimaging. **Chapters 2 and 3** of this thesis develop and test a model of how neurodevelopmental programs progress across the human cortex during childhood and adolescence. **Chapter 2** introduces a model of cortical developmental heterochronicity, proposing that a unifying axis of cortical feature organization captures the progression of cortical developmental plasticity and plasticity-associated vulnerability. **Chapter 3** harnesses a functional neuroimaging signature of developmental plasticity illuminated by animal studies to empirically test this model.

Animal studies of cortical plasticity: pyramidal cells, parvalbumin interneurons, and non-neuronal plasticity-limiters

Animal studies provide the opportunity to conduct causal experimental manipulations with significantly more control and neurobiological precision than is afforded in human studies. Decades of research on cortical development in animal models have provided extensive insights into hallmarks and mechanisms of developmental plasticity that are conserved across species. Phylogenetic conservation indicates that these insights could eventually be drawn on to probe plasticity in humans. As described below, developmental hallmarks center around the refinement of excitatory pyramidal neuron connectivity, the maturation of inhibitory parvalbumin interneurons, and the growth of non-neuronal structures that surround and stabilize neurons.

During earlier periods of postnatal development, there is a programmed over-proliferation of dendrites, spines, and synapses on excitatory glutamatergic pyramidal neurons (Innocenti and Price, 2005); highly interconnected excitatory pyramidal cells are a central feature of more developmentally juvenile cortices. The over-proliferation of pyramidal cell neurites and synapses ultimately allows for a vast and diverse range of possible connections to form. These connections will subsequently be strengthened, stabilized, or eliminated during protracted periods of developmental sculpting throughout which pyramidal neurons remain plastic. Initial plasticity in pyramidal neurons is maintained by numerous mechanisms intrinsic to these cells themselves, particularly mechanisms that depend on and facilitate sustained or synchronized excitatory neuronal activity. Younger pyramidal neurons, for example, contain a higher proportion of NMDA receptor GluN2B subunits, which lengthen the time course of glutamatergic activity, sustain excitatory activity, and facilitate synaptic plasticity (Flores-Barrera et al., 2014; Gambrill and Barria, 2011; Lohmann and Kessels, 2014; Wang et al., 2008). Synaptic plasticity is furthermore achieved through the "unsilencing" of immature, silent synapses (i.e., the insertion of AMPA receptors into dormant excitatory synapses); sufficient levels of synchronized neuronal activity can strengthen and integrate silent synapses into the developing circuit (Huang et al., 2015; Rumpel et al., 1998; Sun et al., 2018). Synchronized activity in pyramidal cells can also trigger the synthesis and release of brain derived neurotrophic factor (BDNF), which is itself a major driver of neuronal plasticity (Hogan et al., 2020).

As developing pyramidal neurons continue to be refined through cell-intrinsic mechanisms, their plasticity also becomes increasingly extrinsically regulated by parvalbumin-expressing inhibitory interneurons. Enhanced extrinsic regulation occurs as excitatory drive onto parvalbumin interneurons matures, key proteins (e.g., NARP, NRG1, and Otx2) are expressed at excitatory-parvalbumin synapses, and a shift in parvalbumin interneuron GABAergic signaling is initiated (Cheong Lee et al., 2017; Gu et al., 2016, 2013; Reh et al., 2020; Sugiyama et al., 2008; Takesian and Hensch, 2013). This shift results in parvalbumin interneurons exerting powerful control over the excitability and plasticity of the developing neural circuit (Fagiolini and Hensch, 2000; Hensch, 2005; Takesian and Hensch, 2013)—likely through their coordination of oscillatory network activity (Lensjø et al., 2017; Reh et al., 2020; Winkel et al., 2021) and the creation of an extracellular environment that is more permissive to structural changes (Takesian and Hensch, 2013). Importantly, during periods of interneuron-enabled plasticity, excitatory pyramidal cells undergo extensive pruning. Moreover, because parvalbumin interneuron maturation appears exquisitely sensitive to experience, this pruning is particularly experience-dependent. Hence, internally-driven plasticity may be more characteristic of earlier phases of development, whereas environment- and experience-dependent plasticity appears to dominate following an initial developmental enhancement of parvalbumin interneuron signaling.

While an initial increase in parvalbumin interneuron signaling triggers a rise in circuit plasticity in juvenile cortex (Fagiolini and Hensch, 2000; Gu et al., 2016; Iwai et al., 2003; Tang et al., 2014), further maturation of parvalbumin interneurons actually serves to limit developmental plasticity (Hensch, 2018). Accordingly, there is a two-threshold model of inhibitory maturation wherein the initial strengthening of GABAergic neurotransmission (above threshold one) facilitates plasticity that will persist until a higher threshold of inhibitory signaling (above threshold two) is reached and maintained (Cisneros-Franco and Villers-Sidani, 2019; Gu et al., 2016; Harauzov et al., 2010). The transition from plasticity-facilitating to plasticity-limiting actions of parvalbumin interneurons occurs as myelin and perineuronal nets form around this class of neurons (Akbik et al., 2013; Beurdeley et al., 2012; Carulli et al., 2010; Lensjø et al., 2017; McGee et al., 2005; McRae et al., 2007; Micheva et al., 2016; Yang et al., 2012). Cortical myelin and perineuronal nets are therefore understood to be major restrictors of developmental plasticity that stabilize inhibitory interneurons and reduce the pruning of pyramidal neurons.

Critically, developmental plasticity mechanisms appear to be largely conserved across brain regions: NMDA GluN2B subunits, Otx2, NARP, parvalbumin interneurons, myelin, and perineuronal nets have been found to regulate plasticity in both sensory and association cortices (Carulli et al., 2010; Cheong Lee et al., 2017; Flores-Barrera et al., 2014; Lensjø et al., 2017; McGee et al., 2005; Reichelt et al., 2019; Yang et al., 2012; Yoshimura et al., 2003). The existence of spatially conserved mechanisms indicates that the same markers of plasticity can be studied to elucidate developmental timing across the cerebral cortex. Animal studies examining plasticity marker maturation across cortical regions have found that developmental changes—including pruning of pyramidal neurons, increases in GluN2B prevalence, developmental shifts in parvalbumin interneurons, and proliferation of perineuronal nets—occur temporally later in development in association cortices than in sensory cortices (Canetta et al., 2022; Condé et al., 1996; Drzewiecki et al., 2020; Flores-Barrera et al., 2014). However, the cortex of murines and non-human mammals undergoes faster and relatively more contemporaneous development than the human cortex. Moreover, murines do not have the same association cortices that are present in the human brain, and the association cortex is less expanded in non-human primates than in humans. Consequently, to understand how these same developmental processes play out over the expanded, slow-developing, association cortex-dominated human brain and develop a comprehensive account of human developmental heterochronicity, the insights gained from animal models must be translated to techniques that can be employed to investigate developmental plasticity in humans.

Leveraging biologically-informed neuroimaging to study human developmental plasticity

Magnetic resonance neuroimaging methods offer the possibility of studying neurochemical, structural, and functional signatures of neurodevelopmental plasticity non-invasively in the human brain (Sydnor and Satterthwaite, 2022). Though there is not a direct one-to-one mapping between cellular or molecular cortical properties and signals derived from human neuroimaging, advances in neuroimage acquisition and analysis techniques have provided new avenues for biologically-informed developmental neuroimaging. As exemplified by the three studies described below, recent efforts employing such techniques have found evidence that the hallmarks of developmental plasticity identified in animal models are also observable in vivo in the human brain.

The first study employed 7T neurochemical imaging to delineate age-related changes in cortical glutamate levels during late childhood and adolescence. This work showed that glutamate levels robustly declined throughout prefrontal association regions in this developmental window, potentially consistent with an extensive period of excitatory pyramidal neuron pruning in association cortex (Perica et al., 2022). Given animal model findings linking parvalbumin interneuron-mediated GABAergic signaling and developmental plasticity, a second investigation by Larsen et al. (2022) aimed to study the development of cortical inhibition in youth. Translating functional MRI signatures associated with the administration of a GABA receptor agonist to a developmental population, these authors found evidence for enhancements in inhibitory signaling in association but not sensory cortex during adolescence (Larsen et al., 2022). A third study calculated the cortical T1-weighted to T2-weighted ratio, an MR measure sensitive to cortical myelin content, and provided data consistent with an early childhood increase in cortical myelin in somatomotor cortex and a post-adolescent wave of myelination in association cortex

(Grydeland et al., 2019). These studies demonstrate that non-invasive neuroimaging measures may indeed show sensitivity to biological changes (pruning, inhibitory signaling strengthening, myelination) associated with developmental plasticity. Furthermore, they reveal that these changes are happening later in the association cortex than in the sensory cortex in humans, suggestive of prolonged plasticity in association cortices. Nonetheless, these innovative studies did not chart developmental trends for putative plasticity-related measures in every cortical region nor account for the full spectrum of temporal developmental variability, and thereby did not describe the full patterning of cortical developmental heterochronicity.

Characterizing rich spatial and temporal variability in the development of a proposed imaging measure of plasticity necessitates a measure that is quantifiable within every cortical region across a wide age range in a large developmental sample. One promising approach to identifying such a measure is to elucidate whether the neurochemical and structural changes that drive changes in cortical plasticity alter cortical activity in a stereotyped manner. This approach has significant potential given that aspects of cortical activity can be studied using both invasive neural recordings in animals (e.g., electrophysiology, calcium imaging) and non-invasive brain recordings in humans (e.g., functional MRI), signifying that this approach could be translated across species. Strikingly, animal studies have now revealed that stereotyped changes in cortical activity do arise over the course of development. Furthermore, these stereotyped changes in activity produce consistent and quantifiable changes in features derived from recordings of the activity.

As detailed in the prior section, developing cortical circuits exhibit an early strengthening of excitatory connectivity facilitated by synchronized, intrinsically-generated neural activity. This is followed by a developmental shift in inhibitory signaling that briefly enhances oscillatory network activity. Continued cortical maturation is characterized by further increases in inhibitory tone and extensive excitatory neuron dendritic and synaptic pruning; these processes lead to a reduction in a circuit's excitation: inhibition ratio and a suppression of intrinsic neural activity. Cortical maturation is thus characterized by neurochemical and structural changes that produce alterations in the prevalence and synchrony of intrinsic neural activity. Indeed, studies of the developing animal sensory cortex have shown that earlier stages of development with heightened plasticity are characterized by the presence of robust and synchronized intrinsic cortical activity (Martini et al., 2021). As plasticity declines and the cortex matures, intrinsic activity evolves from prevalent and globally synchronized to suppressed and sparse (Frye and MacLean, 2016; Golshani et al., 2009; Martini et al., 2021; Nakazawa et al., 2020). Moreover, development-linked changes in the prevalence and patterning of intrinsic activity elicit observable changes in the amplitude of recordings of this activity: as plasticity declines and the cortex matures, recordings of intrinsic activity evolve from higher amplitude to lower amplitude. Accordingly, changes in activity-related signals may provide an ongoing readout of local circuit plasticity, with synchronized, high amplitude intrinsic activity recordings serving as a functional hallmark of still-malleable cortices (Laumann and Snyder, 2021; Lensjø et al., 2017; Luhmann et al., 2016; Reh et al., 2020). The amplitude of intrinsic cortical activity can be measured in humans using functional MRI, providing the opportunity to study the spatial and temporal maturation of a putative in vivo indicator of cortical plasticity across the developing cortex. **Chapter 3** leverages this functional measure to elucidate how intrinsic activity is spatially and temporally refined across the developing cortex in humans. It furthermore investigates whether the development of this measure differs in children raised in qualitatively different neighborhood environments.

A socioeconomic gradient of cortical development and risk for developmental psychopathology

The cortex requires input from the environment to develop and will adapt to meet environmental demands and the level of environmental complexity. Deprivation of expected environmental inputs during development has a large and lasting effect on the formation of cortical circuits. This critical importance of environmental exposures for sculpting developing cortical circuits was first highlighted by sensory deprivation experiments in animal models. In the developing murine visual cortex, for example, visual deprivation of one eye results in most neurons becoming responsive to input from the visually non-deprived eye (Hubel and Wiesel, 1970; Wiesel and Hubel, 1963). Cortical remapping in response to sensory deprivation has now also been documented in humans: in congenitally blind individuals, the occipital cortex encodes auditory information and processes language (Kanjlia et al., 2019; Lane et al., 2015). Environmental deprivation can also extend beyond sensory modalities, taking the form of cognitive, linguistic, or psychosocial deprivation. These forms of deprivation, which are typically graded rather than absolute, additionally affect cortical circuit maturation. Severe deprivation of cognitive and social stimulation is associated with altered pyramidal neuron pruning and cortical myelination in mice (Hinton et al., 2019; Makinodan et al., 2012) and with changes in gray matter structure and thickness in the association cortex of humans (e.g., in those exposed to institutional rearing) (McLaughlin et al., 2014; Sheridan et al., 2022, 2012).

Children and adolescents can experience a vast spectrum of sensory, cognitive, and social environments that range from more deprived to more enriched. One factor that contributes to this spectrum is the neighborhood socioeconomic environment that each individual is raised in. Neighborhood socioeconomic conditions are typically estimated according to economic measures (e.g., median income or poverty levels), social indicators (e.g., average years of education), work status (e.g., employment rates) and housing quality (e.g., vacant housing). Large disparities in neighborhood socioeconomic conditions are present in most countries, arise from structural wealth and education inequity, are socio-politically reinforced, and disproportionately disadvantage racial and ethnic minorities (Acevedo-Garcia et al., 2020; Webb et al., 2022). Importantly, poorer socioeconomic environments are not inherently characterized by deprivation, and similar levels of sensory, cognitive, and psychosocial enrichment can be experienced across the entire socioeconomic spectrum. But research has shown that poorer socioeconomic conditions greatly increase the likelihood of relatively higher deprivation being experienced in one or more domains (Bradley and Corwyn, 2002; Rosen et al., 2018; Sheridan and McLaughlin, 2014; Tooley et al., 2021), leading to societally constructed inequities in many developmental outcomes.

Socioeconomic conditions have vast and graded effects on cognitive and socioemotional outcomes (Luo and Waite, 2005), with lower socioeconomic status being associated with—at the population level—lower performance on most tests of cognitive ability (Hackman et al., 2021, 2015; Hackman and Farah, 2009; Rosen et al., 2020) and a higher prevalence of psychopathology and diagnosed psychiatric disorders (Farah, 2017; Kivimäki et al., 2020; Modabbernia et al., 2021; Reiss, 2013; Webb et al., 2022). Indeed, socioeconomic disadvantage in children and adolescents has been linked to a two to three times increased risk of developing a mental health condition (Reiss, 2013). The socioeconomic environment is thus an important marker of youths' environmental inputs that captures a gradient of cognitive and psychiatric outcomes produced by the unequal and unjust distribution of social determinants of health across the population. Understanding how differences in the socioeconomic environment become biologically embedded during development to produce disparities in youth mental health may aid the design of interventions or lend empirical support to policy recommendations that could alleviate such disparities (Farah, 2018; Luby et al., 2020).

Over the last decade, research on the social determinants of health has revealed that not only is the socioeconomic environment one of the largest predictors of neurodevelopmental outcomes, it also explains a large degree of variation in cortical properties in youth populations (Farah, 2017). During late childhood and adolescence, more advantaged socioeconomic environments are associated with greater cortical surface area and volume (Gur et al., 2019; Judd et al., 2020; McDermott et al., 2019; Modabbernia et al., 2021; Noble et al., 2015; Piccolo et al., 2016), with larger effects typically seen in the association cortices in these developmental stages. Developmental trajectories also differ by socioeconomic conditions; for example, association cortex thinning and functional segregation appear to occur more rapidly in childhood and plateau earlier in adolescence in youth from disadvantaged socioeconomic environments (Piccolo et al., 2016; Tooley et al., 2021). These findings demonstrate that like the sensory cortex, the association cortex is neurobiologically prepared to be molded by and adapt to the demands of the environment. Furthermore, these findings suggest that a gradient of developmental trajectories across socioeconomic conditions could contribute to the observed gradient of cognitive and psychiatric outcomes.

Evidence from animal studies suggests that variation in developmental trajectories associated with socioeconomic (dis)advantage may arise in part from differences in the expression of plasticity-regulating mechanisms. Environmental enrichment in murines has been shown to engender enhancements in excitatory glutamatergic neurotransmission (Nichols et al., 2007) and to increase neurite density and the connectivity of pyramidal neurons (Tooley et al., 2021), whereas deprivation appears to accelerate the pruning of glutamatergic connections. Environmental enrichment is also associated with a reduction in local cortical inhibition in the adult cortex (when stronger inhibition limits plasticity) (Baroncelli et al., 2010; Greifzu et al., 2014; Sale et al., 2007) and with a change in the constitution of parvalbumin interneurons that enhances structural synaptic plasticity (Donato et al., 2013; Favuzzi et al., 2017). Accordingly, environmental enrichment appears to confer a more juvenile cortical state. In support of this interpretation, environmental enrichment is associated with increased expression of BDNF (Baroncelli et al., 2010; Huang et al., 2021; Sale et al., 2007), which facilitates synaptic plasticity, and reduced density of perineuronal nets (Favuzzi et al., 2017; Sale et al., 2007), which limit circuit plasticity.

These and related studies have informed the theory that cortical plasticity varies across the socioeconomic spectrum in developing youth (Baroncelli et al., 2010; Tooley et al., 2021). Specifically, it has been hypothesized that enriched environments are associated with either a greater capacity for plasticity or more temporally protracted plasticity in youth. Physical, cognitive, and psychosocial environmental deprivation, on the other hand, are theorized to lead to a decreased potential for ongoing plasticity or to less prolonged windows of developmental plasticity. Reductions in developmental plasticity may represent an adaptive response to environmental adversity, enabling earlier stability in uncertain or harsh environments or earlier attainment of adult-like cognitive and behavioral abilities.

However, reductions in the capacity for or timescale of developmental plasticity may also contribute to differences in cognitive learning or produce variation in circuit properties that enhance risk for psychiatric symptomatology. If differences in developmental plasticity partly explain or influence documented relationships between socioeconomic disadvantage and cognitive or psychiatric risk, this could help to inform environmental enrichment or enhancement efforts or plasticity-facilitating interventions. Yet testing for associations between the socioeconomic environment and cortical plasticity has been difficult in humans, given the previously described paucity of non-invasive indexes of brain plasticity. **Chapter 3** leverages a functional imaging measure inspired by animal models of plasticity to study developmental changes in cortical malleability across the environmental deprivation-enrichment spectrum. It seeks to elucidate the nature, timing, and regional specificity of brain-environment relationships over the course of childhood and adolescence.

Reward responsiveness as an intervention target for psychiatric risk in adolescence

Symptoms of mental illness often first emerge during the course of cortical development. Approximately 35-50% of lifetime psychiatric disorders present by age 14; 60-75% present by age 24 (Caspi et al., 2020; Kessler et al., 2005; Paus et al., 2008; Solmi et al., 2022). Many psychiatric disorders are therefore understood to be neurodevelopment-linked disorders, with risk for disorder onset heightening throughout adolescence and remaining higher in youth raised in worse socioeconomic conditions in this developmental stage (Farah, 2017; Kivimäki et al., 2020; Modabbernia et al., 2021; Reiss, 2013; Webb et al., 2022). In both youth and young adults, lower socioeconomic status consistently covaries with cortical phenotypes associated with psychiatric disorder risk (Alnæs et al., 2020; Llera et al., 2019; Modabbernia et al., 2021). Moreover, worse socioeconomic conditions tend to covary with behavioral phenotypes linked to disorder risk.

Two of the largest behavioral risk factors for the subsequent development of a diagnosable mental illness are deficits in executive functioning and low reward responsiveness. Executive functioning and reward responsiveness are broad psychological constructs comprised of multiple subdomains, the former involving planning, decision making, and response inhibition and the latter comprising reward sensitivity, reward valuation, and motivation. Poorer executive functioning is predictive of a greater overall psychiatric symptom burden 2 years later in children ages 6 to 14 (Halse et al., 2022; Romer and Pizzagalli, 2021), even when controlling for baseline symptom severity, age, sex, parental education, and family income. Similarly, reduced reward responsiveness is associated with increased risk of subsequently developing depressive, anxiety, bipolar, psychosis spectrum, and stress disorder symptoms (Bennik et al., 2014; Pelizza et al., 2020; Risbrough et al., 2018; Winer et al., 2017). Understanding neural features that contribute to executive difficulties or reward deficits across the entire socioeconomic spectrum thus has the potential to reveal precursors for the emergence of psychiatric disorders. Notably, both executive functioning (Tervo-Clemmens et al., 2022) and reward sensitivity (Galván, 2013; Luna et al., 2013) show particularly large enhancements during the adolescent period. Adolescence thus represents a period of vulnerability for the insufficient development of executive and reward functioning as well as a window of opportunity for the implementation of interventions that aim to mitigate cognitive and reward deficits.

Reward responsiveness is a promising intervention target for the prevention or initial treatment of psychiatric symptomatology given its dimensional nature, transdiagnostic relevance, relationship to environmental conditions, and potential for ambulatory assessment. Reward responsiveness varies continuously across the entire population, with reward deficits being associated with poorer psychological well-being (Taubitz et al., 2015) and with future psychological decline (Bennik et al., 2014) in both non-clinical and psychiatric samples. A severe deficit in reward responding is furthermore itself a transdiagnostic symptom that is present in many psychiatric disorders and predictive of more severe symptoms (Dimick et al., 2021; Pelizza et al., 2020; Winer et al., 2017) and suicidality (Gabbay et al., 2015; Gillissie et al., 2023; Hawes et al., 2018; Pine et al., 1999; Winer et al., 2016, 2014). Diminished responding to and motivation for rewards has been identified as a response to environmental adversity involving material and psychosocial deprivation (Dennison et al., 2019; McLaughlin and Gabard-Durnam, 2022; Sheridan et al., 2018), unpredictable environmental signals (Risbrough et al., 2018), and environmental stressors (Stanton et al., 2019), suggesting that alterations in reward-related processing may impact relationships between socioeconomic disadvantage and youth mental health. Finally, components of reward responsiveness can be indexed via clinical interview, questionnaires, games, or tasks, and could therefore be assessed in schools, during medical visits, or with ecological momentary assessments, providing practical options for screening and identifying at-risk youth that may benefit from interventions in the adolescent period. Nonetheless, the type of intervention that should be delivered to scaffold healthy development of reward responding is still unclear, necessitating research that identifies neural contributors to reward deficits that could either be directly intervened on or serve as biological indicators for assessing intervention efficacy (Krystal et al., 2020).

The neural circuits that support reward processing have been extensively studied in rodents, non-human primates, and humans (Haber and Knutson, 2010). Reward regions in the transmodal association cortex—including regions of the orbital and medial prefrontal cortex and the anterior and posterior cingulate—form an interconnected network with subcortical reward areas in the ventral striatum, thalamus, and midbrain (Bartra et al., 2013). Human functional MRI studies have shown that lower reward responsiveness is associated with lower activity and functional connectivity within this reward network in individuals both with and without psychiatric diagnoses (Harvey et al., 2010; Keller et al., 2013; Sharma et al., 2017; Smoski et al., 2009). Yet, the neurobiology underlying such hypofunction and hypoconnectivity has only been sparsely investigated. One candidate neurobiological mechanism that could underlie reductions in local activity and long-range functional connectivity is a reduction of glutamatergic neurotransmission within reward regions.

Although dopamine is canonically associated with reward processing, glutamate is also a major modulator of reward network functioning (Geisler and Wise, 2008; Haber and Knutson, 2010; Höflich et al., 2018; Sesack et al., 2003; Sesack and Grace, 2010). Transmodal association cortices that process reward communicate via glutamatergic pyramidal neurons. Moreover, subcortical reward pathways (e.g., the mesolimbic dopamine pathway) are engaged by glutamatergic inputs from transmodal cortices (Haber, 2016; Sesack et al., 2003; Stuber et al., 2012). Diminished reward responsiveness could thus conceivably arise from decreased glutamate signaling between reward-related cortical and subcortical regions. Notably, reductions in glutamatergic signaling and pyramidal neuron connectivity have been observed in response to decreased environmental enrichment, providing a potential mechanistic link between socioeconomic disadvantage, decreases in reward responsiveness, and risk for developmental psychopathology. The nature of relationships between reward responsiveness and glutamate availability in the human brain is unknown, however, in large part due to limitations in our ability to measure glutamate in the brain in vivo. **Chapter 4** of this thesis harnesses a novel approach to imaging brain glutamate at ultra-high field that offers high sensitivity, spatial coverage, and spatial resolution. It employs this method to examine associations between reward responsiveness and reward network glutamate availability in a transdiagnostic sample during the primary developmental window of psychiatric symptom emergence.

Harnessing human neuroimaging to study cortical developmental plasticity, environmental susceptibility, and psychiatric vulnerability

How does developmental plasticity spatially and temporally progress across the human cortex during childhood and adolescence? Do youths' neighborhood socioeconomic environments influence the capacity for the cortex to remain developmentally malleable through adolescence? Can we identify neural contributors to individual differences in reward responsiveness, a psychiatric risk factor, during the adolescent period? This thesis aims to integrate the fields of developmental, environmental, and clinical neuroscience to provide new insight into these three interrelated questions. Together, these lines of inquiry can help to elucidate when during development cortical areas subserving distinct psychological functions are plastic, and thus malleable by positive and negative environmental exposures or amenable to targeted interventions aimed at mitigating psychiatric disorder risk.

Chapter 2, titled "Neurodevelopment of the Association Cortices: Patterns, Mechanisms, and Implications for Psychopathology", puts forth a new framework for understanding and relating spatial feature heterogeneity and temporal developmental heterochronicity across the cortical landscape. It proposes that there is an evolutionarily-rooted, unifying, archetypal sensorimotor-association (S-A) axis of cortical organization that spans between primary and transmodal cortices. This axis captures concerted spatial variability in the layout of structural, metabolic, cellular, molecular, and electrophysiological properties across the cortex and aligns with previously described anatomical, functional, and evolutionary cortical hierarchies (**Figure 1-1A**). **Chapter 2** additionally introduces a model of cortical development, which posits that developmental programs unfold along the S-A axis during childhood and adolescence. Specifically, this developmental model hypothesizes that plasticity progressively declines along the S-A axis throughout youth (**Figure 1-1B**), endowing transmodal association cortices with a uniquely protracted period of plasticity that is enhanced during adolescence. Prolonged plasticity in transmodal cortices is postulated as a defining feature of human development, but is predicted to heighten vulnerability of these cortical areas to environmental adversity, putting humans at risk for developmental psychopathology.

Chapter 3 of this thesis, titled "Intrinsic Activity Development Unfolds Along a Sensorimotor-Association Cortical Axis in Youth" seeks to empirically test the S-A axis model of cortical development by harnessing a functional signature of neurodevelopmental plasticity illuminated by animal studies (**Figure 1-1BC**). Using functional MRI data collected from over 1,000 youth ages 8 to 23 years old, it characterizes spatially-localized, age-dependent changes in the amplitude of intrinsic cortical activity, a proposed functional maker of circuit plasticity. It relates developmental changes in this functional measure to the maturation of cortical myelin and assesses the extent to which developmental change is spatially patterned along the S-A axis from childhood to adulthood. **Chapter 3** furthermore examines relationships between neighborhood socioeconomic conditions and the development of this functional marker to test the hypothesis that youth raised in disadvantaged environments experience reduced or less protracted association cortex plasticity (**Figure 1-1D**). Moreover, it explores whether the effects of the socioeconomic environment on the developing cortex evolve over time as cortical malleability is refined.

Chapter 4 of this thesis, titled "Diminished Reward Responsiveness is Associated with Lower Reward Network GluCEST: An Ultra-high Field Glutamate Imaging Study" endeavors to uncover neurochemical correlates of individual differences in reward responding, a psychiatric risk factor, during adolescence and young adulthood (**Figure 1-1CD**). It takes advantage of recent improvements in non-invasive chemical imaging to measure brain glutamate levels with 7T glutamate chemical exchange saturation transfer (GluCEST) imaging. Using GluCEST, the work in this chapter images brain glutamate across a neuroanatomically expansive portion of the reward network while capitalizing on improvements in sensitivity and signal-to-noise ratio afforded by high field strengths. This final chapter is motivated by the possibility that understanding more about reward deficits during prodromal or early stages of psychiatric symptom emergence may ultimately aid mental health prevention or treatment efforts in at-risk youth.

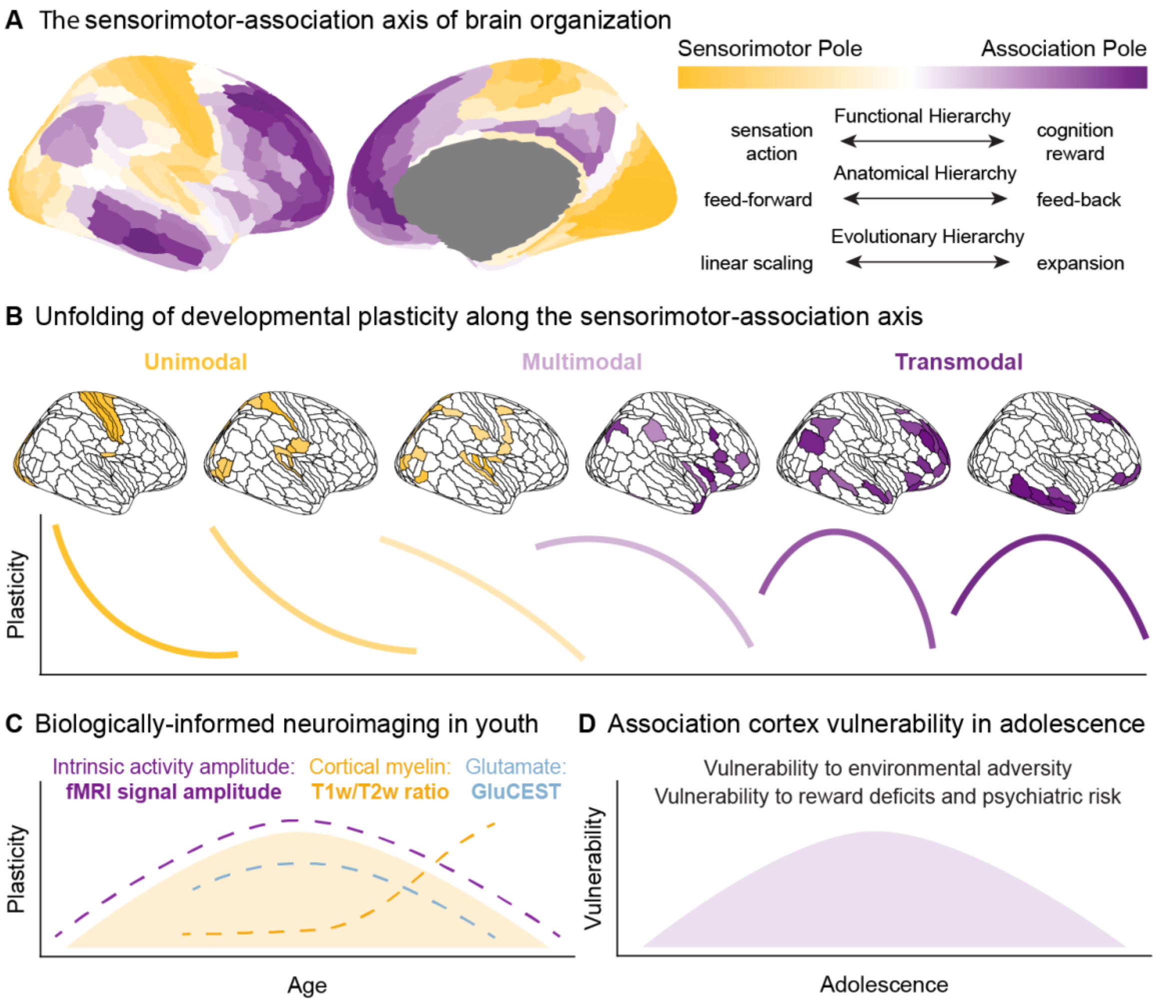

Figure 1-1. A Sensorimotor-Association Axis Model of Cortical Developmental Plasticity and Vulnerability
This thesis introduces a model of cortical development that posits that maturational programs unfold along an evolutionarily-rooted, hierarchical axis of cortical organization: the sensorimotor-association axis. **A**) The sensorimotor-association axis is a large-scale axis of human brain organization that spans continuously from functionally-specific primary sensory and motor regions (sensorimotor pole; yellow), to modality-specific, multimodal, and then integrative transmodal association cortices (association pole; purple). The sensorimotor-association axis captures spatial variation in diverse neurobiological properties and is aligned to the cortex's functional, anatomical, and evolutionary hierarchies. **B**) The sensorimotor-association axis model of cortical development posits that developmental plasticity progressively declines along this axis with age, endowing

transmodal association cortices with heightened plasticity through the adolescent period. **C**) This thesis harnesses biologically-informed neuroimaging to explore spatiotemporal patterns of cortical development and the neural correlates of psychiatric risk during youth. Functional MRI (fMRI) and the T1-weighted to T2-weighted (T1w/T2w) ratio are used to characterize the development of cortical intrinsic activity amplitude and cortical myelination during childhood and adolescence. Glutamate chemical exchange saturation transfer (GluCEST) imaging is used to explore relationships between brain glutamate levels and reward responsiveness, a major psychiatric risk factor, during adolescence and early adulthood. **D**) The sensorimotor-association axis model of cortical development predicts that transmodal association cortices will exhibit heightened vulnerability to environmental adversity and psychopathology-related insults during adolescence due to their prolonged malleability. This prediction is tested by studying relationships between association cortex properties, socioeconomic-related environmental adversity, and diminished reward responsiveness during the adolescent period.

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CHAPTER 2: NEURODEVELOPMENT OF THE ASSOCIATION CORTICES: PATTERNS, MECHANISMS, AND IMPLICATIONS FOR PSYCHOPATHOLOGY

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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 multi-modal 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 late 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—comprised 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 new insight into the global arrangement of cortical properties and the degree of similarity amongst 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 the *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 central framework for understanding the progression and the biobehavioral outcomes of cortical development. We next review relevant evidence from studies that have employed 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 to 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 feed-forward 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 feed-back communication. This 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 via a graded ordering of features along a simplified spatial dimension.

Based on 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—employing 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, 2008, 1998).

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 as compared to 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. Though 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 2-1**).

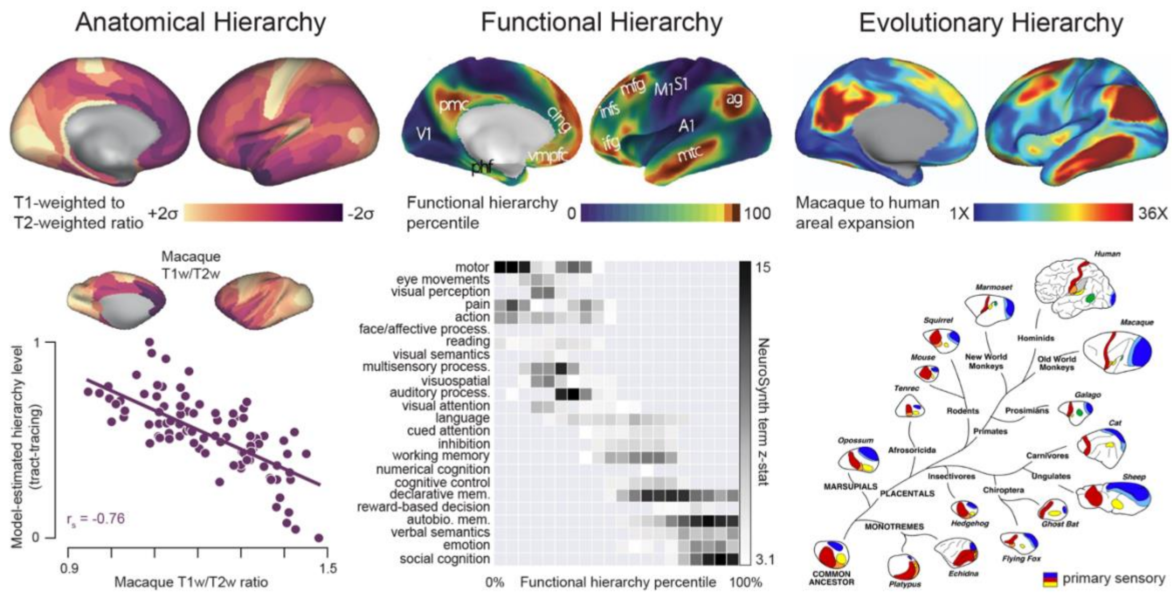

Figure 2-1. Anatomical, Functional, and Evolutionary Cortical Hierarchies
Anatomical Hierarchy: The human cortical anatomical hierarchy is revealed by inter-regional variation in the neuroimaging-derived T1-weighted to T2-weighted (T1w/T2w) ratio. The T1w/T2w ratio strongly negatively correlates with 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. copyright © 2018 with permission from Springer Nature, Nature Neuroscience. Functional Hierarchy adapted with permission from Margulies et al. copyright © 2016 via the PNAS License to Publish. Evolutionary Hierarchy reprinted from Xu et al. (2020) with permission

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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 nonlinear (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—while historically grounded—have accelerated substantially in recent years. These data-driven efforts have demonstrated that while 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 regions to transmodal association areas: the S-A axis of cortical organization (García-Cabezas et al., 2019; Huntenburg et al., 2018; Mesulam, 2008, 1998) (**Figure 2-2**).

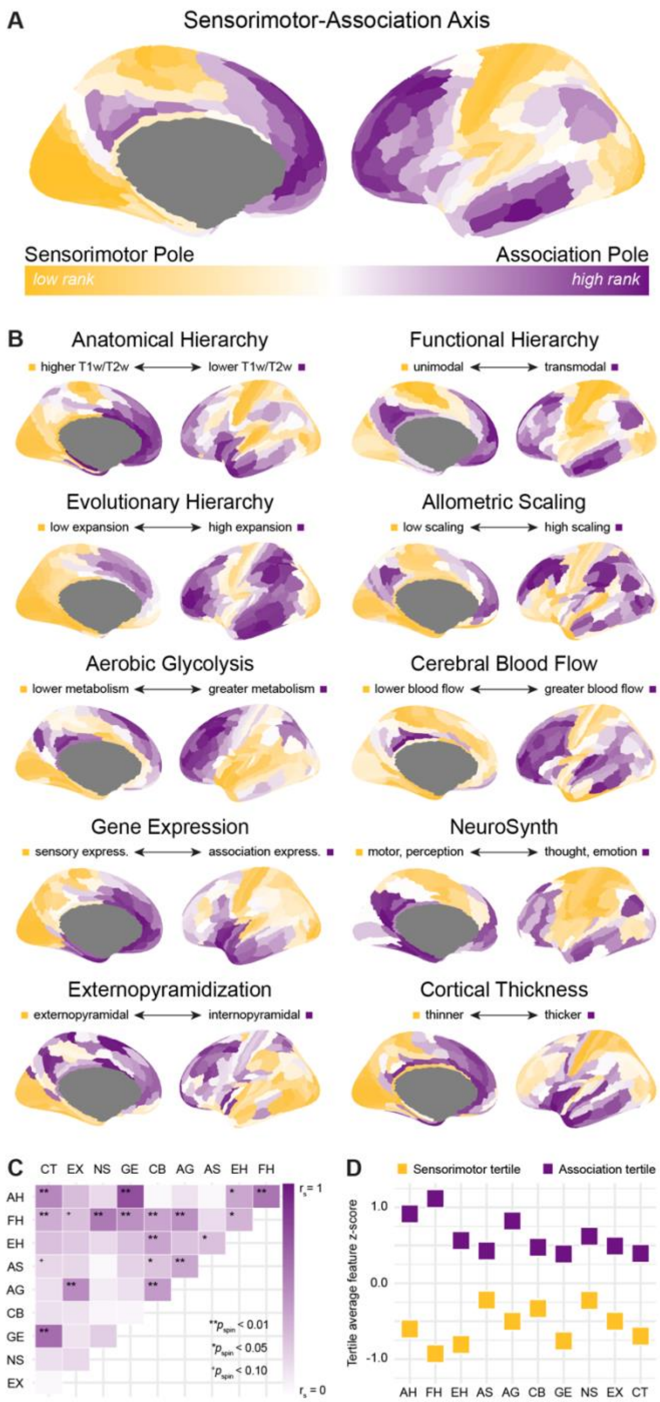

A
Sensorimotor-Association Axis
Sensorimotor Pole
Association Pole
low rank
high rank
B
Anatomical Hierarchy
higher T1w/T2w
lower T1w/T2w
Functional Hierarchy
unimodal
transmodal
Evolutionary Hierarchy
low expansion
high expansion
Allometric Scaling
low scaling
high scaling
Aerobic Glycolysis
lower metabolism
greater metabolism
Cerebral Blood Flow
lower blood flow
greater blood flow
Gene Expression
sensory express.
association express.
NeuroSynth
motor, perception
thought, emotion
Externopyramidization
externopyramidal
internopyramidal
Cortical Thickness
thinner
thicker
C
CT EX NS GE CB AG AS EH FH
AH FH EH AS AG CB GE NS EX
$r_s = 1$
$r_s = 0$
$^{**}p_{spin} < 0.01$
$^{*}p_{spin} < 0.05$
$^{+}p_{spin} < 0.10$
D
Sensorimotor tertile
Association tertile
Tertile average feature z-score
1.0
0.0
-1.0
AH FH EH AS AG CB GE NS EX CT

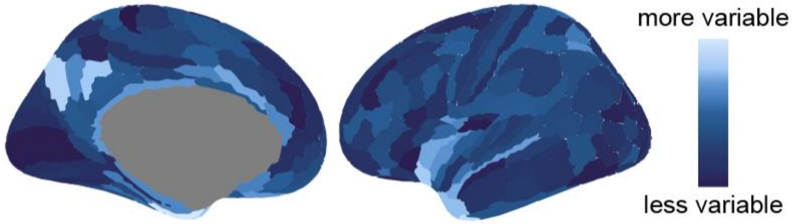
Figure 2-2. The Sensorimotor-Association Axis of Cortical Organization
Diverse neurobiological properties reveal a principal sensorimotor-association (S-A) axis of topographical feature variation and organization. Cortical measures derived from 10 different data types were independently averaged within 180 left hemisphere parcels (Glasser et al., 2016), and parcels were rank ordered based on value from 1 (low rank; yellow; sensorimotor-like) to 180 (high rank; purple; association-like). **A**) Individual parcel rankings from the 10 cortical maps displayed in (B) were averaged to derive an archetypal S-A axis. **B**) Cortical maps for 10 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 utilization (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); Cortical Thickness (CT), quantified from structural MRI (Human Connectome Project S1200 data). **C**) A Spearman's rank (r_s) correlation matrix for the 10 cortical features. Correlation significance (p_{spin}) was assessed with a conservative parcel-based spatial permutation spin test that preserves spatial covariance structure, as implemented in Váša et al., 2018. **D**) The archetypical S-A axis shown in (A) captures divergence between sensorimotor and association cortices across all 10 cortical features, as revealed by average sensorimotor tertile versus association tertile feature z-scores. Sensorimotor and association tertiles include 60 cortical parcels with the lowest and the highest average ranks, respectively, based on the multi-modal map computed in (A).

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 2-1**). While 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 outwards 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, 2010). This principle proposes that the high-dimensional information space comprised 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, 2010). This principle of functional continuity, which parallels the notion of gradients of cognitive function introduced by Elkhonon Goldberg (Elkhonon 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, 2010; 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 transmodal 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, 2008, 1998). Mesulam divided the cortex into ordered, spatially continuous zones based on decreasing cytoarchitectonic differentiation and increasing level in a sensory-fugal processing hierarchy. The resulting 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 zones based on 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 2-2D**), as well as subtler differences within unimodal and within association cortices (**Figure 2-2B**), 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 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 balance and electrophysiological information processing. The S-A axis captures not only facets of regional structure and neurochemistry, but also a distance-based spectrum of functional connectivity profiles. Primary and unimodal sensorimotor cortices preferentially connect to local cortical areas, paralimbic cortices exhibit a balance of local and distant connectivity, and heteromodal cortices overwhelmingly display distributed, long-distance connections (Sepulcre et al., 2010). Heteromodal association areas therefore utilize a circuit architecture that enables communication with more functionally heterogenous portions of the cortex.

Box 2-1. Boundaries and Nonuniformities in the Sensorimotor-Association Axis and Alternate 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 to integrate organizational trends observed across studies, spatial scales, and species. Further, it is now apparent that the systematic ordering of cortical regions along this axis based on 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 based on intracortical 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 based on diversity of inter-regional structural connections, distance of functional connections, and evolutionary expansion). Furthermore, when comparing across axes derived from 10 fundamental cortical features (**Figure 2-2B**), 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 (**Box 2-1 Figure**).



Box 2-1 Figure: Variability in S-A Axis Ordered Position

These nonuniformities 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, alternate 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's hypothesized that the dorsal-ventral axis may emerge due to 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 cognitive versus affective functioning (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.

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, i.e., 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 to transmodal association areas. In what follows, we review evidence of a neurodevelopmental hierarchy derived from both *in vivo* neuroimaging and complimentary histological, electrophysiological, and transcriptomics studies, and 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 two 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 non-linear 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. Though 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 due to 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 largely driven 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 timeframe 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 earlier, 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 as compared to 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., 2010b, 2010a; Raznahan et al., 2011; Wierenga et al., 2014), reaching a global peak around 9 to 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 largely driven by additional folding of secondary and tertiary sulci and by increasing sulcal depth (Hill et al., 2010b, 2010a; 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 higher-order, 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 highest-order 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-subject 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 regions 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 areas 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. Further, it may signify that anatomical plasticity is less constrained by myelin-related proteins in superficial cortical layers within regions falling higher in the S-A hierarchy.

Whereas reductions in thickness are seen across the cortex from early childhood, both myelin-sensitive imaging and post-mortem 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 were robustly activated by language, comprehension, theory of mind, and mentalizing-related tasks in prior 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 primarily occurs 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 towards 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). Further, 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, and 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, namely 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 and/or axon 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), though 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 refers to 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 this axis, within primary visual cortex, heteromodal cortex, and paralimbic cortex (Baum et al., 2017; Park et al., 2021). This 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 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 feed-forward feed-back circuit architecture, and minimal inter-individual topographical variability. Higher-order systems exhibit long-range, distributed connections, non-canonical circuit organization, and substantial 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, while the default mode system is only weakly connected around 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 during adolescence leads 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 towards 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, alternate 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 capacities 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 2-3**).

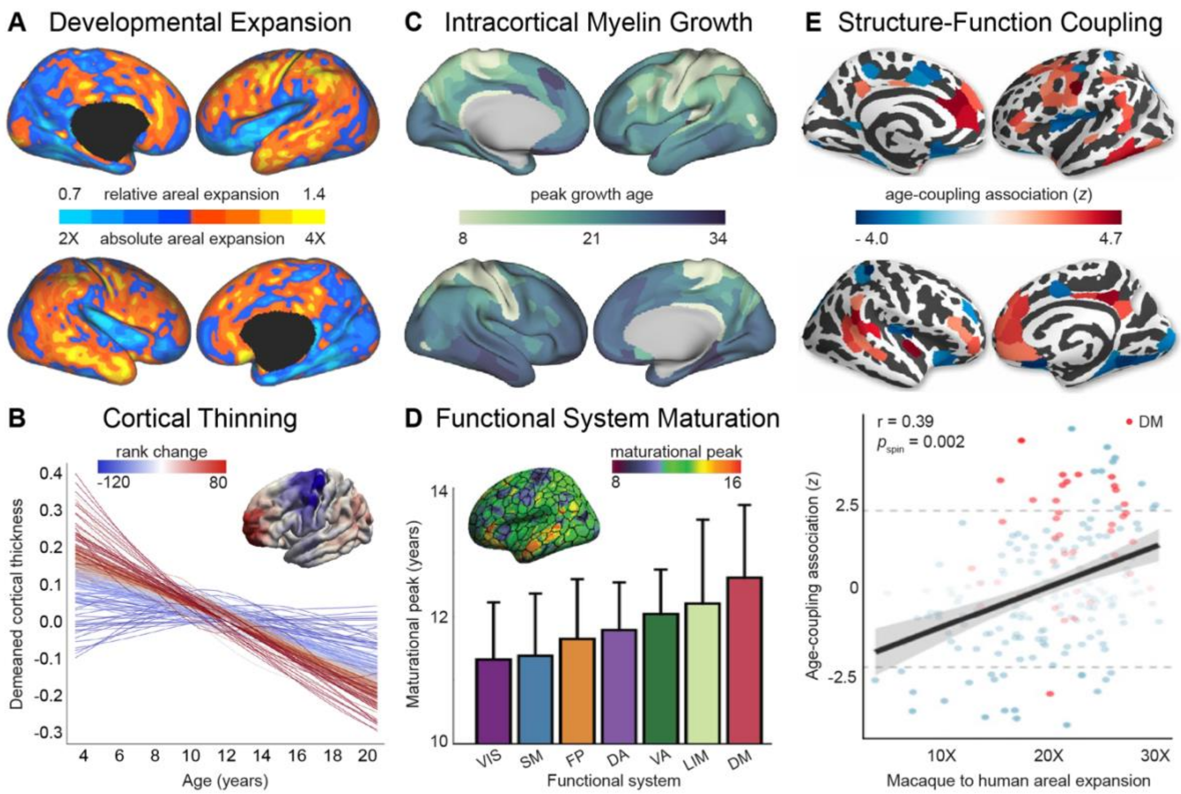


Figure 2-3. Hierarchical Neurodevelopment in Youth
The magnitude and timing of development-related changes varies across the cortical mantle during childhood and adolescence and is linked to anatomical, functional, and evolutionary hierarchies. Consequently, compared to primary and unimodal visual, auditory, 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. A) adapted with permission from Hill et al. (2010a) copyright © 2010 via the PNAS License to Publish. B) and E) adapted from Ball et al. (2020b) and Baum et al. © 2020 with permission https://creativecommons.org/licenses/by-nc-nd/4.0/. C) Adapted from Grydeland et al. copyright © 2019 with permission https://creativecommons.org/licenses/by/4.0/. D) Adapted from Dong et al. copyright © 2020 with permission https://creativecommons.org/licenses/by-nc/4.0/.

Microscale mechanisms driving macroscale development 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. Though 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 in 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 from primary to unimodal, heteromodal, and paralimbic cortices along the S-A axis, 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 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 modulation, 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 for continued 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 parvalbumin (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, putatively exhibiting lowest expression in paralimbic cortices, hence variability in the expression of PV cells may serve as a cellular basis of the GABAergic 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 due to the maturation of PV interneurons (Fung et al., 2010) and to 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 till the adolescent period in association cortices (though never reaching sensory cortex levels) (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 due to 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-inducing 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 (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 to 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 associative (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 to 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 2-4)**. As discussed below, this multi-scale maturation has fundamental 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.

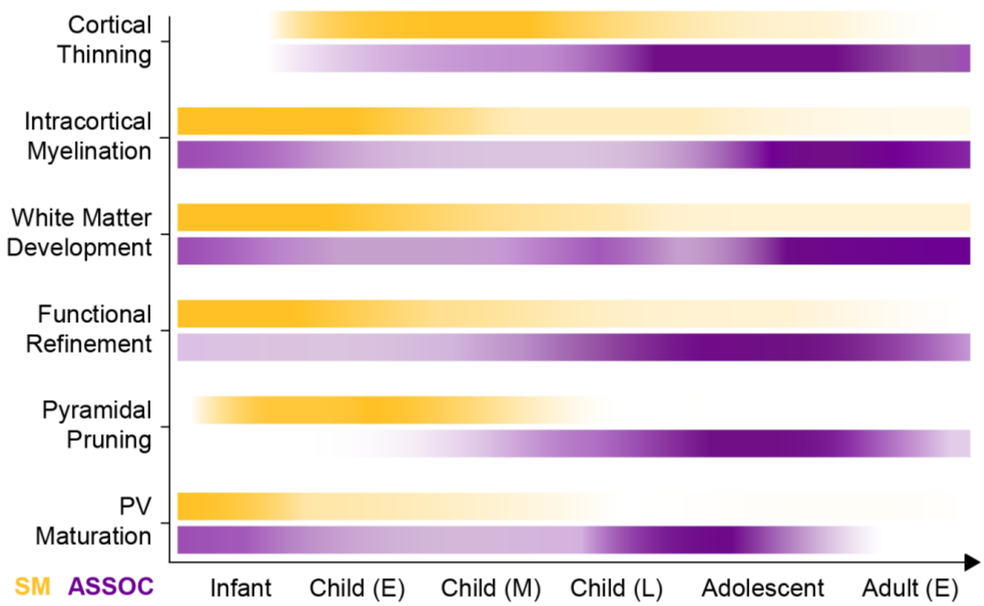


Figure 2-4. Multi-Scale Temporal Neurodevelopment in Sensorimotor and Association Cortex
The time course and tempo of major developmental changes in sensorimotor cortex (SM; yellow) and association cortex (ASSOC; purple) are illustrated; darker shading indicates larger magnitude changes. This qualitative synthesis of the reviewed literature underscores how the temporal neurodevelopmental axis indexes heterochronous changes between lower-order versus high-order cortical regions. This synthesis further reveals prolonged association cortex neurodevelopment marked by substantial changes in late childhood and adolescence. Convergent data arises from neuroimaging-derived measures and plasticity-related cellular changes. E: early, M: middle, L: late, PV: parvalbumin.

Microcircuit activity

As excitatory neurons are pruned and GABAergic interneurons mature—early in sensory cortices and later in association cortices—the cortical excitation to inhibition (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 these 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. Significantly, 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 heterogenous 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

Though 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, lower PV interneuron density, and reduced intracortical myelination. The confluence of these macro and microscale features gives rise to electrophysiological and circuit differences that yield two emergent 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 2-5**). At one end of this gradient, sensory and motor brain regions exhibit short intrinsic timescales characterized by rapid-onset, adaptable, high frequency 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, integration, and modulation (Honey et al., 2012)—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).

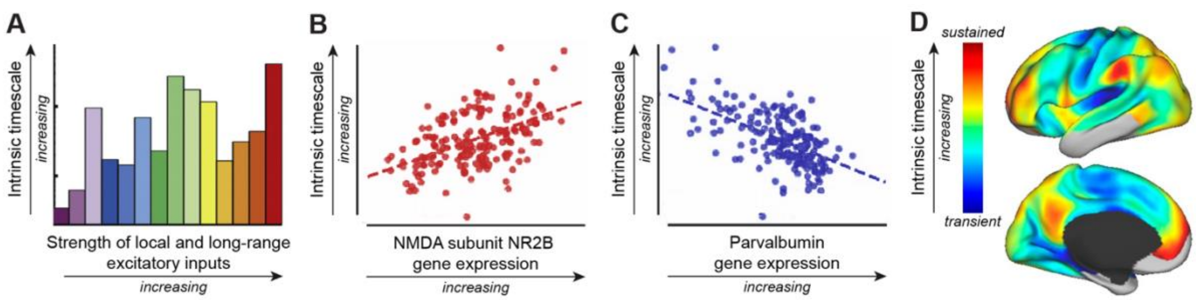


Figure 2-5. Excitatory and Inhibitory Feature Variability Produces a Gradient of Information Processing Timescales
A) Results from an anatomically-informed computational model of the macaque cortex support a link between longer intrinsic timescales and stronger local and long-range excitatory inputs. 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 (purple to red): V1, V4, 8m, 8I, TEO, 2, 7A, 10, 9/46v, 9/46d, TEpd, 7m,

7B, 24c. **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). **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. A) adapted from Chaudhuri et al. copyright © 2015 with permission from Elsevier. B) and C) adapted from Gao et al. copyright © 2020 with permission https://creativecommons.org/licenses/by/4.0/. D) adapted with permission from Raut et al. copyright © 2020 via the PNAS License to Publish.

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 a 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, allows for 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 employed 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 them 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. This 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, while 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 multimodal, 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 as compared to 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 new evidence that evolution-linked, human accelerated genes (genes that display elevated divergence in humans compared to other primates) are most highly expressed in paralimbic and heteromodal 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 impact brain development. However, the specific impact of a given environmental stimulus is critically dependent upon the neurotemporal context, i.e., 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 impacts 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 impact later development of connected association regions (Rosen et al., 2019). Remarkably, cognitive, social, and emotional experiences significantly impact 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 timeframe 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 2-6**). Strikingly, heightened neurobiological variability within transmodal associative as compared to 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.

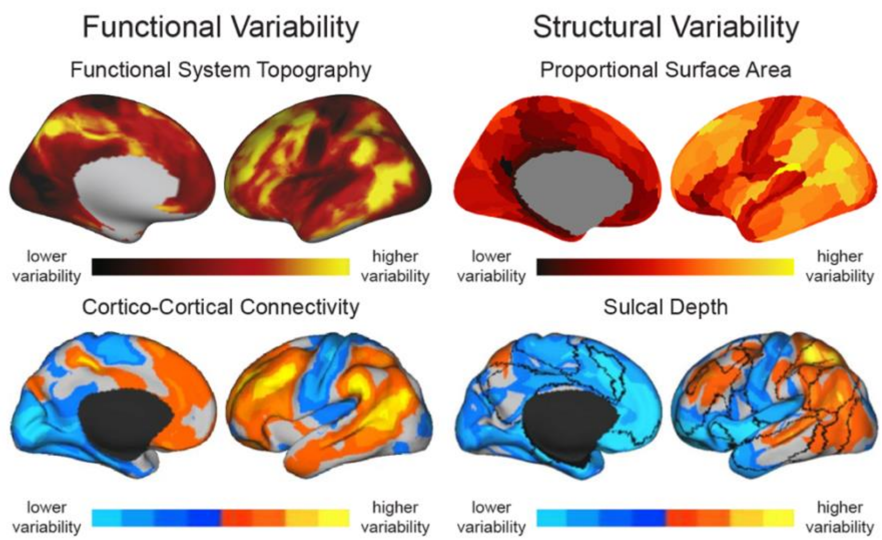


Figure 2-6. Inter-Individual Variability in Functional and Structural Properties Across the Cortical Mantle
Inter-individual variability in functional system topography, cortico-cortical functional connectivity architecture, proportional surface area, and sulcal depth varies by the S-A organizational axis and is generally highest in transmodal heteromodal association regions. Functional system topography adapted from Cui et al. copyright © 2020 with permission from Elsevier. Cortico-cortical connectivity and sulcal depth adapted from Mueller et al. 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). While 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 impact 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., 2020) (**Figure 2-7A**). 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., 2020). Moreover, these diverse symptoms are associated with microstructural modifications in white matter 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 macro 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 2-7B**). 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 2-7C**). Extending 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 between association cortex maturation, plasticity, and diverse psychopathologies 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.

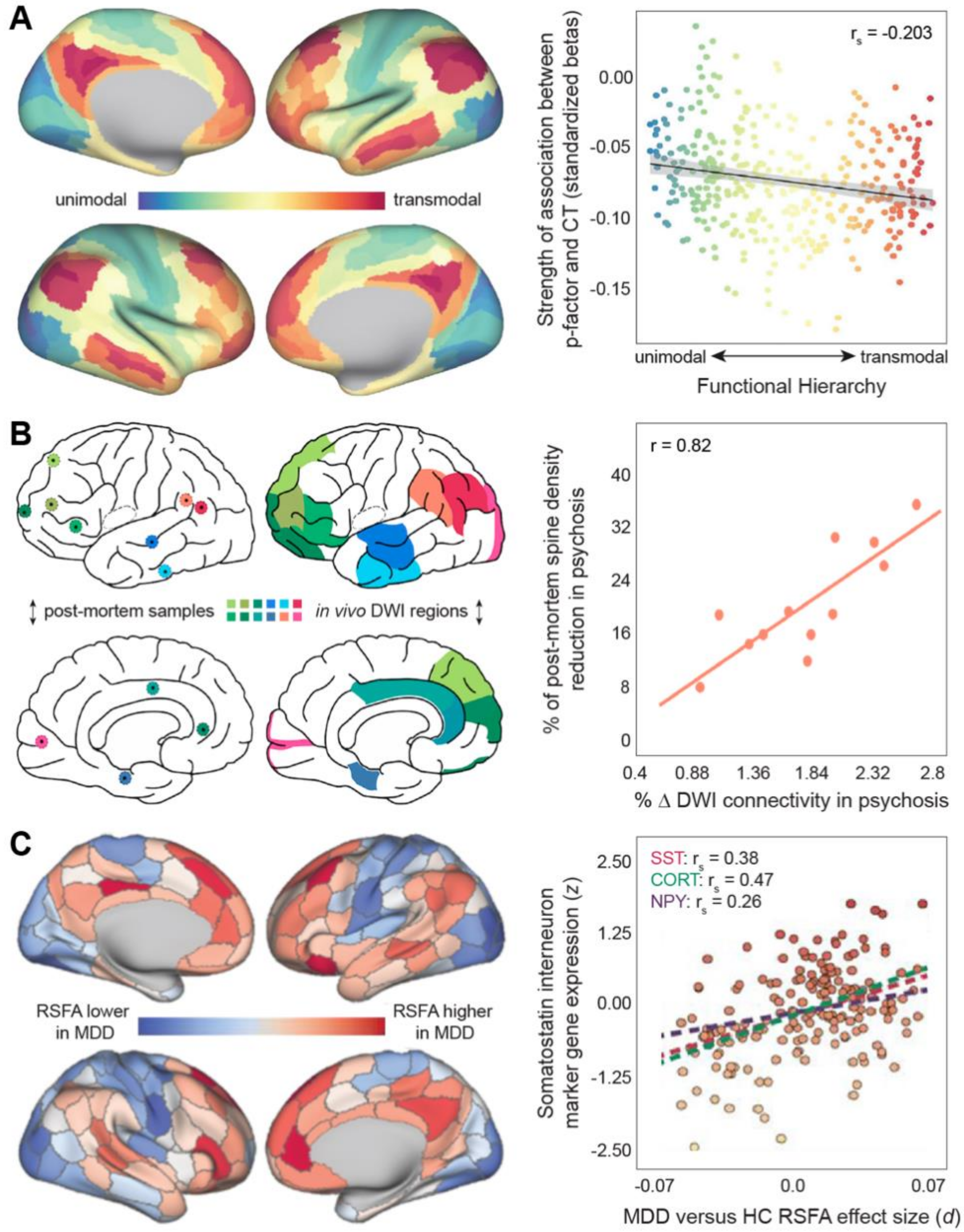

A
unimodal
transmodal
r_s = -0.203
Strength of association between p-factor and CT (standardized betas)
0.00
-0.05
-0.10
-0.15
unimodal
transmodal
Functional Hierarchy
B
post-mortem samples
in vivo DWI regions
r = 0.82
% of post-mortem spine density reduction in psychosis
40
32
24
16
8
0
0.4
0.88
1.36
1.84
2.32
2.8
% Δ DWI connectivity in psychosis
C
RSFA lower in MDD
RSFA higher in MDD
SST: r_s = 0.38
CORT: r_s = 0.47
NPY: r_s = 0.26
Somatostatin interneuron marker gene expression (z)
2.50
1.25
0.00
-1.25
-2.50
-0.07
0.0
0.07
MDD versus HC RSFA effect size (d)

Figure 2-7. 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 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. 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/.

Future Exploration of the Sensorimotor-Association Axis of Human Neurodevelopment: Intrinsic Drivers, Individualization, and Interventions

Though the human cortex exhibits nearly unparalleled complexity, the S-A axis represents one important large-scale 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. Further, 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 yet enhanced 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. Though only cortical maturation was considered, subcortical regions that execute heterogeneous, multi-order functions including the striatum, thalamus, hippocampus, and cerebellum display regional sensorimotor-association 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 2-2)**. 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.

Box 2-2. 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 due to interactions amongst 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 alternate 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 impact the timing and the nature of human developmental plasticity? Are hormonal effects spatially localized, sex-specific, or variable amongst 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?

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CHAPTER 3: INTRINSIC ACTIVITY DEVELOPMENT UNFOLDS ALONG A SENSORIMOTOR-ASSOCIATION CORTICAL AXIS IN YOUTH

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Abstract

Animal studies of neurodevelopment have shown that recordings of intrinsic cortical activity evolve from synchronized and high amplitude to sparse and low amplitude as plasticity declines and the cortex matures. Leveraging resting-state functional MRI (fMRI) data from 1,033 youths (ages 8–23 years), we find that this stereotyped refinement of intrinsic activity occurs during human development and provides evidence for a cortical gradient of neurodevelopmental change. Declines in the amplitude of intrinsic fMRI activity were initiated heterochronously across regions and were coupled to the maturation of intracortical myelin, a developmental plasticity regulator. Spatiotemporal variability in regional developmental trajectories was organized along a hierarchical, sensorimotor–association cortical axis from ages 8 to 18. The sensorimotor–association axis furthermore captured variation in associations between youths' neighborhood environments and intrinsic fMRI activity; associations suggest that the effects of environmental disadvantage on the maturing brain diverge most across this axis during midadolescence. These results uncover a hierarchical neurodevelopmental axis and offer insight into the progression of cortical plasticity in humans.

Introduction

Elucidating how developmental plasticity spatially and temporally progresses across the human cortex has implications for understanding healthy brain development and windows of developmental vulnerability and opportunity (Cooper and Mackey, 2016; Sisk and Gee, 2022; Sydnor and Satterthwaite, 2023) . In particular, demarcating regionally specific periods of enhanced and diminished malleability can provide insight into which cortical regions will be maximally impacted by insults and interventions at distinct developmental stages. Prior studies have therefore aimed to uncover the spatiotemporal evolution of neurodevelopmental change across the cortical mantle. Such studies have consistently shown that postnatal neurodevelopment is heterochronous, with sensory and motor cortices maturing earlier than association cortices (Sydnor et al., 2021) ; this temporal trend has been shown for cortical volume (Bethlehem et al., 2022; Gogtay et al., 2004) , connectivity (Dong et al., 2021) , myelination (Grydeland et al., 2019; Paquola et al., 2019) and cellular properties (Huttenlocher and Dabholkar, 1997; Larsen and Luna, 2018). However, beyond this coarse division, there is marked spatiotemporal developmental variability that remains undercharacterized. We recently proposed a unifying framework that contextualizes asynchronous maturation between sensorimotor and association cortices as two ends of a continuous axis of neurodevelopmental plasticity (Sydnor et al., 2021). This framework posits that during childhood and adolescence, developmental plasticity progresses along the sensorimotor–association (S–A) cortical axis: a dominant, hierarchical axis of human brain organization along which diverse neurobiological properties are patterned (García-Cabezas et al., 2019; Hilgetag et al., 2022; Huntenburg et al., 2018; Margulies et al., 2016; Sydnor et al., 2021).

In the present study, we aimed to empirically evaluate our hypothesis that plasticity unfolds along the S–A axis by studying the developmental refinement of intrinsic (that is, spontaneous or non-evoked) activity, a putative functional marker of local plasticity described in animal models. Studies of the developing murine sensory cortex have provided evidence that a potentiation of high-amplitude, synchronized intrinsic activity characterizes earlier stages of development with heightened plasticity (Lensjø et al., 2017; Martini et al., 2021; Reh et al., 2020). As plasticity declines and the cortex matures, intrinsic activity evolves from prevalent and globally synchronized to suppressed and sparse, becoming more heterogeneously distributed in space and time in the adult cortex (Frye and MacLean, 2016; Golshani et al., 2009; Martini et al., 2021; Nakazawa et al., 2020). This stereotyped refinement of intrinsic activity has been linked to maturational increases in inhibitory neurotransmission and intracortical myelination, two plasticity-regulating processes that refine cortical circuit dynamics (Chini et al., 2022; Fagiolini and Hensch, 2000; Lensjø et al., 2017; McGee et al., 2005; Toyoizumi et al., 2013). Accordingly, this stereotyped refinement of intrinsic activity provides an ongoing readout of local circuit plasticity, with more correlated, high-amplitude spontaneous neural recordings serving as a functional hallmark of still-malleable cortices (Laumann and Snyder, 2021; Lensjø et al., 2017; Luhmann et al., 2016; Reh et al., 2020). Importantly, intrinsic cortical activity can be studied non-invasively with resting-state functional MRI (fMRI), which provides an opportunity to characterize the spatiotemporal maturation of a potential plasticity signature in the human brain.

Simultaneous fMRI with electrophysiology or calcium imaging has demonstrated how low-frequency fluctuations in the resting fMRI blood oxygen level-dependent (BOLD) signal are coupled with changes in intrinsic neural activity patterns (Lake et al., 2020; Ma et al., 2022; Magri et al., 2012; Shmuel and Leopold, 2008). A greater level of intrinsic activity and more synchronized activity—activity characteristic of immature, plastic cortices—can increase the amplitude of low-frequency BOLD fluctuations. It has therefore been hypothesized that the amplitude of low-frequency fluctuations (Yu-Feng et al., 2007), or BOLD 'fluctuation amplitude', will be higher when cortical plasticity is enhanced (Fair and Yeo, 2020; Laumann and Snyder, 2021). Indeed, experimentally manipulating biological regulators of developmental plasticity has been shown to elicit changes in local BOLD fluctuations (Markicevic et al., 2020). Moreover, in a recent landmark study of human brain plasticity, deprivation-induced somatomotor cortex plasticity produced local increases in BOLD fluctuation amplitude (Newbold et al., 2020).

Here, we harness BOLD fluctuation amplitude to index spatially localized, age-dependent changes in intrinsic activity and test the overarching framework that developmental programs cascade hierarchically along the cortex's S–A axis during youth. We expected that the development of fluctuation amplitude would be primarily characterized by heterochronous declines along the S–A axis. Moreover, we predicted that declines in fluctuation amplitude would be influenced by the maturation of intracortical myelin, which constrains plasticity in developing neural circuits and refines spontaneous firing (McGee et al., 2005). Last, we hypothesized that youths' developmental environments would impact the maturation of this measure. Instrumental work in animal models has shown that enriched (versus deprived) developmental environments affect the maturation of plasticity-regulating mechanisms, including intracortical myelin (Hinton et al., 2019), inhibitory interneurons (Greifzu et al., 2014) and perineural nets (Favuzzi et al., 2017), typically in a manner that facilitates continued plasticity (Tooley et al., 2021). Data from human studies have additionally shown that individuals raised in more socioeconomically disadvantaged environments exhibit characteristics that could reflect a faster pace of biological and brain development (Colich et al., 2020; McDermott et al., 2021; Tooley et al., 2021). Cross-species findings thus indicate that environmental deprivation may accelerate cortical development and prematurely limit plasticity. We explore this possibility by studying whether greater environmental disadvantage is associated with functional markers suggestive of lower cortical plasticity during youth. As described below, our in vivo analysis of a signature of neurodevelopmental plasticity illuminated by animal models reveals that the S–A axis captures not only the hierarchical layout of diverse cortical properties but also the temporal unfolding of developmental change and effects of the developmental environment

Results

We studied how intrinsic activity is refined across the developing cortex in a cross-sectional sample of 1,033 youths aged 8–23 years old. Fluctuation amplitude, computed as the average power of low-frequency (0.01–0.08 Hz) fluctuations in the time-varying fMRI signal, was used to index the overall level and coherence of intrinsic cortical activity. Greater and more synchronized neural activity increases the power of neural recordings and has been shown to increase the amplitude of BOLD fluctuations (Ma et al., 2022; Magri et al., 2012; Shmuel and Leopold, 2008). To characterize maturational changes in BOLD fluctuation amplitude in individual cortical regions, we fit region-specific generalized additive models (GAMs) with a smooth term for age; sex and in-scanner head motion were included as linear covariates. Each GAM estimates a smooth function (the model age fit) that describes the relationship between fluctuation amplitude and age, thereby modeling a region's developmental trajectory. The first derivative of this smooth function represents the rate of change in fluctuation amplitude at a given developmental timepoint. We tested whether GAM-derived developmental effects provide support for a hierarchical neurodevelopmental framework. We also confirmed that developmental effects were robust to controls for in-scanner motion, medication use, vascular effects, T2* signal strength, global BOLD properties and cortical atlas.

Development of intrinsic fMRI activity varies across the cortex

Fluctuation amplitude significantly changed with age in the developmental window studied in nearly all cortical regions (false discovery rate-adjusted P value (P_{FDR}) < 0.05 in 95% of regions). To provide insight into the overall magnitude and direction of regional age effects, we calculated the variance explained by age (partial R^2; the effect magnitude) and the sign of the average derivative of the age fit (the effect direction). The magnitude and direction of age effects differed across the cortex (**Figure 3-1a**), signifying that there is variability in the maturation of intrinsic activity across the developing cortex. Indeed, by visualizing age fits across regions, we observed a cortical continuum of developmental trajectories ranging from large and prolonged decreases to inverted U-shaped curves (**Figure 3-1b**). Nearly all sensory regions showed continuous declines in fluctuation amplitude from early childhood to adolescence, as illustrated by the model fit for area V1 (**Figure 3-1c**), which significantly decreased until the age of 18 years. This age fit is consistent with a progressive reduction, sparsification or decorrelation of non-evoked cortical activity with age. By contrast, in select cortical regions such as the midcingulate gyrus (**Figure 3-1c**), fluctuation amplitude only began to decline in later childhood or early adolescence. Finally, many regions in transmodal association cortex (for example, the dorsolateral prefrontal cortex; **Figure 3-1c**) displayed significant increases in fluctuation amplitude until early to midadolescence, typically followed by amplitude decreases. This inverted U-shaped trajectory suggests that there is heightened, synchronized activity in transmodal cortices at the start of adolescence.

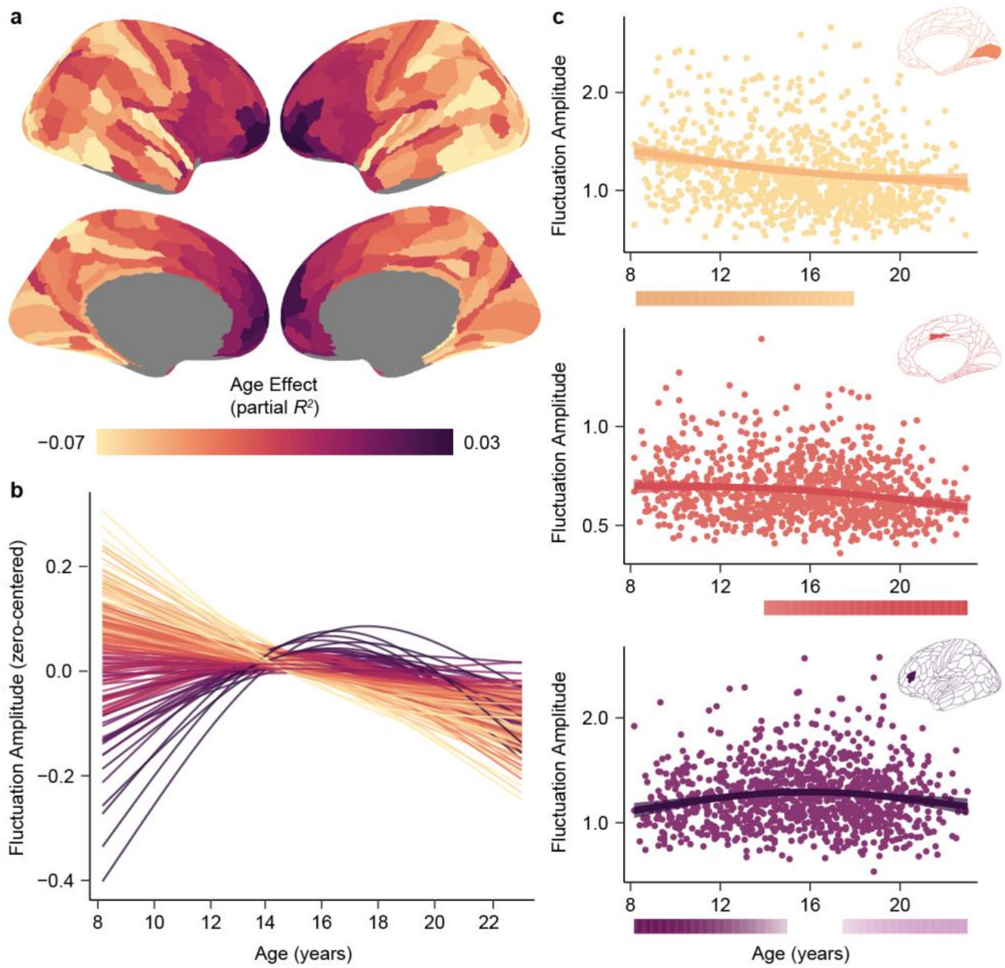

Figure 3-1. Developmental Refinement of Fluctuation Amplitude Varies Across the Cortex
a) The heterogeneous patterning of fluctuation amplitude age effects (partial R^2) is displayed across the cortical surface. **b**) Fluctuation amplitude developmental trajectories (zero-centered GAM smooth functions) are shown for all left hemisphere cortical regions, revealing a spectrum of age-related change. Trajectories are colored by each region's age effect using the color bar in **a**. **c**) Fluctuation amplitude developmental trajectories are shown overlaid on data from all participants for the primary visual cortex (area V1; top, yellow), the midcingulate gyrus (area p24pr; middle, pink) and the dorsolateral prefrontal cortex (area IFSa; bottom, purple). Regional trajectories

represent the GAM-predicted fluctuation amplitude value at each age with a 95% credible interval band. The color bars below each regional plot depict the age window(s) wherein fluctuation amplitude significantly changed in that region, shaded by the rate of change, as determined by the first derivative of the age function. Windows of significant age-related change are developmental periods wherein the simultaneous 95% confidence interval for the first derivative did not include 0 (two sided).

We examined whether regional age fits differed by sex or could be accounted for by differences in participant pubertal stage. We first tested for age-by-sex interactions in each cortical region and found no significant effects ($P_{\mathrm{FDR}} > 0.05$ for all interactions), indicating that the timing of developmental change did not significantly differ between males and females in this age range. Next, we explored the potential impact of puberty by including participant pubertal stage (prepubertal, midpubertal or postpubertal) as a factor in regional GAMs. While the linear effects of pubertal stage on fluctuation amplitude tended to cohere with the observed age effects (positive effects in frontal transmodal regions and negative effects in posterior unimodal regions), pubertal stage did not explain significant variance in fluctuation amplitude above and beyond age in any cortical region ($P_{\mathrm{FDR}} > 0.05$ for all pubertal stage effects). Moreover, accounting for pubertal stage did not alter regional age fits or age effects; age effects were highly correlated when age was modeled alone and when both age and pubertal stage were modeled together ($r = 0.89$). These findings suggest that age-dependent changes in intrinsic fMRI activity amplitude are heterogeneous across the cortex, are present across sexes and are not driven by pubertal stage. More broadly, the present results establish that maturational trajectories diverge between sensory and association cortices.

Development of intrinsic fMRI activity mirrors myelin maturation

Prior work in animal models has shown that as the cortex transitions from plastic to mature, intrinsic cortical activity develops from prevalent and synchronized, producing high-amplitude neural recordings, to sparse and decorrelated, producing lower-amplitude recordings. These observations suggest that age-dependent changes in the amplitude of BOLD fluctuations could, in part, reflect changes in cortical plasticity (Laumann and Snyder, 2021; Newbold et al., 2020). We therefore endeavored to understand whether the development of fluctuation amplitude is related to the maturation of intracortical myelin, a key regulator and restrictor of cortical plasticity.

We leveraged the recent work of Baum et al. (2022) who studied the development of the T1-weighted/T2-weighted (T1w/T2w) ratio, a structural MRI measure sensitive to cortical myelin content, in an independent sample of youths ($n = 628$; 8–21 years old). These authors quantified the magnitude of age-related myelination (the partial R^2 of the T1w/T2w ratio age effect) and demarcated the age of maximal myelin growth (the age with a maximal rate of T1w/T2w ratio increase) within individual cortical regions. In comparing T1w/T2w ratio and fluctuation amplitude neurodevelopmental features, we unveiled substantial spatial and temporal correspondence between the refinement of these measures with age. Age-related changes (indexed by the signed partial R^2) in these two putative plasticity-sensitive measures were strongly inversely correlated across cortical regions ($r = -0.67$, spin test P value ($P_{\text{spin}}) = 0.00045$), with regions showing larger increases in myelin content from childhood to early adulthood also undergoing larger decreases in BOLD signal amplitude (**Figure 3-2a,b**). This finding accords with ample evidence of causal, bidirectional relationships between changes in neural activity patterns and changes in myelination (de Faria et al., 2021; Kato et al., 2020) and suggests a possible mechanistic link between microstructural refinement and changes in circuit activity during brain development.

To further study this link, we investigated whether there was a temporal relationship between increases in the T1w/T2w ratio and decreases in fluctuation amplitude. We first quantified the age at which fluctuation amplitude began to significantly decrease in each region and found that initial decreases in fluctuation amplitude were staggered heterochronously across the cortex, with select medial prefrontal and frontopolar regions showing no period of significant decline. Nearly half of regions (46%) showed a significant decrease in fluctuation amplitude at age 8, implying that BOLD amplitude in these regions likely begins to decline before the youngest age studied in this dataset. Across the rest of the cortex, however, fluctuation amplitude began to decline later in youth; in these cortices, a greater delay in the onset of fluctuation amplitude decline was associated with a later peak rate of T1w/T2w-indexed cortical myelin growth ($r = 0.64$, $P_{\text{spin}} = 0.01565$; **Figure 3-2c,d**). Notably, ages of fluctuation amplitude decrease onset and maximal T1w/T2w increase were not simply correlated but also showed a minimal temporal offset in years, indicating that they were closely coupled in time (average offset of 0.7 years; see also the best fit line for **Figure 3-2d**). Taken together, these results appear to link later-onset reductions in the amplitude of spontaneous fMRI activity to delayed maturation of a main regulator of developmental plasticity.

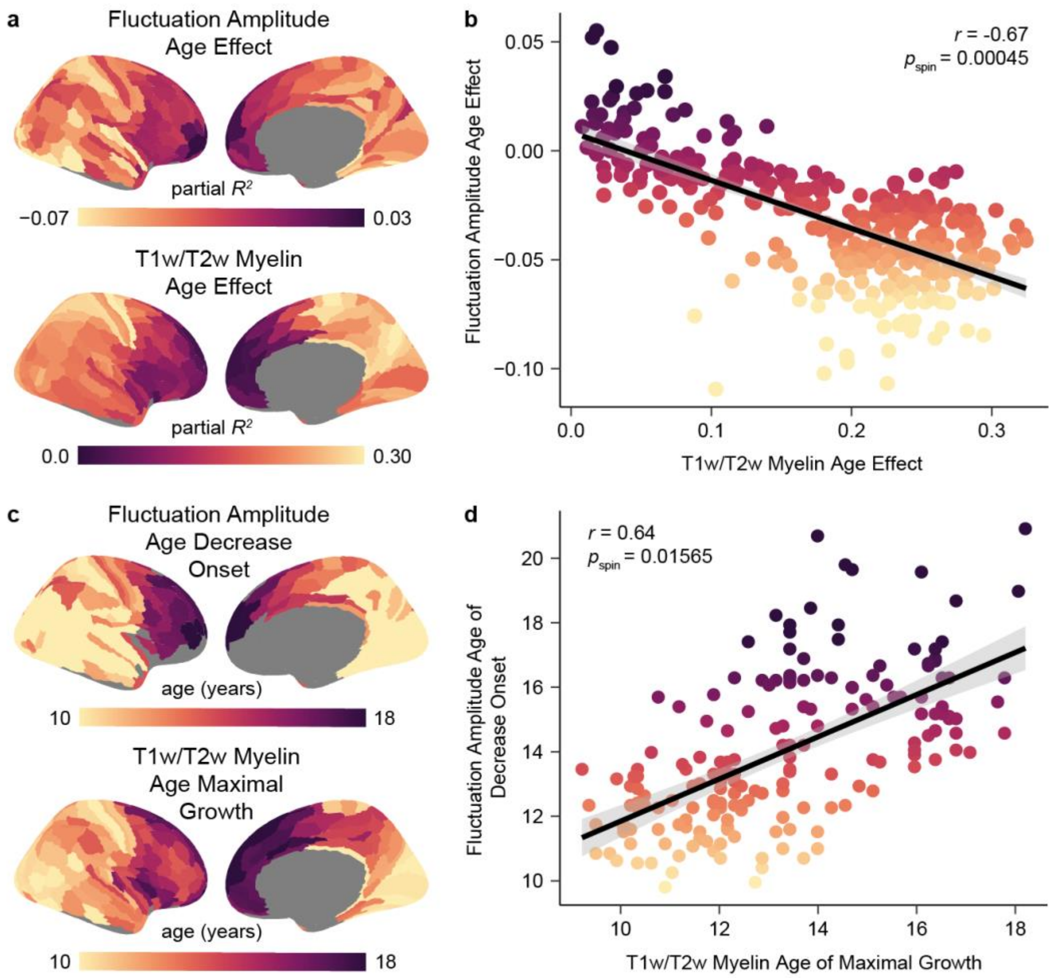

Figure 3-2. Development of Fluctuation Amplitude Spatially and Temporally Parallels Cortical T1w/T2w Ratio Development

a) The cortical distribution of fluctuation amplitude age effects closely resembles the distribution of T1w/T2w ratio age effects, suggesting interdependent refinement of cortical function and microstructure in youth. Age effects (partial R^2) are signed by the sign of the average first derivative of the age smooth function. **b**) Regions that show larger declines in fluctuation amplitude during childhood and adolescence additionally exhibit greater increases in the cortical T1w/T2w ratio in this developmental period. A Spearman's correlation between age effects for these two measures was significant ($r = -0.67$, $P_{spin} = 0.00045$) as assessed by a conservative spin-based spatial rotation test. The negative linear fit between these measures is shown with a 95% confidence interval. **c**) Maps depicting the age at which fluctuation amplitude began to decrease (earliest significant negative derivative of the age function) and the age of maximal T1w/T2w-indexed myelin growth (largest significant derivative of the age function) reveal temporal similarity in the development of these two measures in youth. **d**) Across regions, the age at which fluctuation amplitude began to significantly decrease is closely coupled to the age at which the T1w/T2w ratio shows a maximal rate of increase, providing evidence for temporal coordination between functional and structural maturation. A Spearman's correlation between these temporal measures was significant ($r = 0.64$, $P_{spin} = 0.01565$) as assessed by the spatial rotation test procedure. The positive linear relationship between these two measures is plotted with a 95% confidence interval.

Developmental variability is patterned along the S–A axis

A primary goal of this work was to systematically assess whether the sequence of neurodevelopmental change progresses hierarchically across the cortical mantle. Having observed that fluctuation amplitude development tightly paralleled development of a structural plasticity regulator and broadly diverged between sensorimotor and association cortices, we next sought to determine whether developmental patterns spatially conformed to the S–A axis4 . The S–A axis is a prominent axis of cortical organization that is rank ordered from primary cortices supporting sensation and movement (lowest ranks), to multimodal cortices supporting multisensory integration and attention (middle ranks), to transmodal cortices supporting cognitive control and socioeomotional functioning (highest ranks). This axis captures concerted variability in the layout of heterogeneous structural, metabolic, cellular, molecular, transcriptomic and electrophysiological properties across the cortex (Burt et al., 2018; García-Cabezas et al., 2019; Hilgetag et al., 2022; Huntenburg et al., 2018; Margulies et al., 2016; Sydnor et al., 2021). Moreover, the S–A axis is spatially coupled to the brain's anatomical (Burt et al., 2018), functional (Margulies et al., 2016) and evolutionary (Hill et al., 2010) hierarchies; thus, each cortical region's rank in the axis reflects its relative position in a global cortical hierarchy.

We first examined whether interregional differences in the development of fluctuation amplitude reflected interregional differences in S–A axis rank. Age effects and S–A axis ranks were correlated across regions ($r = 0.54$, $P_{spin} = 0.00215$), with large negative age effects characterizing the S–A axis's sensorimotor pole and smaller positive age effects distinguishing its association pole. We additionally observed continuous variation in the age at which fluctuation amplitude began to significantly decrease along this organizational axis. When considering regions that showed an initial onset of decline within the age range studied as above, we found that fluctuation amplitude began to decline at a progressively later age in regions ranked higher in the S–A axis ($r = 0.68$, $P_{\text{spin}} = 0.00110$). Hence, cortices at the top of the cortical hierarchy exhibit the smallest and latest-onset declines in the amplitude of intrinsic fMRI fluctuations during childhood and adolescence.

Following this initial analysis, we further probed the extent to which maturational trajectories differed as a function of S–A axis rank by mapping the principal spatial axis of fluctuation amplitude development. To accomplish this mapping, we performed a principal-component analysis (PCA) on the age fits estimated by regional GAMs (**Figure 3-1b**); this approach considers the entire fluctuation amplitude developmental trajectory rather than only one property of the age fit (for example, the age at which it starts to decline). The first PC from this PCA explained 87% of the variance in developmental profiles and can therefore be conceptualized as the principal axis of intrinsic fMRI activity development. This principal developmental axis closely resembled the S–A axis (**Figure 3-3a**). Accordingly, regional loadings onto the principal developmental axis were very highly correlated with regional S–A axis ranks ($r = 0.70$, $P_{\text{spin}} < 0.0001$; **Figure 3-3b**), demonstrating that a substantial degree of spatiotemporal variance in developmental profiles was explained by the S–A axis.

The PCA of developmental fits suggests that the spatial and temporal maturation of intrinsic cortical activity conforms to the hierarchical organization of the cortex. In support of this conclusion, we confirmed that principal developmental axis loadings additionally correlated with anatomical ($r = -0.61$)

(Burt et al., 2018), functional ($r = 0.60$) (Margulies et al., 2016) and evolutionary ($r = 0.32$) (Hill et al., 2010) cortical hierarchies. However, the principal developmental axis was significantly more correlated with the S–A axis than with these three hierarchies, which were defined using unimodal data ($P < 0.001$ for all three statistical tests comparing the magnitude of two dependent, overlapping corrections). Neurodevelopmental trajectories were therefore more parsimoniously captured by the S–A axis, which combines information from all three cortical hierarchies and multiple additional data types. To directly illustrate the manner in which developmental trajectories for fluctuation amplitude evolve from the sensorimotor to the association end of the S–A axis, we divided the axis into 10 decile bins and averaged age fits across all regions in a bin. The continuous spectrum of developmental trajectories visible at the regional level (**Figure 3-1b**) was recapitulated by S–A axis deciles (**Figure 3-3c**).

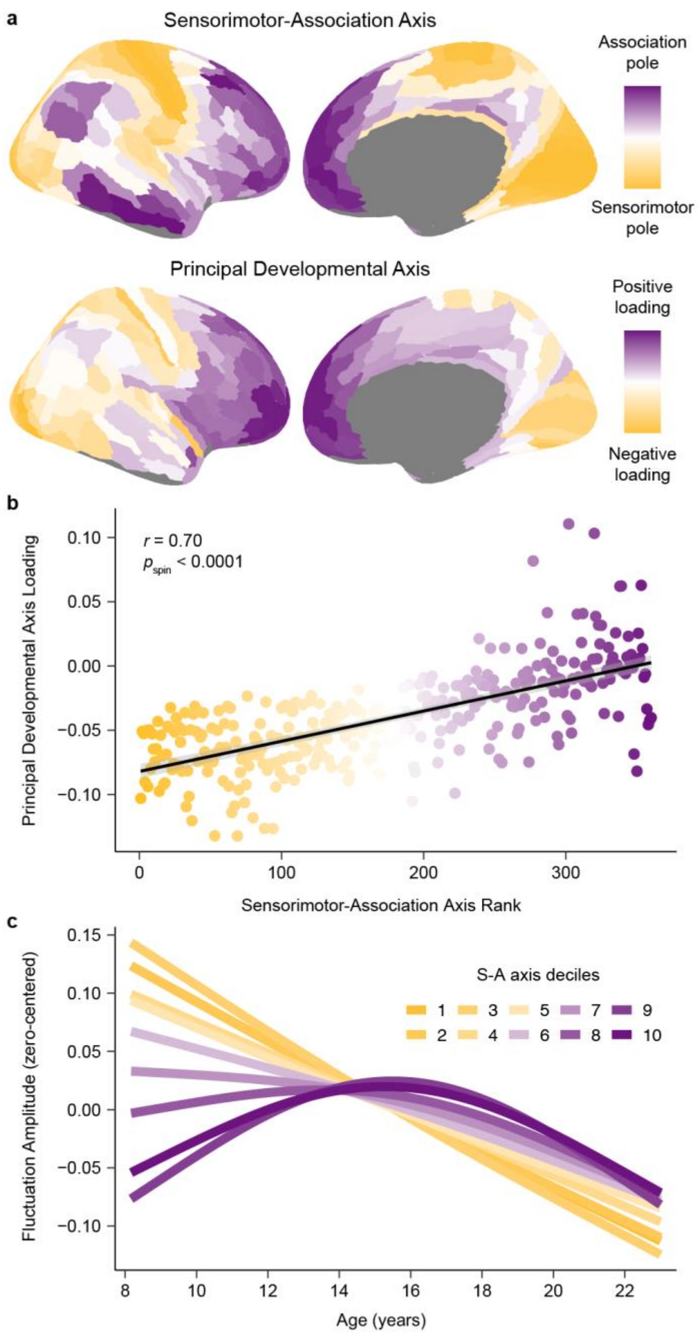
a
Sensorimotor-Association Axis
Association pole
Sensorimotor pole
Principal Developmental Axis
Positive loading
Negative loading
b
r = 0.70
p_spin < 0.0001
Principal Developmental Axis Loading
0.10
0.05
0.00
−0.05
−0.10
0
100
200
300
Sensorimotor-Association Axis Rank
c
S-A axis deciles
1
2
3
4
5
6
7
8
9
10
Fluctuation Amplitude (zero-centered)
0.15
0.10
0.05
0.00
−0.05
−0.10
8
10
12
14
16
18
20
22
Age (years)

Figure 3-3. The Principal Axis of Fluctuation Amplitude Development Exhibits Convergent Spatial Embedding with the S-A Axis

a) The principal axis of fluctuation amplitude development closely resembles the S–A axis, illustrating that the spatiotemporal maturation of intrinsic fMRI activity amplitude aligns to the brain's global cortical hierarchy. The S–A axis, derived in Sydnor et al.4, is a dominant axis of cortical feature organization that spans continuously from primary and unimodal sensory and motor cortices (sensorimotor pole; dark yellow) to transmodal heteromodal and paralimbic association cortices (association pole; dark purple). The principal developmental axis is the first component from a PCA conducted on regional fluctuation amplitude maturational trajectories. This component quantitatively captures cortex-wide differences in maturational patterns along a unidimensional spatial gradient. **b**) Across the cortex, principal developmental axis loadings are strongly related to S–A axis ranks (linear association shown with a 95% confidence interval). The Spearman's correlation between these two measures, which represent developmental and organizational maps, was significant ($r = 0.70$, $P_{spin} < 0.0001$), as assessed by a conservative spin-based spatial rotation test. **c**) Average model fits depicting the relationship between fluctuation amplitude and age are shown for deciles of the S–A axis. To generate average decile fits, the S–A axis was divided into 10 bins each consisting of 33 or 34 regions, and age smooth functions were averaged across all regions in a bin. The first decile (darkest yellow; linear decline) represents the sensorimotor pole of the axis, and the tenth decile (darkest purple; inverted U) represents the association pole of the axis. Maturational trajectories diverged most between S–A axis poles and varied continuously between them.

Development is hierarchical through adolescence

The above results underscore that between the ages of 8 and 23 years, age-related changes in fMRI-indexed intrinsic activity amplitude are patterned along the brain's S–A axis. We next aimed to elucidate whether this neurodevelopmental pattern was most pronounced during a specific age range or if it was equally present across all ages studied. To explore these possibilities, we first calculated each cortical region's rate of change in fluctuation amplitude at 1-month intervals between ages 8 and 23 years. Notably, visualizing regional rates of change across the S–A axis (**Figure 3-4a**) confirmed that preadolescent increases in fluctuation amplitude were uniquely confined to higher-order association cortices. Using these data, we next performed an age-resolved analysis, where at each 1-month interval, we calculated the correlation between regional rates of amplitude change and regional S–A axis ranks. This procedure generates age-specific correlation values that quantify the extent to which maturational change is spatially ordered along the hierarchy of the S–A axis at a given developmental timepoint. This analysis confirmed a robust correlation between developmental change and S–A axis rank from age 8 to 17 years (**Figure 3-4b,c**). A maximal correlation value of $r = 0.68$ (95% credible interval of 0.66 to 0.70) was observed at age 15.0 years (95% credible interval of 14.7 to 15.3 years), indicating peak alignment between neurodevelopment and the S–A axis in midadolescence. However, following this peak, the correlation between regional developmental effects and S–A axis position rapidly declined, dropping to 0 by age 19.3 years (95% credible interval of 18.7 to 20.2 years). These findings suggest that the brain's developmental program is hierarchical through late adolescence. Following adolescence, however, there may be a programmed switch in the spatial organization of subsequent age-related change.

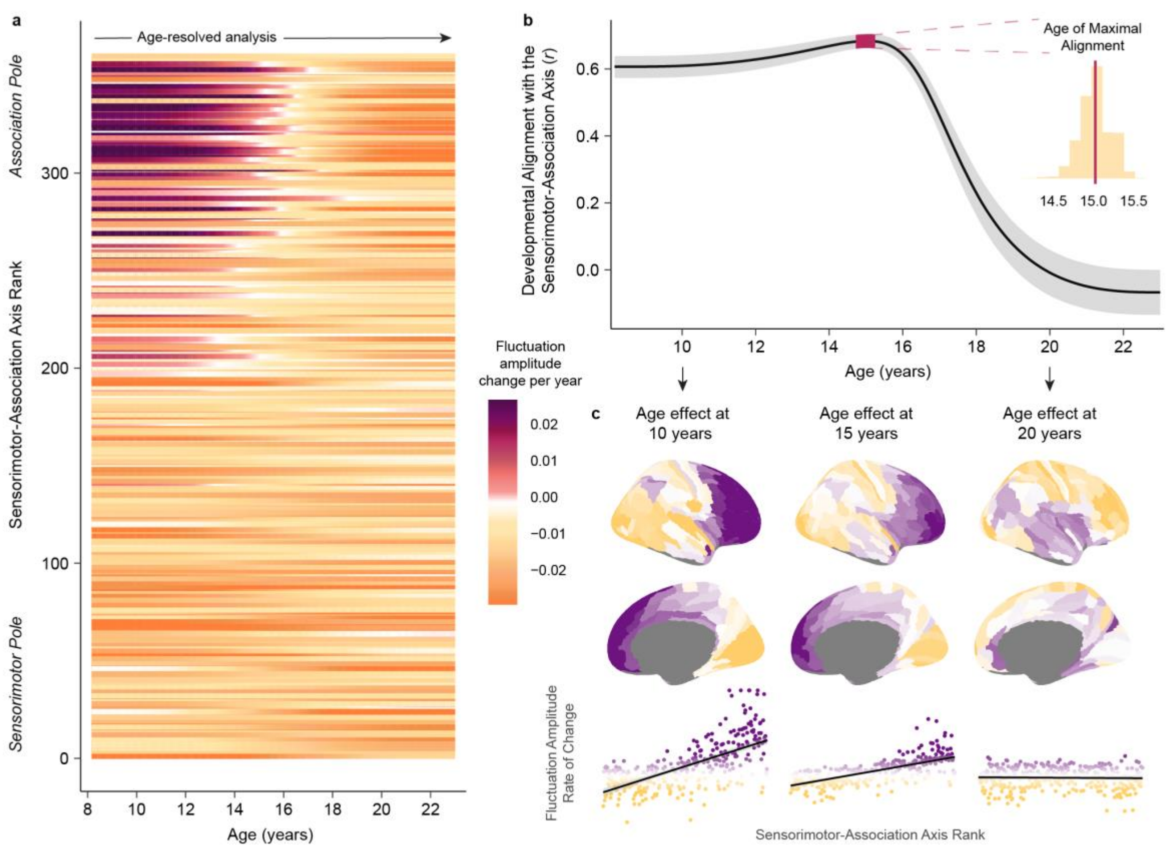

Figure 3-4. Neurodevelopment Unfolds Along the S-A Axis Until Late Adolescence
a) The rate and direction of developmental change in fluctuation amplitude is displayed for each cortical region from ages 8 to 23 years. Regions are ordered along the y axis by S–A axis rank. Fluctuation amplitude rate of change, expressed as the change in amplitude per year, was estimated from the first derivative of each region's GAM smooth function for age. Cortical regions near the association pole of the S–A axis exhibit unique increases in fluctuation amplitude through childhood that culminate in adolescent BOLD amplitude peaks. **b**) Developmental change in intrinsic fMRI activity amplitude aligns with the S–A axis from childhood until late adolescence. The line plot displays age-specific correlation values (r) between regional rates of fluctuation amplitude change and regional S–A axis ranks from ages 8 to 23 years. To obtain reliable estimates of this correlation value at each age, we sampled 10,000 draws from the posterior derivative of each region's age smooth function and quantified age-specific correlations between derivatives and S–A axis ranks for each draw. The median correlation value obtained across all draws is depicted by the black line, and the 95% credible interval around this value is represented by the gray band. We additionally determined the age of maximal alignment between fluctuation amplitude change and S–A axis rank for all 10,000 draws. The 95% credible interval for the age of maximal alignment is depicted on the line plot by the pink band. The full distribution of ages obtained from all draws is portrayed in the inset histogram. **c**) Age-specific developmental effects (first derivative maps) are visualized on the cortical surface at ages 10, 15 and 20 years. Maps are shown above scatter plots that depict the linear relationship (with a 95% confidence interval band) between regional S–A axis ranks and regional age-specific rates of fluctuation amplitude change. Scatter plot points are colored by age-specific rates of change. Developmental refinement of fluctuation amplitude is governed by the S–A axis at ages 10 and 15 years. By age 20, further refinement of fluctuation amplitude is unrelated to the S–A axis.

Development results are robust to methodological variation

To ensure that the developmental effects observed were robust to methodological variation and potential confounds, we performed six sensitivity analyses. We evaluated if age-dependent changes in regional fluctuation amplitude were driven by in-scanner head motion, medication use, local cerebral blood flow, regional mean signal intensity, global amplitude differences or the choice of cortical atlas. In the first two sensitivity analyses, regional GAMs were rerun in two-thirds of the sample with the lowest in-scanner head motion ($n = 690$; **Figure 3-5a**) and in a sample that excluded individuals with current psychoactive medication use or a history of psychiatric hospitalization ($n = 893$; **Figure 3-5b**). In the next two sensitivity analyses, regional GAMs were refit while additionally controlling for regional cerebral blood flow estimated from arterial spin labeling (ASL) data ($n = 1{,}002$; **Figure 3-5c**) or regional mean

T2* signal intensity (**Figure 3-5d**). In the final two sensitivity analyses, regional GAMs were refit with whole-brain mean-normalized fluctuation amplitude (**Figure 3-5e**) or fluctuation amplitude averaged within Schaefer-400 atlas regions (**Figure 3-5f**) as the dependent variables.

In each of the six sensitivity analyses, region-specific fluctuation amplitude maturational trajectories closely mirrored the developmental fits from the main analysis, with negative age effects observed in most cortices but positive effects seen in select transmodal association cortices. Consequently, regardless of the sample used or controls performed, a cortical region's age effect was fundamentally and significantly (all $P_{spin} < 0.05$) related to its position in the S–A axis (main analysis: $r = 0.54$; low-motion sample: $r = 0.56$; no psychiatric treatment: $r = 0.51$; vascular control: $r = 0.51$; T2* signal control: $r = 0.49$; mean normalization: $r = 0.66$; atlas replication: $r = 0.43$). Furthermore, for all sensitivity analyses, the age-resolved analysis confirmed a strong correlation between the rate of fluctuation amplitude change and S–A axis rank from childhood to late adolescence, with the peak age of neurodevelopmental alignment to this axis occurring during adolescence. These analyses verify that findings concerning the nature and patterning of age-dependent changes in spontaneous cortical fMRI activity are robust to methodological variation.

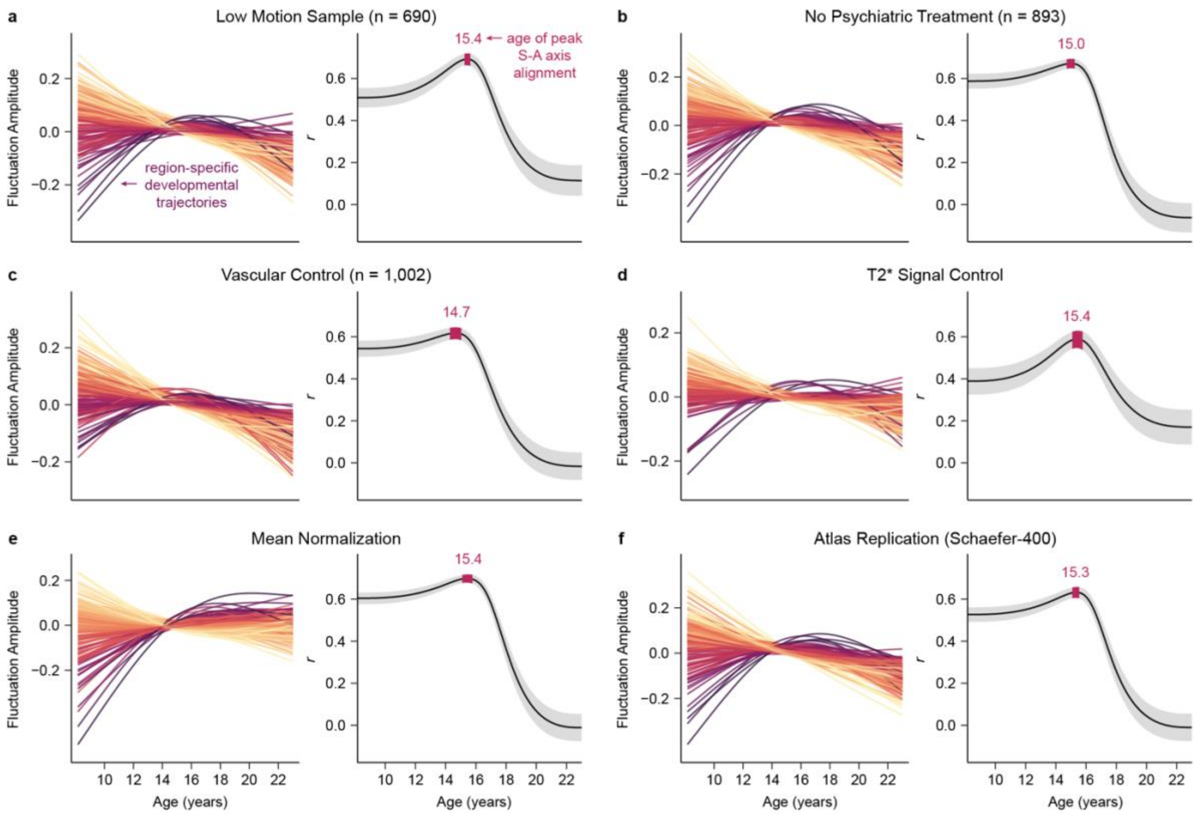

Figure 3-5. Region-specific and Cortex-wide Developmental Patterns are Robust to Methodological Variation **a**–**f**) Key results are shown for each of the six sensitivity analyses performed. For each analysis, the left plot shows fluctuation amplitude developmental trajectories (zero-centered GAM smooth functions) for left hemisphere regions colored by age effects. The right plot presents the age-resolved analysis of the correlation between developmental change in fluctuation amplitude and S–A axis rank from ages 8 to 23 years. Both the medial correlation value (r) and the 95% credible interval around this value are shown for the age-resolved analysis. All six sensitivity analyses yielded convergent region-specific and cortex-wide results, confirming that our developmental findings were not being driven by head motion in the scanner (**a**), the use of psychotropic medications (**b**), age-related changes in cerebrovascular perfusion (**c**), interscan differences in T2* signal strength (**d**), global effects (**e**) or the specific atlas used for cortical parcellation (**f**).

Environmental effects vary along the S–A axis in adolescence

During brain maturation, environmental inputs can interact with neurodevelopmental malleability to become cortically embedded, suggesting that variability in children's environments may be reflected in individual differences in development-linked brain changes. We therefore explored whether interindividual differences in cortical intrinsic fMRI activity may be partly explained by variability in youths' neighborhood environments. Multivariate features of each child's neighborhood socioeconomic environment were summarized using a single previously published factor score (Moore et al., 2016). Higher factor scores indicate that an individual lived in a neighborhood with a higher median family income, lower population density, fewer vacant housing lots, a greater percentage of residents who are married, employed and high school educated and a lower percentage of residents in poverty (**Figure 3-6a**). We focused on the neighborhood environment specifically, as the factor score robustly aggregates across a wide range of measures related to the physical, social and cognitive environment, captures socioeconomic inequality at the societal and systems levels and has been shown to account for individual differences in brain function and behavior beyond the household environment (Moore et al., 2016; Tooley et al., 2020).

We first modeled linear associations between neighborhood environment factor scores and regional fluctuation amplitude using GAMs while controlling for developmental effects (age) and other covariates (in-scanner motion and sex). Forty-two percent of cortical regions showed a significant association between fluctuation amplitude and the neighborhood environment ($P_{\text{spin}} < 0.05$ in 141 regions). Higher environment factor scores were associated with higher fluctuation amplitude across the association cortex, but with lower fluctuation amplitude nearly exclusively within primary and early sensory and motor cortices (**Figure 3-6b**). This pattern of relationships indicates that youth raised in neighborhoods with higher income, education and employment rates and with lower population density and poverty tended to have greater-amplitude intrinsic fMRI fluctuations in higher-order cortices and lower-amplitude fluctuations in modality-specific cortices. Strikingly, environment effects and S–A axis ranks were significantly correlated across the cortical mantle ($r = 0.48$, $P_{spin} = 0.05$; **Figure 3-6c**), supporting a potentially stronger role for neighborhood-level (dis)advantage rather than household socioeconomic position.

To better appreciate the nature of associations between the neighborhood environment and fMRI activity amplitude from a developmental perspective, we modeled age-dependent changes in fluctuation amplitude as a function of environment factor score. We visualized developmental trajectories for low and high environment factor scores for deciles of the S–A axis (stratifying **Figure 3-3c** by factor score). A higher neighborhood environment factor score (indicative of more advantaged socioeconomic circumstances) was associated with a steeper reduction in fluctuation amplitude in sensorimotor regions (deciles 1 and 3) during childhood and adolescence and with a greater peak in fluctuation amplitude in association regions (deciles 8 and 10) particularly during midadolescence (**Figure 3-6d**). Factor score-stratified developmental trajectories thus suggested that environment effects may be largest and most divergent between sensorimotor and association cortices during adolescence.

To study this possibility further, we divided the sample into child (8–12 years), adolescent (13–17 years) and young-adult (18–23 years) groups and quantified regional associations between environment factor scores and fluctuation amplitude at each developmental stage. Regional environment effect estimates were quite correlated across the three groups, suggesting relative stability in associations across development ($r = 0.72$ between child and adolescent t values, $r = 0.70$ between adolescent and young-adult t values, and $r = 0.65$ between child and young-adult t values). However, small differences in regional associations were present across developmental stages (**Figure 3-6e**) and together resulted in environment effect estimates becoming most strongly differentiated across the S–A axis in adolescence. The correlation between regional environment effects and S–A axis ranks was $r = 0.32$ ($P_{spin} = 0.00765$) in children, $r = 0.65$ ($P_{spin} < 0.0001$) in adolescents and $r = 0.31$ ($P_{spin} = 0.01280$) in young-adults.

Given initial evidence that developmental timing may affect the global expression of brain–environment associations, we used GAMs to formally model regional age-by-environment interactions, which estimate how relationships between environment factor scores and fluctuation amplitude vary continuously with age. This approach allowed for the derivation of age-specific environment effect estimates, providing insight into how the magnitude of effects changed over the developmental window studied in individual sensorimotor and association regions (**Figure 3-6f**). Moreover, this approach facilitated a second age-resolved analysis in which we calculated the correlation between age-specific environment effects and S–A axis ranks at 1-month intervals between ages 8 and 23 years (**Figure 3-6g**). The goal of this second age-resolved analysis was to investigate whether subtle changes in regional environment effects contribute to a shift in the global patterning of brain–environment associations with age. This analysis revealed that regional environment effects and regional S–A axis ranks were maximally correlated in adolescence at 15.5 years of age (95% credible interval of 14.4 to 16.6 years), providing convergent results to the grouped developmental stage analysis. The spatial correlation between environment effects and the S–A axis did not significantly differ from 0 at the very youngest (21.0 years old) ages studied. These results collectively suggest that the expression of brain–environment associations along this principal axis of brain organization is most prominent in adolescence.

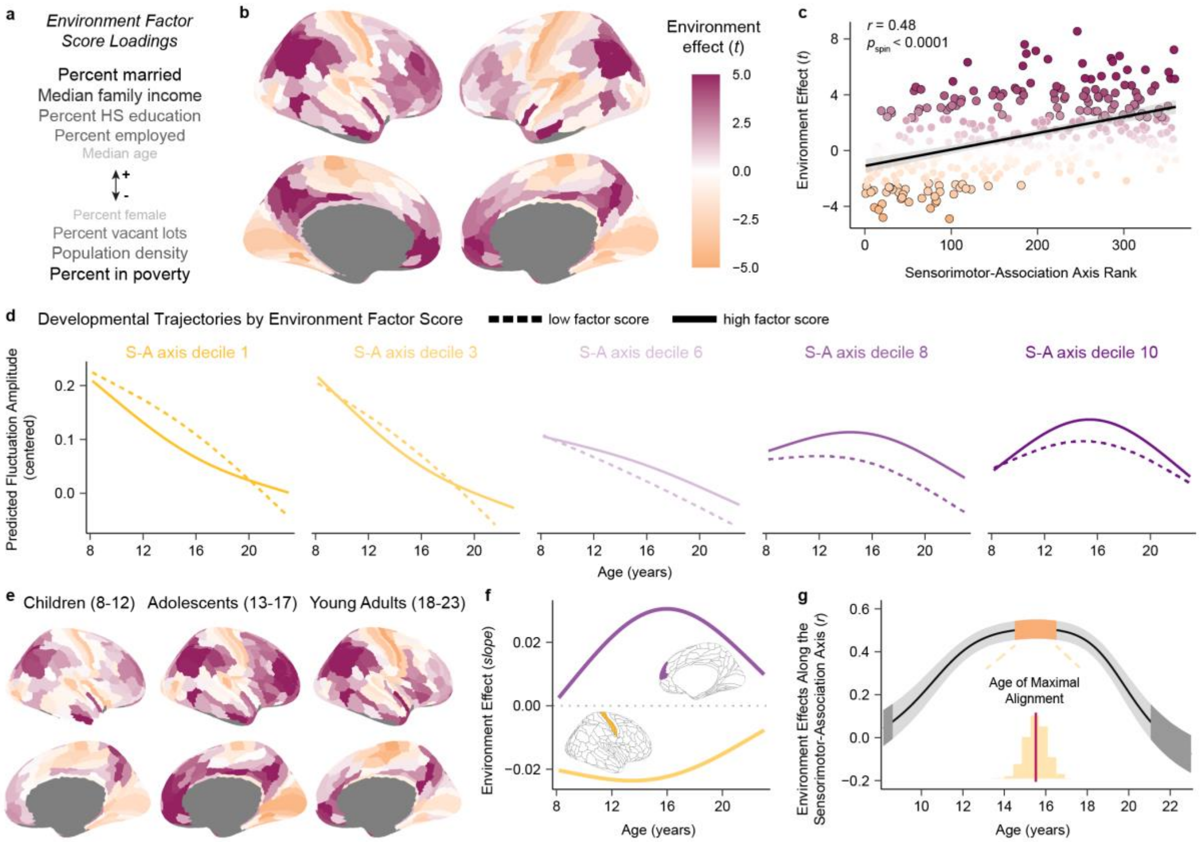

Figure 3-6. Associations Between Fluctuation Amplitude and the Developmental Environment Vary Along the S-A Axis in Adolescence

a) An environment factor score captures multiple features of each child's neighborhood environment. Variables listed above (+) and below (–) the arrow positively and negatively loaded onto the factor score, respectively. Darker and larger text indicates stronger loadings. Higher factor scores reflect greater neighborhood-level socioeconomic advantage; HS, high school. **b**) A cortical map displaying regional associations (quantified by model t values) between environment factor scores and fluctuation amplitude is displayed; the map partly recapitulates the S–A axis. **c**) Each region's environment effect (t value) is plotted against its S–A axis rank (linear fit shown with a 95% confidence interval). Regions with a significant environment effect following correction for multiple comparisons are outlined in black. The S–A axis explains significant variability in brain–environment associations (Spearman's correlation with a spatial rotation-based significance test: $r = 0.48$ and $P_{spin} < 0.0001$). **d**) Fluctuation amplitude developmental trajectories are displayed for low and high environment factor scores for five deciles of the S–A axis, illustrating environment-associated differences in this measure by developmental timing. **e**) Cortical maps depicting regional associations between environment factor scores and fluctuation amplitude (as in **b**) in child, adolescent and young-adult groups show subtle differences in associations throughout development. Magenta and orange denote positive and negative environment effects (t values), respectively, as in **b**. **f**) Age-specific environment effects are shown for an exemplar primary sensorimotor region (primary somatosensory cortex area 3b; yellow) and transmodal association region (medial prefrontal cortex area 9m; purple). The magnitude of effects is largest in adolescence in these regions. **g**) Regional differences in environment associations are most organized along the S–A axis in adolescence, as revealed by age-specific correlations between regional environment effects and S–A axis ranks. The plot depicts the median correlation value (r) at each age (black line) and the 95% credible interval around this value (gray band) obtained by sampling the posterior distribution of regional age-by-environment interaction GAMs 10,000 times. The orange and dark gray bands respectively designate credible intervals for the ages of maximal and zero correlation of environment effects with the S–A axis.

Discussion

During embryonic and early postnatal cortical development, developmental programs are spatially and temporally governed by major organizing axes. Cortical arealization is cooperatively controlled by thalamocortical inputs and transcription factors expressed along anterior–medial to posterior–lateral axes (O'Leary et al., 2007). Neurogenesis terminates along an anterior to posterior axis (Charvet and Finlay, 2014). The alignment of developmental programs with neuroaxes is thus a fundamental element of early cortical development. In the current study, we demonstrate that the maturation of intrinsic cortical activity conforms to the hierarchical S–A axis from ages 8 to 18 years, supporting that this core facet of development extends to childhood and adolescence. Specifically, we observed that declines in the amplitude of intrinsic fMRI activity are temporally coupled to the increasing expression of a plasticity-limiting factor and temporally staggered along the S–A axis of cortical organization. We additionally found that the S–A axis captures not only interregional variation in maturational profiles but also variation in the effects of children's developmental environment on cortical fMRI activity. Together, these results provide evidence of a hierarchical axis of neurodevelopment in youth.

Intrinsic neural activity has a profound influence on the immature brain, impacting neuron survival, circuit wiring, topographic map formation, synaptic connectivity and overall cortical volume (Ackman et al., 2012; Benders et al., 2015; Martini et al., 2021; Winnubst et al., 2015). Prominent changes in the prevalence and patterning of this activity occur during development, engendered by shifts in the maturity of the cortex and in the level of cortical plasticity. Here, we identified prolonged declines in fMRI fluctuation amplitude, an in vivo measure sensitive to intrinsic cortical activity, throughout the protracted course of human neurodevelopment. Moreover, we observed substantial interregional heterochronicity in periods of decline, with fluctuation amplitude beginning to decline around 8–12 years of age in unimodal sensory and motor regions, 13–16 years in many association cortices and 18–22 years in prefrontal transmodal cortices. These region-specific windows of declining fluctuation amplitude occur after peak gray matter volume is obtained (Bethlehem et al., 2022) and coincide with regional windows of extensive synaptic pruning (Huttenlocher and Dabholkar, 1997). In addition, we demonstrated that each region's onset of decline in fluctuation amplitude was linked to its period of maximal increase in a non-invasive measure of intracortical myelin growth. Maturational refinement of this functional measure is thus temporally linked to developmental changes in multiple indicators of shifting circuit plasticity, suggesting the presence of a graded axis of neurodevelopmental plasticity during childhood and adolescence.

Indeed, in support of our proposed framework on developmental chronology (Sydnor et al., 2021), we found that regional differences in maturational profiles were systematically explained by the asynchronous patterning of developmental change across the S–A axis. Regional developmental trajectories diverged in a continuous fashion across this axis, in a manner that suggests that a maturational sequence progresses along the brain's cortical hierarchy with age. This underscores that the S–A axis can be considered both a dominant spatial feature axis and a primary neurodevelopmental axis and intimates that spatial feature variability may in part emerge from temporal developmental variability (Charvet and Finlay, 2014; Sydnor et al., 2021). Recent work has shown that cortical microstructure (Paquola et al., 2019) and functional connectivity (Dong et al., 2021) increasingly differentiate across the S–A axis during late childhood and adolescence, when development is maximally organized by this axis. Hence, one main outcome of hierarchical development may be the strengthening of variation along the S–A axis, with a consequent strengthening of the cortex's hierarchical topography (Sydnor et al., 2021).

Although this non-invasive imaging study could not establish the mechanisms underlying the sensorimotor-to-associative sequence of fMRI activity refinement, prior work suggests that it may be produced by the hierarchical maturation of plasticity-regulating structural and chemical features. Key plasticity-regulating processes include the growth of intracortical myelin (McGee et al., 2005; Takesian and Hensch, 2013), the strengthening of parvalbumin interneuron signaling (Fagiolini and Hensch, 2000; Takesian and Hensch, 2013) and the assembly of perineuronal nets (Carulli et al., 2010; Lensjø et al., 2017). These processes elicit transitions in the prevalence, synchronicity and recorded amplitude of spontaneous activity (Anderson et al., 2020; Chini et al., 2022; Kato et al., 2020; Lensjø et al., 2017), indicating that they could possibly contribute to developmental changes in fMRI activity amplitude. In the adult cortex, the cortical distribution of parvalbumin interneurons is coupled to regional differences in fMRI fluctuation amplitude, with parvalbumin interneuron-associated genes accounting for an enriched degree of heritable variance in this measure (Anderson et al., 2020). In the developing cortex, cortical myelin and perineuronal nets preferentially form around parvalbumin interneurons (Carulli et al., 2010;

Lensjø et al., 2017; Micheva et al., 2016) limiting developmental plasticity while simultaneously altering a circuit's excitation:inhibition ratio and the production of intrinsic activity (Larsen and Luna, 2018; Takesian and Hensch, 2013). Critically, it has been established that cortical myelin (Baum et al., 2022; Grydeland et al., 2019) and parvalbumin interneurons (Condé et al., 1996; Larsen and Luna, 2018; Reh et al., 2020) mature earlier in sensory cortices and later in association cortices, indicating that their temporal development parallels the developmental reductions in the amplitude of intrinsic fMRI activity characterized here. The amplitude of intrinsic fMRI activity also uniquely increased in transmodal cortices in adolescence (frequently until 13–17 years), suggesting that a functional signature of more highly malleable cortices increases in association areas in this developmental window. The neurobiological events that could contribute to potential late increases in association cortex plasticity in the human brain have yet to be identified. Candidate events identified in animal studies include slower degradation of molecules that can delay the onset of plasticity (for example, polysialic acid (Takesian and Hensch, 2013) and histone deacetylases (Reh et al., 2020)) or late increases in plasticity facilitators (for example, brain-derived neurotrophic factor, thalamocortical inputs and homeoprotein Otx2 (Benoit et al., 2022; Takesian and Hensch, 2013)).

It has been hypothesized that age-dependent changes in the distribution of cortical plasticity should allow the same external inputs to exert differential influences on the human brain, depending on developmental timing. The present work provides empirical support for this hypothesis. Specifically, we studied relationships between individual differences in intrinsic activity amplitude and environment factor scores; these scores index disparities in neighborhood-level socioeconomic conditions that should be recognized as a manifestation of systemic wealth and education inequity that is rooted in structural racism and racial inequity (Acevedo-Garcia et al., 2020). We found that youth living in neighborhoods with greater poverty, unemployment rates and population density exhibited reduced fluctuation amplitude across the association cortex—most prominently, a reduced peak in amplitude in transmodal cortex during midadolescence. Yet, youth from more disadvantaged environments also had higher-amplitude intrinsic fMRI activity in unimodal sensory and motor cortices. Together, these opposing environment effects in sensorimotor and association cortices indicate that greater environmental deprivation is associated with diminished differentiation of a putative functional plasticity signature across the maturing cortex. We speculate that this association could reflect reduced versus accelerated development of plasticity-restricting features such as myelin in sensorimotor and association cortices, respectively, in youth from poorer socioeconomic environments (Norbom et al., 2022).

Importantly, the cortical expression of brain–environment associations was not uniform across the entire age range studied. An age-resolved analysis revealed that environment effects diverged most between sensorimotor and association cortices during adolescence, coincident with when regional differences in developmental change were most hierarchically organized. In fact, both developmental and environmental effects exhibited maximal variation across the cortex's S–A axis at 15 years of age. This temporal concurrence uncovers interdependence between ongoing neurodevelopmental refinement and environmental influences, revealing how the effects of the environment on the youth brain depend on developmental stage. Our analyses of youths' neighborhood environments thus provide data consistent with the hypothesis that environmental influences are both sensitive to and capable of refining a cortical area's current developmental plastic state.

Several limitations and possible direct extensions of this work should be highlighted. First, this was a cross-sectional investigation of neurodevelopment in youth. Future investigations with longitudinal study designs could characterize within-individual changes in cortical intrinsic activity and the effects of the environment on the pace of an individual's development. Longitudinal studies will also be better suited to examine temporal precedence between developmental refinement of intrinsic fMRI activity and maturation of plasticity-regulating features. Second, we used resting-state fMRI to study intrinsic cortical activity; however, the BOLD signal is sensitive to neural, vascular and respiratory factors. While sensitivity analyses aimed at assessing and mitigating these factors provided highly convergent results, future studies using more direct measures of neural activity will therefore be helpful for extending the present findings. Third, it is difficult to directly establish the extent to which age-related changes in non-invasive neuroimaging measures represent changes in developmental plasticity versus other processes, given that there is no gold standard or singular measure of cortical plasticity in the human brain. To address this challenge, we studied an fMRI-derived measure that is modulated by changing the activity of cells that drive developmental plasticity (Anderson et al., 2020; Markicevic et al., 2020; Reh et al., 2020), is enhanced by behaviorally inducing plasticity (Fair and Yeo, 2020; Newbold et al., 2020) and, as shown here, appears to be refined during development in tandem with a biological regulator of plasticity. Fourth, only a coarse measure of pubertal stage was available in this sample, and it was only collected in individuals 10 years of age and older. This limited our ability to fully ascertain whether regional fluctuation amplitude was influenced by puberty or hormone levels, especially in the youngest participants. Rodent studies have shown that pubertal hormones can affect synaptic pruning and inhibitory signaling in the association cortex (Piekarski et al., 2017), highlighting this as an area for further investigation. Fifth, we aggregated a set of interrelated neighborhood variables into one factor score, precluding inference about specific proximal or distal causes of the brain–environment associations observed in these data. Potential causes may involve neighborhood features that are socioeconomically stratified and sociopolitically determined, including access to physical and educational resources, exposure to environmental enrichment and community programs or experiences of psychological safety and chronic stress. Developing a more nuanced understanding of the causes and behavioral correlates of these environment effects may ultimately help to inform interventions or policies that equitably support healthy child neurodevelopment across socioeconomic circumstances.

The present study demonstrates that during childhood and adolescence, the spatiotemporal patterning of developmental change in intrinsic cortical fMRI activity coheres with a hierarchical axis of cortical organization. The observed refinements in fMRI fluctuations lend support to the theory that shifts in circuit plasticity temporally progress along this axis, calling for studies that can mechanistically test for neurobiological events driving an S–A gradient of neurodevelopment. Such events may include the maturation of neurochemical and structural plasticity-regulating features and successive expression of molecules that can orchestrate developmental timing, for example, circadian clock genes and temporally organized transcription factors (Kobayashi et al., 2015; Konstantinides et al., 2022; Reh et al., 2020). Given the relevance of the S–A axis for understanding cortical development in childhood and adolescence, future work should explore whether this and other major organizing axes (for example, anatomical axes) play a role in cortical refinement during infancy and early childhood. Studies of the infant brain have shown that developmental change in thalamocortical structural connectivity and cortico-cortical functional connectivity is more pronounced within the sensorimotor cortex than within the association cortex, suggesting maturational relevance of the S–A axis in the first years of life (Nielsen et al., 2022). Continued discovery of temporal axes of neurodevelopment across the multidecade maturational course of humans will help elucidate how plasticity is distributed across brain regions at different developmental stages. Such insights into the temporal progression of plasticity will facilitate an understanding of how the effects of experience and the environment on the brain change as cortical malleability is refined, and may thus ultimately help to guide interventions in youth that align with each child's neurotemporal context.

Methods

Participants

Participants were recruited as part of the Philadelphia Neurodevelopmental Cohort (Satterthwaite et al., 2014a), a community study of child and adolescent brain development. Demographic, clinical, environmental and neuroimaging data from 1,033 youths were included in the present cross-sectional study. Study sample demographics include an age range of 8 to 23 years (mean age of 15.7 ± 3.3 years), a sex distribution of 467 males and 566 females (sex was self-reported; intersex was not assessed) and a race and ethnicity distribution that was 0.3% American Indian or Alaskan Native, 0.7% Asian, 41% Black or African American, 11% identifying as multiracial and 47% White. All participants over the age of 18 gave written informed consent before study participation. Participants under the age of 18 gave informed assent with written parental consent. All individuals received monetary compensation for participation in the study. All study procedures were approved by the Institutional Review Boards of the University of Pennsylvania and the Children's Hospital of Philadelphia.

MRI data acquisition

T1w structural MRI and resting-state fMRI data were used in the present study. All MRI scans were acquired on the same 3T Siemens TIM Trio scanner (software version VB17) at the University of Pennsylvania with a 32-channel head coil. T1w structural images were acquired with a magnetization-prepared rapid acquisition gradient-echo sequence with the following parameters: repetition time of 1,810 ms, echo time of 3.51 ms, inversion time of 1,100 ms, flip angle of 9°, field of view of 180 × 240 mm, matrix of 192 × 256, 160 slices and a voxel resolution of 0.94 × 0.94 × 1 mm. Resting-state functional images were acquired with a single-shot, interleaved multislice gradient-echo echo planar imaging sequence with the following parameters: repetition time of 3 s, echo time of 32 ms, flip angle of 90°, field of view of 192 × 192 mm, matrix of 64 × 64, 46 slices, a voxel resolution of 3 mm3 and 124 volumes. To enable susceptibility distortion correction of resting-state functional images, a map of the main magnetic field (a B0 field map) was additionally collected using a dual-echo, gradient-recalled echo (GRE) sequence with the following parameters: repetition time of 1,000 ms, echo time 1 of 2.69 ms, echo time 2 of 5.27 ms, flip angle of 60°, field of view of 240 × 240 mm, matrix of 64 × 64, 44 slices and a voxel resolution of 3.8 × 3.8 × 4 mm.

MRI data processing

T1w images and resting-state fMRI time series were processed with fMRIPrep 20.2.3 (Esteban et al., 2019). The T1w image was corrected for intensity non-uniformity with Advanced Normalization Tools (Avants et al., 2011) (ANTs; 2.3.3) N4BiasFieldCorrection, the skull was stripped with a Nipype (1.6.1) implementation of the ANTs brain extraction workflow, and tissue segmentation was performed with FSL (5.0.9) fast. The processed T1w image was then used for cortical surface reconstruction with FreeSurfer (6.0.1) (Dale et al., 1999). The T1w image was additionally non-linearly registered to the MNI152 T1 template (volume-based spatial normalization) with antsRegistration.

To preprocess functional scans, a skull-stripped reference BOLD volume was first generated, and a B0 field map was co-registered to this reference volume. The B0 field map was estimated based on the phase-difference map calculated with the dual-echo GRE sequence, converted to a displacements field map with FSL's fugue and SDCflow tools and used for susceptibility distortion correction of the reference BOLD volume. The susceptibility-corrected BOLD reference was then rigidly co-registered (6 degrees of freedom) to the T1 reference using boundary-based registration implemented with FreeSurfer's bbregister. The fMRI time series were slice-time corrected using 3dTshift from AFNI 20160207 and resampled onto their original native space by applying a single composite transform to correct for susceptibility distortions and in-scanner head motion. Head motion parameters were calculated with respect to the reference BOLD volume before any spatiotemporal filtering using FSL mcflirt; six rotation and translation parameters were calculated. BOLD time series were additionally resampled into standard space, generating preprocessed time series in the MNI152NLin6Asym T1 template, and onto the fsaverage surface. Finally, to project functional time series onto the fsLR cortical surface for study analyses, grayordinates files containing 32,000 vertices per hemisphere were generated using the highest-resolution fsaverage as an intermediate standardized surface space. Volumetric resampling was performed using antsApplyTransforms configured with Lanczos interpolation to minimize the smoothing effects of other kernels. Surface resampling was performed using FreeSurfer's mri_vol2surf.

fMRIPrep was additionally used to estimate the following 36 confounds from the preprocessed time series: six head motion parameters, three global signals (mean cerebrospinal fluid, white matter and whole-brain signals), temporal derivatives of the six head motion parameters and the three global signal estimates and quadratic terms for the motion parameters, tissue signals and their temporal derivatives (Ciric et al., 2018, 2017). These confound matrices were used within xcp_d 0.0.4, which is an extension of the top-performing eXtensible Connectivity Pipeline (XCP) Engine specifically developed to mitigate motion-related artifacts and noise in resting-state fMRI data from developmental samples. With xcp_d, preprocessed functional time series on the fsLR cortical surface underwent nuisance regression using the 36 confounds listed above. Confounds were regressed using linear regression as implemented in Scikit-Learn (0.24.2).

Fluctuation amplitude quantification

To calculate fluctuation amplitude, defined as the power of low-frequency fMRI recordings, processed fsLR surface BOLD time series were first transformed from the time domain to the frequency domain, and a power spectrum was generated in the 0.01- to 0.08-Hz range. The mean square root of the power spectrum was then calculated. The mean square root represents the average amplitude (intensity) of time-varying resting-state BOLD fluctuations within this low-frequency band (Yu-Feng et al., 2007). Of note, the fluctuation amplitude measure used here is analogous to other commonly used spectral- or variability-based BOLD measures, including the amplitude of low-frequency fluctuations and resting-state functional amplitude.

Fluctuation amplitude was quantified at the vertex level with xcp_d 0.0.4 and then parcellated with fsLR surface atlases to provide mean fluctuation amplitude within individual cortical regions. The Human Connectome Project multimodal parcellation (HCP-MMP) atlas (Glasser et al., 2016) was used for all primary analyses and the Schaefer-400 atlas (Schaefer et al., 2018) was used for a sensitivity analysis. Parcellation was conducted in R with the ciftiTools package (Pham et al., 2022) using Connectome Workbench 1.5.0. Fluctuation amplitude was not analyzed within cortical regions that exhibited low signal-to-noise ratios in ≥25% of their assigned vertices. Low signal-to-noise ratio vertices were defined identically to our prior work (Cui et al., 2020) as vertices with an average (across-participant) BOLD signal of <670 after normalizing signal to a mode of 1,000. Twenty-four parcels located within the orbitofrontal cortex and the ventral temporal lobe were excluded from both the HCP-MMP atlas and the Schaefer-400 atlas.

MRI sample construction

The study sample used in the present work is comprised of individuals who received an MRI scan as part of the Philadelphia Neurodevelopmental Cohort. No statistical methods were used to predetermine the sample size of the Philadelphia Neurodevelopmental Cohort, as this was designed as a large, publicly available community data resource, but the sample size is similar to that reported in previous publications of youth brain development (Baum et al., 2022; Satterthwaite et al., 2014a; Tooley et al., 2020). One thousand three hundred and seventy-four individuals in the Philadelphia Neurodevelopmental Cohort had T1w images, B0 field maps and identical-parameter (Covitz et al., 2022) resting-state fMRI scans available and were considered for inclusion in this study. From this original sample of n = 1,374, 120 individuals were excluded from the study due to medical problems that could impact brain function or incidentally encountered abnormalities of brain structure. Data from 202 additional participants were excluded due to low-quality T1w images and FreeSurfer reconstructions ($n = 23$) or high in-scanner head motion ($n = 179$). As in our prior work, high in-scanner head motion was defined as a mean relative root mean squared framewise displacement of >0.2 mm during the functional scan. Using data from the remaining sample ($n = 1,052$), we identified fluctuation amplitude outliers at the regional level based on a cutoff of ±4 s.d. from the mean. Individuals with outlier data in more than 5% of cortical regions ($n = 19$) were excluded, producing the final study sample of 1,033 individuals. Participants from this final study sample were not assigned to separate experimental groups or conditions; thus, data collection and analysis did not involve randomization or blinding.

Characterizing developmental effects

GAMs

All statistics were performed in R 4.0.2. To flexibly model linear and non-linear relationships between fluctuation amplitude and age, we implemented GAMs (semiparametric additive models) using the mgcv package in R (Wood, 2017). GAMs were fit with regional fluctuation amplitude as the dependent variable, age as a smooth term and sex and in-scanner head motion as linear covariates. Models were fit separately for each parcellated cortical region using thin plate regression splines as the smooth term basis set and the restricted maximal likelihood approach for smoothing parameter selection. The GAM smooth term for age produces a spline, or a smooth function generated from a linear combination of weighted basis functions, that represents a region's developmental trajectory. To prevent overfitting of the spline, we set the maximum basis complexity (k) to 3 to limit the number of basis functions that could be used to estimate the overall model fit. A value of k = 3 was chosen over higher values (such as k = 4–6) given that this basis complexity resulted in the lowest model Akaike information criterion for many cortical regions and was found to appropriately capture developmental fits using a conservative number of splines. Statistical tests of the k-index (Wood, 2017), which estimate the degree of unaccounted for non-random pattern in the residuals, confirmed that this basis dimension was sufficient.

For each regional GAM, the significance of the association between fluctuation amplitude and age was assessed by an analysis of variance (ANOVA) that compared the full GAM model to a nested, reduced model with no age term. A significant result indicates that the residual deviance was significantly lower when a smooth term for age was included in the model, as assessed with the chi-squared test statistic. We corrected ANOVA P values across all region-wise GAMs using the FDR correction and set statistical significance at PFDR < 0.05. For each regional GAM with a significant age smooth term, we furthermore identified the specific age range(s) wherein fluctuation amplitude was significantly changing by using the gratia package in R. Age windows of significant change were identified by quantifying the first derivative of the age smooth function (Δ fluctuation amplitude/Δ age) using finite differences and determining when the simultaneous 95% confidence interval of this derivative did not include 0 (Simpson, 2018); two sided). To establish the overall magnitude and direction of the association between fluctuation amplitude and age, which we refer to throughout as a region's overall age effect, we calculated the partial R^2 between the full GAM model and the reduced model (effect magnitude) and signed the partial R^2 by the sign of the average first derivative of the smooth function (effect direction).

For each cortical region, we additionally tested the effects of participant sex and pubertal stage on fluctuation amplitude development. We first assessed whether the developmental trajectories of fluctuation amplitude differed between males and females by testing the significance of a factor–smooth interaction term added to the main GAM model (that is, an age-by-sex interaction that allowed age-dependent changes to vary by sex). To assess the potential influence of participant pubertal stage, we added a three-level ordered factor for pubertal stage (with levels for prepubertal, midpubertal and postpubertal) to the main GAM models. Participants self-reported their pubertal stage by viewing pictorial representations and text descriptions of the five Tanner stages of pubic hair growth and reporting which best matched their own development of secondary sex characteristics. Following our prior work in this same sample (Satterthwaite et al., 2014b), we considered Tanner stages 1–3 as 'prepubertal', Tanner stage 4 as 'midpubertal' and Tanner stage 5 as 'postpubertal'. Self-reporting of Tanner staging was only conducted in participants aged 10 and older (n = 949; 518 female). As a result, there were fewer prepubertal participants (n = 176, Tanner stages 1–3) than midpubertal (n = 283, Tanner stage 4) and postpubertal (n = 490, Tanner stage 5) participants. We evaluated whether pubertal stage explained significant variance in fluctuation amplitude above and beyond age in each region by using an ANOVA to compare the full GAM model (with the pubertal stage factor) to a reduced model that did not include pubertal information. We corrected *P* values for multiple comparisons across region-wise GAMs within sex and pubertal stage analyses using FDR correction.

Associations with cortical myelin development

We formally assessed whether the development of intrinsic fMRI activity amplitude was spatially and temporally related to the development of an imaging measure sensitive to intracortical myelin content. Cortical myelin development was previously comprehensively characterized by Baum et al. (2022) using T1w/T2w surface-based myelin mapping in a sample of 628 youths ages 8 to 21 years (336 female) who had data collected as part of the HCP in Development. Using high-resolution (0.8-mm3) T1w and T2w images, HCP processing pipelines and state of the art methods for B1+ transmit field bias correction and partial volume reduction, Baum et al. (2022) investigated the maturational trajectory of increases in the T1w/T2w ratio in each cortical region. In this investigation, the authors fit region-specific GAMs with a smooth term for age using thin plate regression splines as the smoothing basis, paralleling the present work. GAMs included covariates for sex, scanner and B1+ transmit field correction-related variables, following current best practices for statistically comparing the T1w/T2w ratio across individuals.

To test whether the extent to which fluctuation amplitude changed with age was related to the degree to which cortical myelin content changed with age, we calculated the correlation coefficient between the two distinct age effects: those calculated from regional fluctuation amplitude GAMs and those calculated from regional T1w/T2w ratio GAMs reported by Baum et al. (2022). As in the present work, T1w/T2w ratio age effects were determined by a partial R2 derived by comparing the full GAM model to a reduced model with no smooth term for age. The association between fluctuation amplitude age effects and T1w/T2w ratio age effects was quantified with a Spearman's correlation, a non-parametric, rank-based correlation test that does not assume normality. A Spearman's correlation was also used to evaluate whether there was temporal correspondence between the development of fluctuation amplitude and the T1w/T2w ratio across the cortex. Specifically, we calculated the correlation coefficient between the age at which fluctuation amplitude began to significantly decrease in each region and the age at which the T1w/T2w ratio maximally increased in each region. The age at which fluctuation amplitude began to significantly decrease was the youngest age at which the first derivative of the age smooth function was significantly negative. The age at which the T1w/T2w ratio had a maximal rate of increase was the age at which the first derivative of the age smooth function was maximal.

Alignment with the S–A axis

This work sought to test the overarching hypothesis that neurodevelopmental patterns are organized by the S–A axis during childhood and adolescence. We therefore examined whether fluctuation amplitude maturation aligned with the S–A axis derived in our prior work (Sydnor et al., 2021). The S–A axis was derived by averaging rank orderings of ten cortical feature maps that exhibit systematic variation between lower-order sensorimotor cortices, multimodal cortices and higher-order heteromodal and paralimbic association cortices (Sydnor et al., 2021). These maps include the functional hierarchy delineated by the principal gradient of functional connectivity (Margulies et al., 2016), the evolutionary hierarchy defined by macaque-to-human cortical areal expansion (Hill et al., 2010), the anatomical hierarchy as quantified by the adult T1w/T2w ratio (Burt et al., 2018), allometric scaling calculated as local areal scaling with scaling of total brain size (Reardon et al., 2018), aerobic glycolysis measures of brain metabolism (Vaishnavi et al., 2010), cerebral blood flow measures of brain perfusion (Satterthwaite et al., 2014b), gene expression spatial variance indexed by the first PC of brain-expressed genes (Burt et al., 2018), a primary mode of brain function characterized by the first PC of NeuroSynth meta-analytic decodings (Yarkoni et al., 2011), a histological gradient of cytoarchitectural similarity developed using the BigBrain atlas (Paquola et al., 2021) and cortical thickness measured by structural MRI. The resulting S–A axis represents a dominant, large-scale motif of cortical organization that captures the stereotyped patterning of cortical heterogeneity from primary visual, somatosensory and motor regions (lowest ranks in the S–A axis) to transmodal frontal, temporal and parietal association regions (highest ranks in the S–A axis).

We performed the following analyses to ascertain whether the development of fluctuation amplitude is related to the S–A axis. Using Spearman's correlations, we evaluated associations between cortical regions' S–A axis ranks and both (1) their magnitude of fluctuation amplitude development (signed partial R^2) and (2) the age at which their fluctuation amplitude began significantly decreasing (first significant negative derivative). We next conducted a PCA on regional developmental trajectories. The goal of this PCA was to visualize the spatial axis that explained the greatest variance in how an in vivo measure of cortical intrinsic activity changed with age. The input to the PCA was region-wise age fits (zero-averaged smooth function estimates). The first PC generated by this PCA contained regional loadings that capture differences in maturational profiles across one low-dimensional embedding. We quantified the similarity between the first PC (loadings) and the cortex's S–A axis (Sydnor et al., 2021), anatomical hierarchy (Burt et al., 2018), functional hierarchy (Margulies et al., 2016) and evolutionary hierarchy (Hill et al., 2010) with independent Spearman's correlations. We additionally assessed whether the correlation with the S–A axis was significantly greater in magnitude than correlations with the three aforementioned hierarchies using a statistical test for comparing two dependent, overlapping correlations that uses a back-transformed average Fisher's Z procedure; tests were executed using the cocor package in R (hittner2003 test, two sided) (Diedenhofen and Musch, 2015).

Finally, we implemented an age-resolved analysis to evaluate if the development of fluctuation amplitude aligned with the S–A axis throughout the entire developmental window studied. For this analysis, we computed across-region Spearman's correlations between S–A axis rank and the first derivative of the GAM age spline estimated at 200 ages between 8 and 23 years, producing 200 age-specific correlations. In other words, we quantified the relationship between a region's fluctuation amplitude rate of change and its position in the S–A axis at 200 age increments, allowing us to study changes in the extent of S–A axis alignment over the course of development. We determined a correlation coefficient point estimate and a 95% credible interval for these age-specific correlation values at all 200 age increments. To do so, we sampled from the posterior distribution of each region's fitted GAM 10,000 times, generating 10,000 simulated age smooth functions and corresponding derivatives. We then repeated the process of correlating S–A axis rank with the first derivative of the age smooth function at each of the 200 ages for all 10,000 posterior draws, generating a sampling distribution of possible correlation values at each age increment. This distribution was used to calculate the median correlation value (point estimate) and the 95% credible interval of correlation values at each age increment. In addition, the sampling distribution of age-specific S–A axis correlation values was used to identify the age at which fluctuation amplitude development maximally aligned with the S–A axis and the youngest age at which no alignment to the axis was observed. To discover ages of maximal and null alignment, we calculated the age at which the axis correlation was largest and the first age at which the correlation equaled 0 for all 10,000 draws. For both measures, the median age across all draws and a 95% credible interval were calculated.

Sensitivity analyses

We performed a series of sensitivity analyses to confirm that the developmental effects observed were not being driven by potentially confounding factors, including in-scanner head motion, psychiatric medication use, cerebrovascular perfusion, BOLD signal intensity, global amplitude effects or the atlas used for cortical parcellation. For each sensitivity analysis, regional GAMs were refit either in a reduced sample (head motion and psychiatric medication analyses), in the full sample but with an additional model covariate (vascular and BOLD signal intensity analyses) or in the full sample with a modified dependent variable (global amplitude normalization and cortical atlas analyses). GAM-derived fluctuation amplitude trajectories were then visualized, and developmental alignment with the S–A axis was assessed.

The first sensitivity analysis was conducted with a low-motion sample to mitigate the potential confounding effect of in-scanner head motion on fluctuation amplitude. From the main study sample of 1,033 individuals, we excluded 343 individuals with a mean relative root mean squared framewise displacement of > 0.075, retaining a low-motion sample of $n = 690$ (ages 8–23 years; mean age of 16.1 years; 395 female). The second sensitivity analysis was performed to ensure that psychotropic medication use, which was more frequent among older study participants, did not explain the age-related changes in fluctuation amplitude. GAMs were refit after removing all participants ($n = 140$) from the original sample of 1,033 individuals that reported current psychoactive medication use or a history of psychiatric hospitalization (remaining $n = 893$; ages 8–23 years; mean age of 15.6 years; 507 female).

The third sensitivity analysis aimed to address the fact that the hemodynamic BOLD signal has vascular contributions. Prior work has demonstrated that measures of BOLD fluctuation amplitude contain substantial physiological information not attributable to vascular properties, such as cerebrovascular reactivity, rigidity and blood flow (Garrett et al., 2017). Nonetheless, we still evaluated whether changes in vascular reactivity or cerebral perfusion with age could potentially be contributing to our developmental findings concerning fluctuation amplitude. We approached this evaluation by directly controlling for each participant's regional cerebral blood flow, a measure of local blood perfusion, in region-wise GAMs. Cerebral blood flow was estimated from ASL data collected from participants with a pseudocontinuous ASL sequence with the following acquisition parameters: repetition time of 4,000 ms, echo time of 2.9 ms, voxel resolution of 2.29 × 2.29 × 6 mm, label duration of 1,500 ms, postlabel delay of 1,250 ms and 40 paired label and control acquisition volumes. Data were processed using ASLPrep version 0.2.7 using the analysis pipeline reported in Adebimpe et al. (2022). Basic cerebral blood flow maps were generated and parcellated with the HCP-MMP atlas (Adebimpe et al., 2022). Thirty-one participants included in the main study sample did not have ASL data available; thus, this vascular control analysis was performed using data from the remaining 1,002 participants (ages 8–23 years; mean age of 15.7 years; 552 female).

The fourth sensitivity analysis was undertaken to rule out the possibility that interindividual differences in regional mean BOLD signal intensity, rather than BOLD fluctuations per se, could account for our findings. In the full study sample ($n = 1,033$), region-specific GAMs were refit while adding regional mean BOLD signal (the average T2* signal from minimally preprocessed functional time series) as an additional control covariate. Regional mean BOLD signal was calculated from parcellated fsLR surface BOLD time series generated with fMRIPrep by averaging the BOLD signal intensity (T2*) in each parcellated cortical region across all volumes; this measure was calculated before regression of confounding signals.

The fifth sensitivity analysis used mean-normalized fluctuation amplitude as the dependent variable in all regional GAMs to examine the extent to which region-specific changes in fluctuation amplitude with age occurred above and beyond changes in global mean fluctuation amplitude. This sensitivity analysis was motivated by prior work that normalized local brain measures by a whole-brain mean to reduce interindividual differences in global values. It furthermore accounts for potential global differences in the scale of the BOLD signal across scans. Mean-normalized fluctuation amplitude was quantified for all participants ($n = 1{,}033$) by dividing an individual's fluctuation amplitude in each parcellated cortical region by the average fluctuation amplitude computed across all cortical regions. Notably, because whole-brain mean fluctuation amplitude declined across the age range studied, regional trajectories in this sensitivity analysis represent regional age-related decreases or increases relative to this global change.

The sixth and final sensitivity analysis was implemented to verify that the hierarchical sequence of fluctuation amplitude maturation would be observed when using a different atlas for cortical parcellation. As described above, vertex-wise fluctuation amplitude data in fsLR surface space were parcellated with the Schaefer-400 atlas. GAMs were fit using data from the main study sample of 1,033 individuals for each Schaefer atlas region.

Characterizing environmental effects

Neighborhood environment factor scores

We investigated associations between spontaneous BOLD fluctuation amplitude and neighborhood environment factor scores that index differences in neighborhood-level socioeconomic circumstances. The derivation of these factor scores has been previously explained in detail (Moore et al., 2016). Briefly, geocoded information about each individual's neighborhood environment was extracted using their home address and the census-based American Community Survey. The first factor from an exploratory, two-factor factor analysis conducted on census variables by Moore et al. (2016) is used in the present study. This neighborhood environment factor score had positive loadings for the percentage of residents who are married (loading = 0.85), median family income (0.82), the percentage of residents with a high school education (0.74), the percentage of residents who are employed (0.68) and median age (0.61) as well as negative loadings for the percentage of residents in poverty (−0.86), population density (−0.71) and the percentage of houses that are vacant (−0.60) and a weak loading for the percentage of residents who are female (−0.26). There was no correlation between age and neighborhood environment factor scores ($r = 0.01$).

GAMs

GAMs were used to investigate whether variability in youths' neighborhood environments was associated with variability in regional fluctuation amplitude. We first used GAMs to resolve age-independent main effects of the neighborhood environment by modeling environment factor scores as a linear independent variable. For each region in the HCP-MMP atlas, a GAM was fit with fluctuation amplitude as the dependent variable, age as a smooth term and sex, in-scanner motion and the environment factor score as linear covariates. These main effect models thus identify linear associations between factor scores and regional fluctuation amplitude across the entire developmental age range studied. The t value associated with the factor score term in each GAM represents the magnitude and direction of the regional fluctuation amplitude–neighborhood environment association. The significance of this association was assessed with an ANOVA that compared the full GAM model to a reduced model without the environment factor score term; ANOVA P values were FDR corrected across all region-wise GAMs.

The main effect GAMs described above were also used in a follow-up specificity analysis. The specificity analysis was conducted to evaluate whether the observed environmental effects were specific to the neighborhood environment or could be better accounted for by the household-level socioeconomic environment. To investigate this, parental education (one indicator of household socioeconomic position) was included as an additional linear covariate in regional GAMs. For each region, the significance (FDR corrected) of both the environment factor score term and the parental education term was assessed using ANOVAs as indicated above. Parental education was defined as the average years of education obtained by both parents (when data were available; $n = 943$) or by one parent ($n = 83$). Parental education information was not available for seven participants who were thus removed from this secondary analysis. Parental education was used as a proxy for household-level socioeconomic position, as other socioeconomic measures (for example, household income or parental occupational status) were not collected, although we note that individual socioeconomic position may be more robustly operationalized by combining multiple measures.

After assessing the specificity of effects to the neighborhood environment, we conducted two complementary analyses aimed at understanding whether the global cortical patterning of associations between fluctuation amplitude and neighborhood environment factor scores varies by age. We first examined main effect associations between the factor scores and regional fluctuation amplitude in groups of participants at different developmental stages. The study sample was divided into child (8–12 years; $n = 175$; 94 female), adolescent (13–17 years; $n = 405$; 225 female) and young-adult (18–23 years; $n = 299$; 167 female) groups, and region-wise main effect environment GAMs (as described above) were fit independently in each group. Regional environment factor score t values were then obtained for each group. This developmental stage analysis suggested that associations between the neighborhood environment and fluctuation amplitude may vary by age in some regions, producing changes in the cortical expression of environment effects. To further explore this possibility, we examined regional age-by-environment interactions, which explicitly model how associations between the neighborhood environment and regional fluctuation amplitude change continuously with age. In each region, we fit a varying coefficient GAM with fluctuation amplitude as the dependent variable; predictors included an age-by-factor score interaction term, a smooth term for age and control covariates including sex and in-scanner motion. These models use data from the entire sample and allow the linear association between environment factor scores and regional fluctuation amplitude to vary as a smooth function of age. Region-wise varying coefficient GAMs were used for two main objectives. First, we used these models to generate predicted trajectories of fluctuation amplitude development for low (10th percentile) and high (90th percentile) factor scores for every region. We then averaged trajectories for low and high factor scores independently within deciles of the S–A axis for visualization purposes. Second, we used these models to quantify age-specific environment effects in each region. Age-specific environment effects were computed as the slope of the linear association between fluctuation amplitude and environment factor scores at a given age (Δ fluctuation amplitude/Δ factor score). The organization of age-specific environment effects along the S–A axis was then examined across development (detailed further below).

Alignment with the S–A axis

To first assess whether the main effects of the environment on fluctuation amplitude were systematically related to the S–A axis, we tested for an association between neighborhood environment factor score t values and S–A axis ranks using a Spearman's correlation. Correlations between *t* values and S–A axis ranks were quantified for the primary analysis as well as for the follow-up specificity and developmental stage analyses. To additionally understand how the spatial correlation between regional brain–environment associations and S–A axis ranks changed across the entire developmental window studied, we conducted an age-resolved environmental effects analysis. Akin to the age-resolved development analysis, we computed across-region Spearman's correlations between S–A axis ranks and age-specific environment effects (varying coefficient model slopes) at 200 ages between 8 and 23 years. We determined a correlation coefficient point estimate (median correlation value) as well as a 95% credible interval for these age-specific correlation values from 10,000 draws from the posterior distribution of each region's fitted varying coefficient GAM. As in the development analysis, we also identified the age at which variation in environment effects was maximally captured by the S–A axis; a point estimate and a 95% credible interval for the age of maximal S–A axis correlation was calculated.

Spin-based spatial permutation testing

Cortical data often exhibit distance-dependent spatial autocorrelation that can inflate the significance of correlations between two cortical feature maps. To mitigate this issue, we assessed the significance of each Spearman's correlation that compared two whole-brain cortical feature maps with non-parametric, spin-based, spatially constrained rotation tests or 'spin tests' (Alexander-Bloch et al., 2018). Spin tests compute a P value (denoted P_{spin}) by comparing the empirically observed correlation to a null distribution of correlations obtained by randomly spatially iterating (spinning) one of the two cortical feature maps. In particular, spin tests generate a null by rotating spherical projections of one feature map while maintaining its spatial covariance structure. The direction of the empirical Spearman's correlation can be positive or negative; the P value for the correlation is quantified as the number of times the spatial rotation-based correlation is greater than (for positive correlations) or less than (for negative correlations) the empirical correlation divided by the number of spatial rotations. Here, we generated a null distribution based on 10,000 spatial rotations. Spin tests were implemented using the rotate_parcellation algorithm in R (https://github.com/frantisekvasa/rotate_parcellation) (Váša et al., 2018).

Data availability

The current study analyzes an existing, publicly available dataset from the Philadelphia Neurodevelopmental Cohort, available in the Database of Genotypes and Phenotypes (phs000607.v3.p2). Study analyses additionally made use of publicly available cortical atlases, including the HCP-MMP atlas (downloaded from https://github.com/PennLINC/xcp_d/blob/main/xcp_d/data/ciftiatlas/glasser_space-fsLR_den-32k_desc-atlas.dlabel.nii), the Schaefer-400 atlas (downloaded from https://github.com/PennLINC/xcp_d/blob/main/xcp_d/data/ciftiatlas/Schaefer2018_400Parcels_17Networks_order.dlabel.nii) and the S–A axis (downloaded from https://pennlinc.github.io/S-A_ArchetypalAxis/). Data derivatives from the current study, including development effect and environment effect maps, are available for download from https://doi.org/10.5281/zenodo.7606653.

Code availability

Neuroimaging data were processed with containerized software packages available on dockerhub. Resting-state fMRI data were processed with fMRIPrep 20.2.3 (https://hub.docker.com/r/nipreps/fmriprep/tags) and xcp_d 0.0.4 (https://hub.docker.com/r/pennlinc/xcp_abcd/tags). Following image processing, all subsequent analyses and statistics were conducted in R 4.0.2 (https://www.r-project.org) using original analysis code and Connectome Workbench 1.5.0 tools (https://www.humanconnectome.org/software/get-connectome-workbench). Original code, including code used to calculate regional fluctuation amplitude, fit regional GAMs, contextualize developmental and environmental effects and perform sensitivity analyses, has been deposited at Zenodo and is available at https://doi.org/10.5281/zenodo.7606653. A detailed description of the code and guide to code implementation is additionally provided at https://pennlinc.github.io/spatiotemp_dev_plasticity/.

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CHAPTER 4: DIMINISHED REWARD RESPONSIVENESS IS ASSOCIATED WITH LOWER REWARD NETWORK GLUCEST: AN ULTRA-HIGH FIELD GLUTAMATE IMAGING STUDY

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Abstract

Low reward responsiveness (RR) is associated with poor psychological well-being, psychiatric disorder risk, and psychotropic treatment resistance. Functional MRI studies have reported decreased activity within the brain's reward network in individuals with RR deficits, however the neurochemistry underlying network hypofunction in those with low RR remains unclear. This study employed ultra-high field glutamate chemical exchange saturation transfer (GluCEST) imaging to investigate the hypothesis that glutamatergic deficits within the reward network contribute to low RR. GluCEST images were acquired at 7.0 T from 45 participants (ages 15–29, 30 females) including 15 healthy individuals, 11 with depression, and 19 with psychosis spectrum symptoms. The GluCEST contrast, a measure sensitive to local glutamate concentration, was quantified in a meta-analytically defined reward network comprised of cortical, subcortical, and brainstem regions. Associations between brain GluCEST contrast and Behavioral Activation System Scale RR scores were assessed using multiple linear regressions. Analyses

revealed that reward network GluCEST contrast was positively and selectively associated with RR, but not other clinical features. Follow-up investigations identified that this association was driven by the subcortical reward network and network areas that encode the salience of valenced stimuli. We observed no association between RR and the GluCEST contrast within non-reward cortex. This study thus provides new evidence that reward network glutamate levels contribute to individual differences in RR. Decreased reward network excitatory neurotransmission or metabolism may be mechanisms driving reward network hypofunction and RR deficits. These findings provide a framework for understanding the efficacy of glutamate-modulating psychotropics such as ketamine for treating anhedonia.

Introduction

Reward responsiveness (RR) is a psychological construct that indexes an individual's capacity to experience pleasure or positive affect from the anticipation or attainment of rewards, and that falls within the Research Domain Criteria (RDoC) positive valence domain of human functioning. Low RR is a symptom common to diverse psychiatric disorders, including depression and psychosis spectrum disorders, that predicts poor treatment response and prognosis (McMakin et al., 2012; Nutt et al., 2007; Uher et al., 2014; Vrieze et al., 2014; Wolf, 2006). In individuals without a diagnosable psychiatric disorder, low RR is furthermore associated with increased risk of developing psychopathology (Cressman et al., 2015; Pizzagalli, 2014; Winer et al., 2017). RR is thus a dimensional construct associated with psychological well-being (Taubitz et al., 2015) that cuts across both DSM-defined diagnostic categories and clinical versus non-clinical samples. Elucidating neural features that contribute to individual differences in RR has broad implications for understanding the neurobiology of psychiatric illness and pharmacological treatment response.

Functional MRI studies have provided insight into circuit-level correlates of RR, demonstrating that lower RR is associated with lower activity (Harvey et al., 2010; Keller et al., 2013; Simon et al., 2010; Smoski et al., 2009; Stepien et al., 2018; Wacker et al., 2009) and connectivity (Keller et al., 2013; Sharma et al., 2017) within the brain's reward network. This pattern of altered brain function has been observed both in patients with psychiatric disorders that affect RR (Harvey et al., 2010; Sharma et al., 2017; Stepien et al., 2018) and in healthy individuals with non-clinical anhedonia (Keller et al., 2013; Simon et al., 2010; Wacker et al., 2009). Compromised reward network functioning has therefore been directly implicated in the expression of reward-related deficits. Nevertheless, the neurochemical mechanisms underlying such network hypofunction in those with lower RR remain unclear. Although dopamine is classically associated with reward, glutamate is also a major modulator of reward network functioning (Geisler and Wise, 2008; Haber, 2016; Haber and Knutson, 2010; Höflich et al., 2018; Sesack et al., 2003; Sesack and Grace, 2010). Mesolimbic reward pathway dopaminergic inputs from the ventral tegmental area to the ventral striatum are largely activated by glutamatergic neurotransmission (Sesack and Grace, 2010; Stuber et al., 2012), hence glutamate impacts reward anticipation and incentive salience. Furthermore, large glutamatergic efferents connecting the prefrontal cortex to the striatum can influence motivation and evaluation of stimulus valence (Cox and Witten, 2019; Haber, 2016; Sesack and Grace, 2010). Given the potential for glutamatergic signaling to affect diverse aspects of reward responsivity, here we investigate the hypothesis that glutamatergic deficits within the reward network contribute to diminished RR.

This hypothesis is motivated in part by results from preclinical and clinical studies that pharmacologically manipulate the glutamatergic system. In rodents and non-human primates, antagonism of AMPA and group 1 metabotropic glutamate receptors decreases the rewarding effects of drugs and food (Bisaga et al., 2008; D'Souza, 2015; Lee et al., 2005; You et al., 2007). In humans, ketamine—which indirectly drives glutamatergic activation of AMPA receptors on excitatory neurons via interneuron NMDA blockade (Koike et al., 2011; Ronald S. Duman et al., 2019)—is capable of rapidly reducing anhedonia (Ballard et al., 2017; Lally et al., 2015). Though convergent evidence from preclinical and clinical studies indicates that glutamate availability in reward-associated regions may be a critical modulator of RR, validation in humans remains elusive. This noteworthy gap in the literature exists in part due to limitations in our ability to study glutamate in the brain in vivo.

To date, proton magnetic resonance spectroscopy (^{1}HMRS) has been the method most commonly used to study glutamate in vivo (Henning, 2018). A main benefit of ^{1}HMRS is that it can simultaneously measure the concentration of diverse neurochemicals, including glutamate, creatine, choline, myo-inositol, glutathione, and N-acetylaspartate, providing important insight into brain biochemistry and relationships amongst neurometabolites. Its utility in measuring glutamate, however, is principally limited by the low concentration of glutamate in the brain compared to water, as well as by resonance overlap with glutamine and GABA (Hu et al., 2007; Wu et al., 2016). This study therefore harnesses a complementary approach to imaging brain glutamate at ultra-high field (7.0 T): glutamate chemical exchange saturation transfer (GluCEST) imaging (Cai et al., 2012; Nanga et al., 2018). GluCEST is a magnetization transfer-based method that measures glutamate levels via a water pool-dependent imaging contrast, thus largely overcoming the concentration limitations of ^{1}HMRS. Critically, the magnitude of the contrast effect observed, quantified as the GluCEST contrast, is proportional to the local concentration of glutamate (Cai et al., 2012). While both ^{1}HMRS and GluCEST have inherent pros and cons, key advantages of GluCEST include a substantial increase in sensitivity to glutamate (Cai et al., 2012) and the ability to more directly mitigate effects of cerebrospinal fluid contamination on glutamate quantification. Moreover, GluCEST produces a high-resolution image that covers a large expanse of the brain with small voxel sizes (a 5 mm thick sagittal slice with complete in-plane brain coverage), thereby providing enhanced spatial coverage and spatial resolution (Wu et al., 2016).

Here, we quantified the GluCEST contrast in a meta-analytic reward network in individuals with and without diagnosable psychopathologies to test the overarching hypothesis that individual variation in RR is affected by brain glutamate. Based on aforementioned results from functional MRI studies and trials of glutamate-modulating psychotropics, we predicted that reduced RR would be associated with lower levels of reward network GluCEST. Further, because the total reward network is a neuroanatomically expansive network encompassing areas that respond to rewards, areas that respond to negative outcomes, and areas that encode the magnitude of both rewarding and negative outcomes, we undertook analyses designed to provide anatomical and valence specificity regarding the relationship between brain GluCEST and RR.

Methods

Participants

To sample a broad range of RR, we studied healthy individuals and individuals with psychiatric conditions that can affect RR. The final study sample (N = 45, ages 15–29, 30 female) thus included a typically developing group (no axis I diagnoses or subthreshold psychosis symptomatology, no history of psychotropic medication use, N = 15) and a clinical group comprised of individuals classified by doctoral-level clinician scientists (TDS, CK, MEC) as having depressive disorders (N = 11) or psychosis spectrum disorders (N = 19 total, including 12 with clinical high risk symptoms and 7 with a diagnosed psychotic disorder). Study exclusion criteria and participant medication information are reported in Supplementary Information (SI). All procedures were approved by the Institutional Review Boards of the University of Pennsylvania and/or the Children's Hospital of Philadelphia. All participants over the age of 18 provided written informed consent prior to study participation. For minors, informed assent and written parental consent were obtained.

Clinical questionnaires

To assess RR, participants completed the Behavioral Activation System (BAS) Scale (Carver and White, 1994). Factor analyses have identified three independent, empirically derived BAS subscales, which have been validated in both non-clinical and psychiatric samples (Campbell-Sills et al., 2004; Carver and White, 1994; Jorm et al., 1998; Sharma et al., 2017): BAS RR, BAS Drive, and BAS Fun Seeking. The five BAS RR items were reverse scored and summed to produce a dimensional, trait-like measure of RR (Carver and White, 1994; Kasch et al., 2002) ranging from 5 (low RR) to 20 (high RR). Participants additionally completed the Patient-Reported Outcomes Measurement Information System (PROMIS) depression scale and the PRIME Screen-Revised (PS-R) (Kobayashi et al., 2008; Miller et al., 2004). These scales were used to generate graded measures of depression severity and subthreshold positive psychosis symptom severity, respectively.

MRI acquisition

MRI data were acquired on a 7.0 T Siemens Terra at the University of Pennsylvania. Acquisition of GluCEST images and B0 and B1 maps was completed as described in previous studies (Cai et al., 2012; Roalf et al., 2017), and as detailed extensively in SI. Briefly, GluCEST images were acquired in a 5 mm sagittal slice (slice number: 1, slice thickness: 5 mm) positioned in the right hemisphere to cover key reward network regions. This GluCEST field of view (FOV) offers full in-plane brain coverage (matrix size: 224 × 224) with 1 × 1 mm2 in-plane resolution (Cai et al., 2012; Roalf et al., 2017). Structural images including T1-weighted uniform (UNI) images and corresponding INV1 and INV2 images were acquired with a magnetization prepared 2 rapid acquisition gradient echoes (MP2RAGE) sequence (acquisition details in SI) (Marques et al., 2010). GluCEST and MP2RAGE data were originally acquired from a total of 53 participants. Raw and processed UNI images, GluCEST images, B0 maps, and B1 maps from all 53 participants underwent stringent visual quality control procedures. Overall, 8 of the 53 participants were ultimately excluded from the study due to identifiable motion in GluCEST images or the presence of large inhomogeneity artifacts in B0 maps, resulting in the final analytic study sample of $N = 45$ individuals from which all reported results were obtained.

MR image processing

Figure 4-1 provides an overview of the image analysis pipeline. INV2 and UNI images were bias field corrected using advanced normalization tools (ANTs) N4 (Tustison et al., 2010), and used for tissue segmentation and atlas registration, respectively. FSL FAST (Zhang et al., 2001) was employed to generate three tissue segmentation maps and gray matter density maps. In order to register atlases from

MNI space to participant images, UNI images were first nonlinearly registered to the MNI152 nonlinear T1 template using ANTs symmetric diffeomorphic image normalization (Avants et al., 2008).

GluCEST images represent the GluCEST contrast (%) in each voxel (equation in SI). GluCEST images were first corrected for B_0 and B_1 inhomogeneity effects using in-house Matlab software, as previously described (Cai et al., 2012; Roalf et al., 2017). As prior, voxels that had a B_0 offset of greater than ±1 ppm and voxels with relative B_1 values outside of the 0.3–1.3 range were excluded (Roalf et al., 2017), as were voxels labeled as cerebrospinal fluid by tissue segmentation maps.

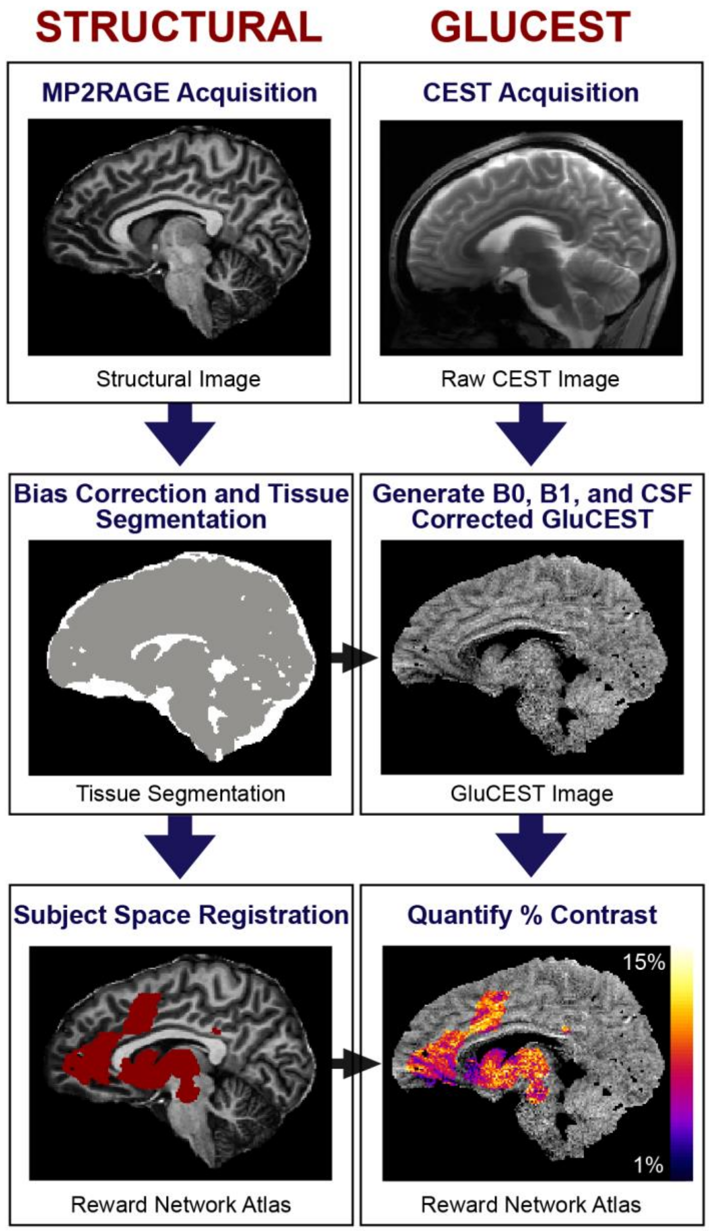


Figure 4-1. Overview of Structural and GluCEST Processing
Structural: Structural images acquired as part of the 7.0 T magnetization prepared 2 rapid acquisition gradient echoes (MP2RAGE) sequence were bias field corrected and used to generate tissue segmentation maps

(cerebrospinal fluid voxels shown in white, brain tissue in gray). Atlases were registered from MNI space to participant images. **GluCEST**: B_0 and B_1 inhomogeneity-corrected GluCEST images were generated from raw chemical exchange saturation transfer (CEST) images, and voxels labeled as cerebrospinal fluid (CSF) by tissue segmentation maps were removed from final GluCEST images. The GluCEST contrast was then estimated in the meta-analytic reward network. The color bar (bottom right) represents the average GluCEST contrast in each $1 \times 1 \times 5$ mm^3 GluCEST voxel, scaled from 1% contrast (dark blue) to 15% contrast (light yellow).

Reward network delineation

To study the relationship between reward network GluCEST and RR, we delineated the reward network using a recent meta-analysis of 206 functional MRI studies (Bartra et al., 2013) (further meta-analysis details are provided in SI). The meta-analytic reward network atlas was aligned from MNI space to GluCEST images by applying the inverse of precomputed composite UNI-to-MNI transforms, and extracting the portion of the atlas that corresponded to a participant's GluCEST FOV. It should be noted that the GluCEST FOV did not provide complete coverage of the reward network. Accordingly, the percent of the network included in each participant's GluCEST acquisition was calculated to provide an estimate of network spatial coverage, and included as a model covariate in a sensitivity analysis.
Given that the reward network is inherently heterogeneous in both regional anatomy and valence encoding, we furthermore subdivided the meta-analytic reward network both structurally and functionally for analyses designed to enhance the anatomical and functional precision of our primary results. Specifically, we independently evaluated cortical and subcortical regions of the network, defined using Harvard–Oxford (Desikan et al., 2006) cortical and subcortical atlases. We additionally partitioned the network into three valence-specific components based on the original meta-analysis (Bartra et al., 2013), including an appetitive/positive valence encoding component, an aversive/negative valence encoding component, and a salience component.

Statistical analysis

Statistical analyses were performed in R 4.0.2. We investigated associations between GluCEST contrast and BAS RR scores across the entire sample using multiple linear regressions. All regressions reported controlled for age and sex and met linearity, homoscedasticity, and normality assumptions. For each multiple regression analysis, the individual predictor t value quantifying the association between GluCEST and BAS RR scores was used to calculate a partial r value (rPARTIAL): an estimate of the association effect size. False discovery rate correction (FDR; pFDR) was employed to correct for multiple comparisons within anatomical and valence-specific follow-up analyses. Following the main analyses, we conducted a series of rigorous sensitivity and specificity analyses to ensure that observed effects were not being driven by reward network gray matter density, reward network coverage, depression symptoms, psychosis symptoms, or scores on other BAS domains. Each of these variables was included as a model covariate in a multiple linear regression.

Code availability

All analytic code is available at https://github.com/PennLINC/sydnor_glucest_rewardresponsiveness_2020.

Results

BAS Reward Responsiveness indexes RR across typically developing and clinical groups

Sample demographics and clinical information are presented in Table 4-1. BAS RR scores were variable across the entire sample (min = 12, max = 20, mean = 17.4, SD = 1.9), reflecting the dimensional nature of this measure, and more variable in the clinical than the typically developing group (Table 1). There was a trend for BAS RR scores to be higher in females than males ($t = 1.79$, $p = 0.081$).

Demographic and clinical variables	Study sample *N* = 45	Typically developing *N* = 15	Clinical *N* = 30	*t*-test or Pearson's chi-squared test
Age	22.78 (2.8)	22.60 (2.9)	22.87 (2.8)	$p = 0.770$
Sex				
Male	15	5	10	$p = 1.000$
Female	30	10	20	
Race				
Asian	1	0	1	$p = 0.442$
Black	24	6	18	
White	17	8	9	
>1 race	3	1	2	
BAS reward responsiveness score	17.36 (1.9)	17.53 (1.4)	17.27 (2.1)	$p = 0.658$
PROMIS depression symptom score	12.84 (6.3)	9.73 (1.8)	14.40 (7.1)	$p = 0.002$[a]
PS-R positive psychosis symptom score	5.98 (9.7)	0.53 (1.1)	8.70 (10.9)	$p < 0.001$[a]

Table 4-1. Sample Demographics and Clinical Characteristics
Age, sex, race, and clinical questionnaire score means are presented for the study sample, as well as for the typically developing and clinical groups that make up the sample. Differences between typically developing and clinical groups (right column) were evaluated using two-sided independent samples t-tests (for age and clinical scores) and Pearson's chi-squared tests (for sex and race).BAS Behavioral Activation System, PROMIS Patient-Reported Outcomes Measurement Information System, PS-R PRIME Screen-Revised. [a]Significant difference between groups in a two-sided independent samples t-test with unequal variances.

Reward network GluCEST does not differ between typically developing and clinical groups

Reward network GluCEST contrast did not significantly differ between the typically developing and clinical group in an ANCOVA controlled for age and sex, indicating that diagnostic status did not influence reward network glutamate level. Diagnostic status was, however, related to the GluCEST signal within specific, anatomically defined regions of interest, in a manner that largely replicated previously published 7.0 T 1HMRS case–control studies (see SI for full results and comparisons to previous 1HMRS studies).

Reward network GluCEST is dimensionally associated with RR

To investigate relationships between the dimensional construct of RR and glutamate within brain regions that do and do not subserve reward-related functions, we conducted a multiple regression with reward network GluCEST and non-reward network GluCEST as predictors of BAS RR. BAS RR scores were significantly positively associated with reward network GluCEST contrast in this model (estimate = 1.01, r_{PARTIAL} = 0.31, p = 0.048; **Figure 4-2**). Highlighting the specificity of this association, BAS RR scores were not significantly associated with non-reward network GluCEST contrast, i.e., with GluCEST in regions not included in the meta-analytic reward network (estimate = 0.11, r_{PARTIAL} = 0.03, p = 0.864). The association between BAS RR scores and reward network GluCEST contrast did not differ between males and females, as indicated by a non-significant interaction term (p = 0.693) between sex and GluCEST contrast for predicting BAS RR.

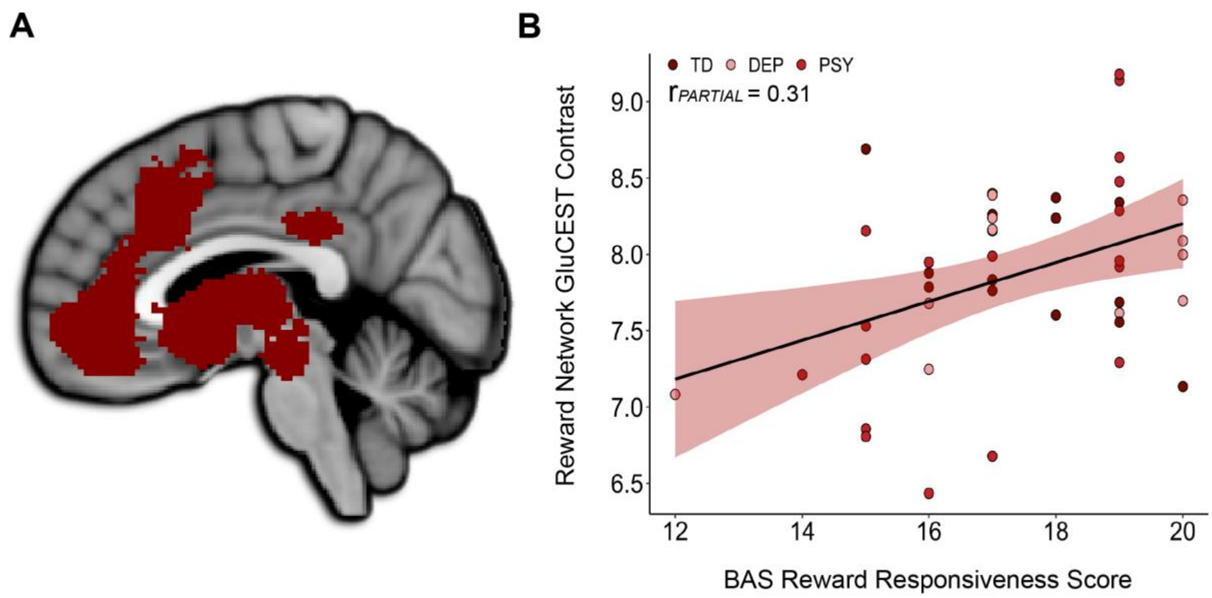


Figure 4-2. Association Between Dimensional Reward Responsiveness and Reward Network GluCEST
A) The meta-analytically defined reward network comprised of cortical, subcortical, and upper brainstem regions. **B)** Reward network GluCEST contrast was positively associated with BAS Reward Responsiveness scores across typically developing and clinical groups. Data points are differently colored for typically developing (TD) individuals, individuals with a depressive disorder (DEP), and individuals with a psychosis spectrum disorder (PSY).

Association between reward network GluCEST and RR is driven by subcortical regions

Anatomical division of the total reward network into cortical and subcortical components (**Figure 4-3A**) revealed a non-significant association between BAS RR scores and cortical reward network GluCEST contrast. There was, however, a significant association between BAS RR scores and subcortical reward network GluCEST (estimate = 0.69, $r_{\mathrm{PARTIAL}} = 0.37$, $p_{\mathrm{FDR}} = 0.027$; **Figure 4-3B**), suggesting that the main result was driven by subcortical reward regions. In an exploratory analysis designed to provide enhanced anatomical resolution, we further divided the reward network into 11 distinct anatomical regions. Region-specific multiple regressions revealed the strongest associations between BAS RR scores and the GluCEST contrast within the caudate, posterior cingulate, and thalamus, followed by the brainstem (midbrain/upper pons) and the nucleus accumbens (**Supplementary Figure 4-1**), though results of these regional analyses did not survive FDR correction.

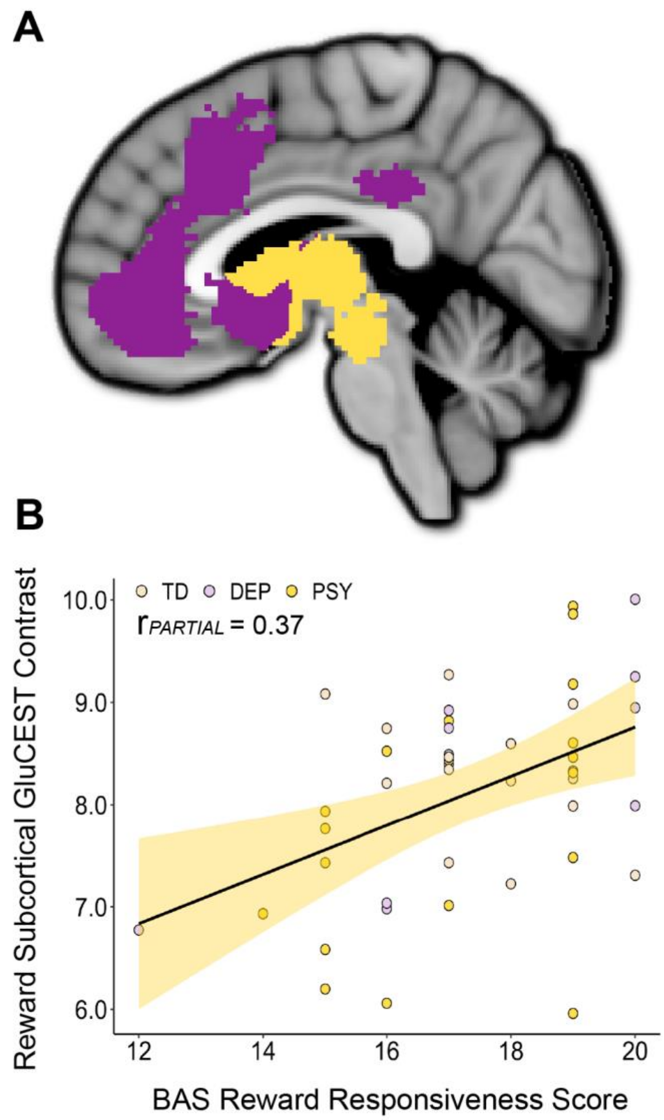
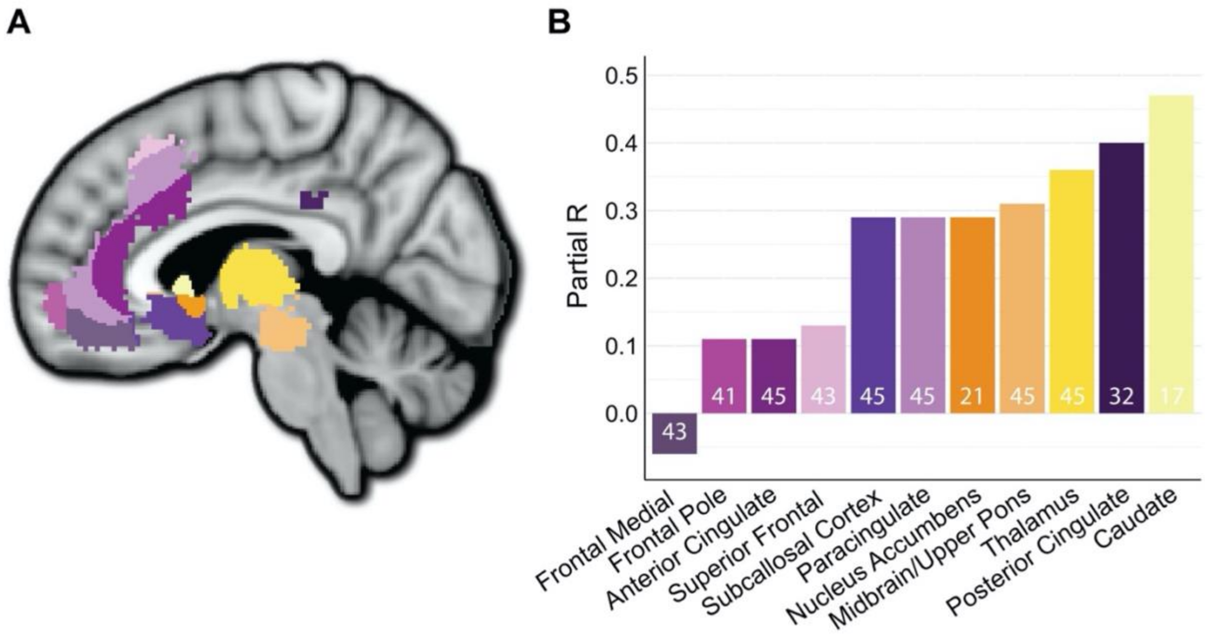


Figure 4-3. Association Between Dimensional Reward Responsiveness and Subcortical Reward Network GluCEST

A) Cortical (purple) and subcortical (yellow) components of the reward network. **B)** GluCEST imaging revealed a significant association between BAS Reward Responsiveness scores and the GluCEST contrast in the subcortical reward network. Individual data points are colored based on diagnosis; TD typically developing, DEP depressive disorder, PSY psychosis spectrum disorder.



Supplementary Figure 4-1. Effect Size by Reward Network Anatomical Subdivision
A) The reward network segmented into 7 cortical (purple/pink) and 4 subcortical (yellow/orange) subregions. **B)** Effect sizes for the association between regional GluCEST contrast and BAS Reward Responsiveness scores across the 11 subregions. Minimum coverage of 50 mm^3 was required for inclusion in this regional analysis. The sample size for each region is indicated within the bar.

Reward network GluCEST findings are influenced by valence encoding

The reward network was next functionally subdivided into (1) areas that are activated by appetitive stimuli only, (2) areas that are activated by aversive stimuli only, and (3) areas that respond to both appetitive and aversive stimuli, and are thus understood to encode the salience of valenced stimuli (Bartra et al., 2013). Independent, valence-specific multiple regressions revealed that the association between BAS RR scores and GluCEST contrast was significant in reward network regions responsive to stimulus salience (estimate = 0.95, rPARTIAL = 0.42, pFDR = 0.014) and trend level in appetitive-encoding regions (estimate = 0.76, rPARTIAL = 0.29, pFDR = 0.083), but not significant in aversive-encoding regions (**Figure 4-4**).

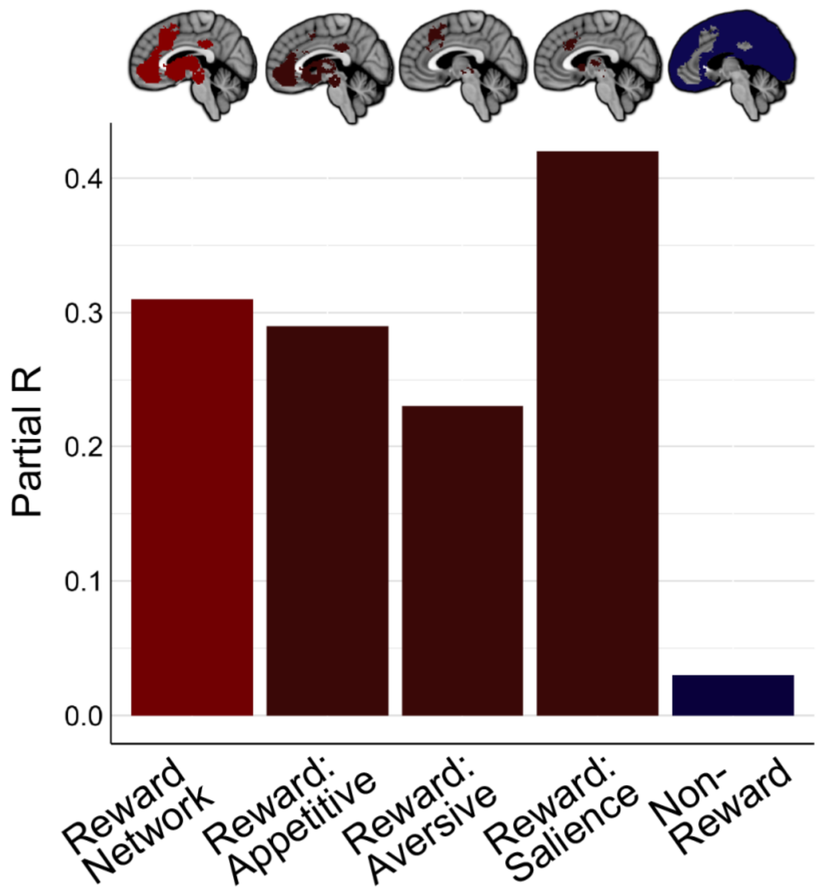


Figure 4-4. Effect Size Determined by Valence Encoding
Effect sizes for the association between brain GluCEST contrast and BAS Reward Responsiveness scores for the total reward network, appetitive-encoding reward network regions, aversive-encoding reward network regions, salience-encoding reward network regions, and non-reward regions (left to right). Partial r values were derived from independent multiple linear regressions, as reported in the text.

Sensitivity analyses provide convergent results

A series of sensitivity analyses (all controlled for age and sex) confirmed that the association observed between total reward network GluCEST contrast and RR was not attributable to other brain features, methodological considerations, or comorbid psychiatric symptoms. Specifically, the association between reward network GluCEST and BAS RR scores remained significant when controlling for reward network gray matter density (estimate = 1.06, $r_{PARTIAL} = 0.36$, $p = 0.020$), indicating that differences in network tissue composition were not driving results. Given that the GluCEST FOV did not encompass the entirety of the reward network, we confirmed that controlling for percent coverage of the total reward network did not alter our findings (estimate = 1.05, $r_{PARTIAL} = 0.35$, $p = 0.022$). To further confirm that differential network coverage was not impacting results, we performed an exploratory analysis that only included reward network voxels for which greater than 50% of participants had GluCEST data. This did not impact significance (estimate = 0.90, $r_{PARTIAL} = 0.35$, $p = 0.022$). Finally, the association between reward network GluCEST and BAS RR scores remained significant when controlling for typically developing versus clinical group (estimate = 1.04, $r_{PARTIAL} = 0.35$, $p = 0.024$).

Reward network GluCEST associations are specific to the construct of RR

To confirm the specificity of the association between reward network GluCEST contrast and RR, we conducted specificity analyses using multiple regressions that included additional measures of clinical features. All models included age, sex, and BAS RR scores as predictors. Notably, in these models we did not find any significant associations between reward network GluCEST contrast and PS-R scores ($p = 0.267$), PROMIS depression scores ($p = 0.383$), BAS Drive scores ($p = 0.685$), or BAS Fun Seeking scores ($p = 0.371$). Conversely, BAS RR remained significant or trend level significant in all of these models ($p = 0.016$ covarying for PS-R, $p = 0.081$ covarying for PROMIS depression, $p = 0.022$ covarying for BAS Drive, $p = 0.085$ covarying for BAS Fun Seeking).

GluCEST and single voxel 1HMRS demonstrate cross-method agreement

Finally, to compare results between GluCEST and 1HMRS, the method most frequently employed to measure brain glutamate in vivo, 1HMRS data were collected from a subsample of the 45 study participants (final $N = 20$ following quality control procedures). 1HMRS data were collected from a single voxel of interest (VOI) positioned in the right anterior cingulate cortex, a frequently studied 1HMRS VOI in psychiatry (Colic et al., 2019; Gabbay et al., 2017, 2012; Moriguchi et al., 2019; Sydnor and Roalf, 2020; Walter et al., 2009). Independent multiple regression analyses revealed that associations of BAS RR scores with both (1) 1HMRS-derived glutamate concentration within the VOI and (2) mean GluCEST within the VOI were similar in strength, suggesting cross-method convergence. Moreover, 1HMRS- and GluCEST-derived measures of glutamate were positively correlated within the VOI. The strength of this correlation was dependent on the degree of anatomical overlap between the 1HMRS VOI and the GluCEST FOV, and ranged from $r_{\text{PARTIAL}} = 0.26$ in all participants to $r_{\text{PARTIAL}} = 0.36$ in those with > 50% anatomical overlap, and to $r_{\text{PARTIAL}} = 0.60$ in those with > 90% anatomical overlap. Extended results and corresponding methods are available in SI.

Discussion

Using a clinically diverse sample and the novel 7.0 T glutamate imaging method GluCEST, we found that a lower GluCEST contrast in the brain's reward network was dimensionally related to diminished RR. This finding links individual differences in RR to differences in neurochemistry within brain regions involved in reward encoding, incentive salience, and valence evaluation. The association observed here between GluCEST and RR was specific to the reward network, and selective for RR but not for other clinical features. This work therefore provides evidence of a neuroanatomically- and construct-specific relationship between reward network glutamate and RR, implicating a main excitatory neurotransmitter and neurometabolite in reward sensitivity and anhedonia.

Glutamate-modulating psychotropics have recently demonstrated efficacy for treating anhedonia (Ballard et al., 2017; Lally et al., 2015), motivating clinical interest in parsing relationships between glutamate and reward functioning. Yet, to our knowledge, this is the first study to demonstrate that an in vivo measure of glutamate quantified in cortical, subcortical, and brainstem reward regions relates to RR. A handful of previous investigations examined associations between anhedonia severity and brain glutamate using ^{1}HMRS, yet these studies predominantly reported null results (Bradley et al., 2018; Colic et al., 2019; Gabbay et al., 2017, 2012; Godlewska et al., 2018; Walter et al., 2009). This discrepancy between past ^{1}HMRS findings and this report is likely attributable to the following technical and conceptual advances offered by the present study: (1) in contrast to previous ^{1}HMRS anhedonia studies, which assessed metabolites within the anterior cingulate cortex (Colic et al., 2019; Gabbay et al., 2017, 2012; Godlewska et al., 2018; Walter et al., 2009) or striatum (Bradley et al., 2018) only, we quantified the GluCEST contrast across a neuroanatomically expansive portion of the reward network; (2) we acquired GluCEST data at 7.0 T (rather than at 3.0 T (Bradley et al., 2018; Gabbay et al., 2017, 2012; Walter et al., 2009)), thus capitalizing on improvements in sensitivity and signal-to-noise ratio obtainable at higher field strengths (Moser et al., 2012); and (3) we studied a transdiagnostic sample using a dimensional measure of RR—an approach distinct from past efforts focused on patients with major depression and severe clinical anhedonia (Bradley et al., 2018; Colic et al., 2019; Gabbay et al., 2017, 2012; Godlewska et al., 2018; Walter et al., 2009). Considered in conjunction with prior studies relating low RR to reduced reward network BOLD activity (Harvey et al., 2010; Keller et al., 2013; Simon et al., 2010; Smoski et al., 2009; Stepien et al., 2018; Wacker et al., 2009), these GluCEST results provide novel evidence that reward region glutamatergic deficits may in part drive the association between reward network hypofunction and low RR.

The circuitry of the reward network has been extensively delineated in rodents and non-human primates, and the importance of glutamatergic projections within this network has been described (Cox and Witten, 2019; Geisler and Wise, 2008; Haber, 2016; Haber and Knutson, 2010; Höflich et al., 2018; Sesack et al., 2003; Sesack and Grace, 2010). Cortical reward glutamatergic efferents converge in the midbrain and striatum, two key regions for reward anticipation and responding, likely explaining the stronger association between GluCEST and RR observed in the subcortical reward network. The relationship between GluCEST and RR was additionally influenced by regional valence-related functioning, as it was stronger in brain areas that encode appetitive stimuli or the salience of valenced stimuli than in those that preferentially respond to aversive stimuli. This finding is consistent with the RDoC classification of RR within the positive valence domain, as well as with theories positing that glutamatergic signaling in brain regions subserving reward mediates stimulus and incentive salience (Batten et al., 2018; Berridge, 2012).

The central role that glutamatergic neurotransmission plays in reward-associated processes provides a direct mechanism—decreased excitatory neural communication—by which lower glutamate levels in reward network regions could lead to network dysfunction and diminished RR. This interpretation accords with preclinical findings that glutamate receptor pharmacological blockade decreases responding to rewards (Bisaga et al., 2008; D'Souza, 2015; Lee et al., 2005; You et al., 2007), whereas optogenetic activation of reward network glutamatergic afferents is rewarding and reinforcing (Britt et al., 2012; Qi et al., 2014; Yoo et al., 2017). Moreover, this interpretation is supported by the fact that the CEST acquisition employed in this study is sensitive to glutamate at the pH found within glutamate-containing synaptic vesicles (pH 5–6) and synaptic and extrasynaptic spaces (pH 7–7.5) (Atluri and Ryan, 2006; Cai et al., 2012; Egashira et al., 2016). Still, GluCEST's sensitivity to glutamate at a pH of ~7 ensures it additionally measures intracellular glutamate present within both neurons and astrocytes. Glutamate located within these cellular compartments plays a vital role not only in neurotransmission, but also in neurometabolism (McKenna, 2007). Accordingly, both decreased excitatory signaling and altered network metabolism could contribute to the association observed between lower reward network GluCEST contrast and lower RR.

Deficits in RR frequently emerge during adolescence (Bennik et al., 2014) and following periods of chronic stress (Pizzagalli, 2014; Stanton et al., 2019). Notably, these are two timeframes characterized by overall reductions in glutamatergic synapses and signaling (Duman, 2014; Shimizu et al., 2017). Our GluCEST results thus provide a framework for understanding the link between the onset of diminished RR and neurobiological changes that occur during neurodevelopment or stress-induced neurodegeneration, i.e., during two vulnerable periods for glutamate perturbations. Given that diminished RR is furthermore a risk factor for development of mood disorders (Bennik et al., 2014; Stringaris et al., 2015; Winer et al., 2017) and suicidality (Hawes et al., 2018; Winer et al., 2016, 2014), we speculate that low reward network glutamate may partially mediate the association between low RR and development of these psychopathologies.

For individuals with diagnosed psychopathologies, anhedonia is a consistent predictor of poor psychotropic treatment response (McMakin et al., 2012; Nutt et al., 2007; Uher et al., 2014; Vrieze et al., 2014; Wolf, 2006). The present work suggests that some patients with anhedonia may have a glutamate-based disruption, potentially explaining why such individuals do not respond to conventional antidepressants, which target monoamines, or conventional antipsychotics, which are dopamine antagonists. Clinical trials that harness 7.0 T GluCEST to assess the role of reward network glutamate level in treatment resistance would thus be highly informative. These trials could provide insight into the utility of ultra-high field neurochemical imaging for predicting treatment response, potentially paving the way to neurochemistry-informed treatment stratification in psychiatry. Currently, clinical translation of 7.0 T GluCEST is limited by a lack of widely available 7.0 T MRIs, the high cost of scanning, and insufficient data available for defining normative versus low ranges of the GluCEST contrast. However, increased integration of 7.0 T imaging into routine clinical care and collection of GluCEST data from large healthy and patient samples would enable the use of objective, evidence-based, neurobiological CEST imaging measures in psychiatric patient care.

GluCEST has inherent limitations (Cai et al., 2012; Roalf et al., 2017), including the acquisition FOV, which limited analysis to a portion of the reward network. Regarding the GluCEST contrast, it must be noted that while at least 70% of the CEST effect is directly attributable to magnetization transfer from glutamate to water, up to 30% of the signal can come from exchangeable protons on other macromolecules (e.g., creatine), though notably none of the signal is from glutamine (Cai et al., 2012).

Unlike ^{1}HMRS, GluCEST does not provide information about other neurochemicals (e.g., myo-inositol or N-acetylaspartate). Future studies may thus consider acquiring both GluCEST and ^{1}HMRS data in a complementary manner. This would simultaneously capitalize on the enhanced spatial coverage and resolution provided by GluCEST and the localized measurement of multiple metabolites enabled by ^{1}HMRS. Last, we did not exclude individuals taking psychotropic medications given our clinical study sample, though medications may impact brain neurochemicals. Adjustment for medication did not, however, alter our results: partial correlations between BAS RR scores and reward network GluCEST, subcortical reward GluCEST, and salience reward GluCEST all remained significant (ps < 0.05) when controlling for psychotropic medication use (yes/no).

In conclusion, by harnessing the ultra-high field glutamate imaging method GluCEST, we identified a significant and selective relationship between RR and the GluCEST contrast in the brain's reward network, implicating reward network glutamatergic deficiencies in diminished reward sensitivity. Future longitudinal studies designed to parse relationships between brain glutamate, RR deficits, and progression to psychopathology are warranted. More broadly, this study demonstrates the utility of in vivo neurochemical imaging, highlighting its potential to identify druggable targets for ameliorating psychiatric symptoms that are frequently treatment-resistant.

Supplementary Information

Participant Recruitment, Study Exclusion Criteria, and Sample Medication Information

Participants were recruited from the community through ongoing research and clinical activities in the Brain Behavior Laboratory, the Lifespan Brain Institute, the Penn Psychosis Evaluation &

Recovery Center, and the Outpatient Psychiatry Center at the Perelman School of Medicine, University of Pennsylvania. Study exclusion criteria included a previous or current significant medical or neurological illness, previous head trauma with loss of consciousness, acute intoxication, acute substance withdrawal, substance abuse or dependence within the past six months, pregnancy, contraindications to receiving an MRI, and GluCEST data that failed rigorous visual quality assurance checks. This study did not exclude individuals with a history of psychotropic medication use from the clinical group. Eighteen individuals in the clinical group reported a history of being prescribed at least one psychotropic medication, representing 40% of the entire sample and 60% of the clinical sample. Reported medications were highly variable across individuals, and included antidepressants ($N = 7$), anxiolytics ($N = 1$), mood stabilizers ($N = 3$), antipsychotics ($N = 2$), stimulants ($N = 4$), and class not reported ($N = 5$).

Additional Information on Clinical Questionnaires

All participants completed clinical questionnaires on the day of the MRI scan, with the exception of two participants who completed questionnaires 6 and 15 days prior to scanning.

Behavioral Activation System Scale: A Measure of Reward Responsiveness

The Behavioral Activation System (BAS) Scale comprises 13 questions answered on a 4-point Likert scale, and provides insight into motivational systems that influence an individual's affect and behavior (Carver and White, 1994). The BAS Reward Responsiveness (BAS RR) subscale is a reliable measure of reward sensitivity that predicts happiness levels during reward anticipation (Carver and White, 1994), behavior on reward tasks (Braem et al., 2012; Capa and Bouquet, 2018; Suhr and Tsanadis, 2007), and brain responses to rewards (Kim et al., 2015; Van den Berg et al., 2011). BAS RR scores have been found to remain stable over time despite fluctuations in clinical state (Kasch et al., 2002).

The Patient-Reported Outcomes Measurement Information System Depression Scale

The Patient-Reported Outcomes Measurement Information System (PROMIS) Depression scale consists of 8 questions answered on a 5-point Likert scale. Questions assess feelings of sadness, helplessness, hopelessness, and worthlessness. To index overall depression severity, the eight PROMIS items were summed into a composite depression symptom severity score.

PRIME Screen-Revised

The PRIME Screen-Revised (PS-R) assesses the presence of positive psychotic symptoms, and is sensitive to both sub- and supra-threshold psychosis symptomatology. The 12 PS-R items, answered on a 7-point Likert scale, were summed into a composite score. Two participants did not have data for one PRIME item; the two missing values were imputed by taking the average of all other items.

Neuroimage Acquisition Parameters

GluCEST

Glutamate is an optimal metabolite to quantify with CEST imaging at 7.0T given that the proton exchange rate with water is slow to intermediate. This exchange regimen allows for continuous application of radiofrequency pulses and a prolonged saturation period, and thus for accumulation of the contrast effect and enhanced methodological sensitivity. The contrast effect is produced when exchangeable amine protons on glutamate that are saturated via frequency-selective radiofrequency pulses exchange with unsaturated protons on water, decreasing the bulk water signal. Hence, a higher concentration of tissue glutamate leads to increased B_1 saturation of glutamate protons, greater proton exchange and attenuation of the water signal, and a higher GluCEST contrast. The GluCEST contrast displays high within-day and between-day reproducibility (Nanga et al., 2018). Mathematically, the GluCEST contrast (%) is defined as:

$$\frac{\mathrm{Msat}(-3\mathrm{ppm}) - \mathrm{Msat}(+3\mathrm{ppm})}{\mathrm{Msat}(-3\mathrm{ppm})} \times 100$$

where Msat(-3ppm) is the amplitude of water proton magnetization during a baseline acquisition when glutamate protons are not saturated, and Msat(+3ppm) is the amplitude of water proton magnetization when the B_1 field is at the resonance frequency for glutamate (3 ppm downfield from water, see (Cai et al., 2012)).

GluCEST data were acquired in a right hemisphere sagittal slice in a field of view (FOV) placed near the midline. This FOV captures major reward network regions including the medial prefrontal cortex, posterior cingulate, ventral striatum, thalamus, and midbrain. Placement of the GluCEST FOV was initiated using ImScribe (https://www.med.upenn.edu/cmroi/imscribe.html). ImScribe was developed for use in group studies wherein acquisition of the same brain region(s) is desired, as it allows for reproducible selection of the same anatomical FOV across individuals.

The GluCEST acquisition parameters utilized in this study included: slice number = 1, slice thickness = 5 mm, FOV = 224 x 224, matrix size = 224 x 224, in-plane resolution = 1 x 1 mm^2, GRE read out TR = 6.4 ms, TE = 3 ms, number of averages = 1, shots per slice = 2, shotTR = 8000 ms. The CEST saturation pulse was as follows: B_{1rms} of 3.06 μT with a 800 ms long saturation pulse train consisting of a series of 95 ms Hanning windowed saturation pulses with a 5 ms interpulse delay (100 ms pulse train). Raw CEST images were acquired at varying saturation offset frequencies from ± 1.5 to ± 4.5 ppm (relative to water resonance) with a step size of ± 0.3 ppm. B_0 maps were acquired using water saturation shift referencing (Kim et al., 2009) with a saturation pulse at B_{1rms} of 0.29 μT with 200 ms long saturation pulse train and saturation offset frequencies from ± 0 to ± 1.5 ppm (relative to water resonance), with a step size of ± 0.15 ppm. A B_1 map was generated from three images obtained using square preparation pulses with flip angles 20°, 40°, and 80°. Total acquisition time was approximately 10 minutes.

MP2RAGE

Parameters for the 3D Magnetization Prepared 2 Rapid Acquisition Gradient Echoes (MP2RAGE) sequence were: 0.82 mm isotropic spatial resolution, 240 mm FOV with 176 slices, $TR/TE/TI_1/TI_2/$ = 5000/2.5/700/2500 ms, α_1/α_2 = 7°/5°, 240 Hz/Px bandwidth, 3 × GeneRalized Autocalibrating Partial Parallel Acquisition (GRAPPA) acceleration in the first phase-encoding direction and 6/8 partial Fourier undersampling in both phase-encoding directions. With MP2RAGE acquisitions, data from short (INV1) and long (INV2) inversion time images can be combined to mitigate B_1 inhomogeneity effects. This produces a more homogeneous T1-weighted image with superior gray matter to white matter contrast, referred to as a uniform (UNI) image.

Reward Network Delineation

The meta-analytically derived reward network atlas (Bartra et al., 2013) utilized in this study is comprised of brain regions that exhibited a significant change in the blood oxygen level-dependent (BOLD) signal in association with diverse rewarding outcomes and/or aversive outcomes across 206 functional MRI studies. The nature of outcomes was variable across these 206 studies and included monetary, social, consumable, and other outcomes. Hence, this network encompasses regions that evaluate or encode positively and negatively valenced outcomes across diverse situations and stimuli. Convergence across hundreds of functional MRI studies solidifies our confidence that these brain regions are central to reward responsiveness (RR).

The total meta-analytic functional reward network was divided into valence-related subcomponents for analyses presented **in Figure 4-4**. This was accomplished using valence maps from Bartra et al. (2013) Fig. 3AC. The appetitive encoding component included voxels that exhibited an increase in BOLD signal to more rewarding outcomes only in the overall meta-analysis (Bartra et al. Fig. 3A, excluding 3C). The aversive encoding component included voxels that exhibited an increase in BOLD signal to aversive or less rewarding outcomes only (Bartra et al. Fig. 3B, excluding 3C). The salience component included voxels that exhibited an increase in BOLD signal to both rewarding and negative outcomes (Bartra et al. Fig. 3C), and are thereby presumed to encode general reward salience.

Supplementary Results: GluCEST and Single Voxel ^{1}HMRS Demonstrate Cross-Method Agreement

Single voxel of interest (VOI) ^{1}HMRS data were collected from the right anterior cingulate cortex in a subsample of study participants to enable a methodological comparison between ^{1}HMRS and GluCEST. ^{1}HMRS data were acquired at the end of the scanning session and were collected from participants only when adequate time permitted. The ^{1}HMRS VOI was positioned in the anterior cingulate to maximize comparability between the present study and the majority of previous investigations that assessed associations between RR and brain glutamate with ^{1}HMRS (Colic et al., 2019; Gabbay et al., 2017, 2012; Godlewska et al., 2018; Walter et al., 2009). Below, we present findings from two sets of comparative analyses. In the first set of analyses, we studied the association between a) BAS RR scores and ^{1}HMRS glutamate concentration within the ^{1}HMRS VOI, and b) BAS RR scores and mean GluCEST contrast within this VOI. In the second set of analyses, we examined correlations between mean GluCEST contrast within the VOI and the concentration of numerous ^{1}HMRS-derived neurochemicals (including glutamate).

^{1}HMRS Acquisition, Neurometabolite Quantification, and Quality Control

The ^{1}HMRS VOI (average size 3000 mm^3) was placed using a semi-automated method via ImScribe; manual adjustment was used to fine-tune VOI positioning for each participant. ^{1}HMRS data were collected with a short echo time custom-modified Point RESolved Spectroscopy (PRESS) sequence with the following acquisition parameters: averages = 8 (water reference) / 128 (water suppressed), TE = 23 ms and TR = 3000 ms. Acquisition time was 36 seconds for the reference spectrum and 6 minutes 48 seconds for the suppressed spectrum. The water reference scan was used to compute the absolute concentration of brain neurochemicals, including absolute glutamate concentration. Water suppression was achieved with variable power RF pulses with optimized relaxation delays (VAPOR) prior to the acquisition. VAPOR implements seven frequency selective RF pulses to reduce sensitivity to variations in the B_1 field (Tkác et al., 1999). Pulse amplitudes were calibrated before measurement to reduce B_1 inhomogeneity by acquiring six localized STimulated Echo Acquisition Mode (STEAM) water spectra at fixed reference voltage and varying flip angle from 0º to 180º with a step size of 30º. The vendor-provided FASTESTMAP shimming method (from vendor Siemens Medical Solutions, Erlangen, Germany) was employed to minimize spectral linewidths (< 30 Hz) of water signal (Gruetter, 1993). Spectra obtained were analyzed using a user-independent spectral fit program, Linear Combination (LC) Model v6.3-1L with the corresponding 7T basis set (Provencher, 1993). To ensure that the ^{1}HMRS data used for comparative analyses was of high quality, participants with 1) a spectral peak full width half maximum (FWHM) > 0.1, 2) a signal-to-noise ratio (SNR) < 10, or 3) Cramer-Rao Lower Bound (CRLB) estimates > 15% for glutamate were excluded from all analyses. ^{1}HMRS data from 25 individuals passed these three ^{1}HMRS quality checks. From these 25 participants, an additional 5 participants were excluded from analyses due to low overlap between the ^{1}HMRS VOI and the GluCEST FOV (additional details below). Thus, 20 participants passed all quality control procedures.

Volume of Interest Processing and GluCEST Quantification

The ^{1}HMRS VOI was extracted from DICOM images and binarized to create a VOI mask using ImScribe. The cerebrospinal fluid volume fraction (fCSF) within the VOI mask was quantified for each participant (mean fCSF = 0.29 ± 0.12), as was the percent of the VOI occupied by reward network (mean percent = 55 ± 14) versus non-reward cortex (mean percent = 45 ± 14). To facilitate comparative analyses between ^{1}HMRS and GluCEST, the portion of the total VOI that was represented in each participant's 5 mm thick GluCEST FOV was extracted. This allowed for 1) quantification of the percent of the ^{1}HMRS VOI that overlapped with the GluCEST FOV, and 2) quantification of mean GluCEST, reward network GluCEST, and non-reward GluCEST within the portion of the ^{1}HMRS VOI included in the GluCEST FOV. For 5 of the 25 participants with ^{1}HMRS data that passed FWHM, SNR, and CRLB quality checks, the percent of the ^{1}HMRS VOI included in the GluCEST FOV was very low (< 20%). These 5 participants were thus excluded from analyses, given that methodological comparisons are not appropriate with such minimal anatomical overlap. GluCEST-^{1}HMRS comparative analyses were performed with the remaining 20 participants (8 typically developing, 1 with a depressive disorder, 3 with a psychotic disorder, 8 clinical high risk). For each of these 20 participants, the percent of the ^{1}HMRS VOI included in the GluCEST FOV was > 45%.

Associations Between BAS RR Scores and Dual Method Anterior Cingulate Glutamate

^{1}HMRS-derived glutamate concentration and mean GluCEST contrast were quantified within the anterior cingulate cortex VOI, and entered as predictors of BAS RR scores in independent multiple linear regressions controlling for age, sex, and fCSF (^{1}HMRS model only). Replicating prior ^{1}HMRS studies of anterior cingulate glutamate and RR (Colic et al., 2019; Gabbay et al., 2012; Godlewska et al., 2018; Walter et al., 2009), neither the ^{1}HMRS-glutamate concentration (estimate = 0.15, $r_{\mathrm{PARTIAL}} = 0.09$, p = 0.733) nor the GluCEST contrast (estimate = 0.15, $r_{\mathrm{PARTIAL}} = 0.06$, $p = 0.798$) within the anterior cingulate VOI were associated with BAS RR scores. Harnessing the high-resolution image generated by the GluCEST acquisition, we were additionally able to parcellate the anterior cingulate VOI into reward and non-reward components, and to quantify mean GluCEST contrast within each component. Supporting this study's main findings, the association between BAS RR scores and mean GluCEST contrast was stronger in the reward network component of the anterior cingulate VOI ($r_{\text{PARTIAL}} = 0.27$) than in the non-reward component of the VOI ($r_{\text{PARTIAL}} = 0.07$). Taken together, this first set of comparative analyses reveals convergent findings across methods, underscores the importance of acquiring neurochemical imaging data from expansive FOVs, and highlights the benefit of function-based parcellation approaches.

GluCEST- and ^{1}HMRS-derived Measures of Brain Glutamate are Positively Correlated

Across the 20 participants included in this methodological comparison, on average 69% (± 23%) of the total ^{1}HMRS VOI was included in the GluCEST FOV. We were thus able to compare GluCEST and ^{1}HMRS measures within overlapping yet non-identical regions of the brain. Despite the fact that measures were derived from non-identical volumes of brain tissue with differing tissue fractions, there was a positive partial correlation (controlled for fCSF) between the GluCEST contrast and ^{1}HMRS-derived glutamate concentration ($r_{\text{PARTIAL}} = 0.26$, $N = 20$). As expected, the strength of this partial correlation was greater within participants who exhibited greater anatomical overlap between the ^{1}HMRS VOI and the GluCEST FOV. Specifically, the partial correlation between GluCEST and ^{1}HMRS glutamate increased in participants with > 50% anatomical overlap between ^{1}HMRS and GluCEST acquisitions ($r_{\text{PARTIAL}} = 0.36$, $N = 13$), and further increased in those with > 90% anatomical overlap ($r_{\text{PARTIAL}} = 0.60$, $N = 5$). Critically, the strength of the partial correlation between the GluCEST contrast and ^{1}HMRS neurochemical concentration was greater for glutamate than for other neurochemicals, including N-acetylaspartate ($r_{\text{PARTIAL}} = 0.02$, $N = 20$), glutathione ($r_{\text{PARTIAL}} = -0.02$, $N = 17$), and creatine/phosphocreatine ($r_{PARTIAL}$ = 0.14, N = 20). (All partial correlations were controlled for fCSF. Three participants were excluded from the glutathione analysis due to CRLB estimates > 15% for glutathione).

Supplementary Results: Diagnostic Group Differences in Regional GluCEST and Relationships to Prior 7.0T ^{1}HMRS Case-Control Studies

The primary goal of this study was to investigate dimensional associations between reward network glutamate level and inter-individual variability in RR across clinical diagnostic categories. However, we additionally capitalized on the inclusion of a diverse clinical population by examining differences in regional GluCEST between the typically developing group and each of the three clinical diagnostic groups (depressive disorders, psychotic disorders, and clinical high risk groups). One aim of these diagnostic group-based, regional analyses was to provide insight into the potential co-occurrence of neurochemical differences related to both a dimensional psychological construct and to patient diagnosis. A second, equally important aim was to assess whether diagnostic group-based differences obtained with GluCEST accord with the previously published 7.0T ^{1}HMRS case-control literature, offering a methodological validation.

Structural and functional MRI studies have implicated the anterior cingulate cortex (Diener et al., 2012; Du et al., 2012; Radua et al., 2012; Zhang et al., 2013) and the thalamus (Chen et al., 2019; Diener et al., 2012; Du et al., 2012; Ramsay, 2019; Zhang et al., 2013) in depressive and negative psychotic symptoms, in agreement with the role of these regions in the reward network. For this reason, prior single voxel 7.0T ^{1}HMRS studies investigating glutamatergic differences between a control group and patients with psychotic (Brandt et al., 2016; Kumar et al., 2020; Marsman et al., 2014; Overbeek et al., 2019; Posporelis et al., 2018; Reid et al., 2019; Rowland et al., 2016; Taylor et al., 2015; Thakkar et al., 2017; Wang et al., 2019) or depressive (Godlewska et al., 2018; Li et al., 2016; Taylor et al., 2017, 2015) disorders have most frequently chosen the anterior cingulate and the thalamus as cortical and subcortical ^{1}HMRS VOIs. As such, to embed the present diagnostic GluCEST data within the prior case-control ^{1}HMRS literature, we anatomically delineated the anterior cingulate cortex and thalamus with Harvard-Oxford atlases, quantified mean GluCEST contrast within these two regions, and examined group differences in regional GluCEST using ANCOVAs controlled for age and sex. ANCOVA results are presented below along with group mean z-scores, computed using control group means and standard deviations. Z-scores are provided to enable comparisons of standardized differences between the typically developing and diagnostic groups across regions and diagnostic categories.

GluCEST is Lower in Individuals Diagnosed with a Psychotic Disorder

Individual 7.0T ^{1}HMRS studies investigating glutamatergic differences between healthy controls and patients with psychotic disorders have produced rather heterogeneous results (Sydnor and Roalf, 2020). For example, prior work has reported either no significant difference in anterior cingulate cortex glutamate concentration between controls and patients (Brandt et al., 2016; Kumar et al., 2020; Posporelis et al., 2018; Rowland et al., 2016; Taylor et al., 2017, 2015) or a lower concentration in patients (Reid et al., 2019; Wang et al., 2019). A recent meta-analysis of pooled data (9 studies, 255 patients, 293 controls) from these 7.0T studies, however, found evidence for an overall reduction in brain glutamate levels in psychosis (Sydnor and Roalf, 2020). In the present study, the GluCEST contrast was numerically lower in individuals with psychotic disorders (*N* = 7) than in typically developing individuals (*N* = 15) in both the anterior cingulate cortex and the thalamus. This difference was not significant in the anterior cingulate cortex (typically developing group mean z-score = 0 hereon, psychotic disorders group mean z-score = -0.43, $F_{1,18}$ = 0.59, *p* = 0.452) but was nearly significant in the thalamus (psychotic disorders group mean z-score = -1.45, $F_{1,18}$ = 4.36, *p* = 0.051). The present GluCEST-derived results thus converge with the 7.0T ^{1}HMRS meta-analysis, as well as with a prior study of GluCEST in psychosis (Roalf et al., 2017).

GluCEST is Not Significantly Different in Depression

To date, four 7.0T ^{1}HMRS studies have examined differences in anterior cingulate cortex (Godlewska et al., 2018; Li et al., 2016; Taylor et al., 2017, 2015) and/or thalamic (Li et al., 2016; Taylor et al., 2017) glutamate concentrations between healthy individuals and those with depression, and all have reported null results. Moreover, a large ^{1}HMRS meta-analysis of all available 1.5, 3.0, 4.0, and 7.0T studies additionally found no significant difference in anterior cingulate/medial prefrontal glutamate concentration between 371 patients with depression and 359 controls (Moriguchi et al., 2019). In accordance with these prior ^{1}HMRS results, we observed no significant difference in GluCEST contrast between typically developing (*N* = 15) and depressive disorder (*N* = 11) groups in either the anterior cingulate cortex (depressive disorders group mean z-score = 0.44, $F_{1,22}$ = 0.88, *p* = 0.358) or the thalamus (depressive disorders group mean z-score = -0.22, $F_{1,22}$ = 1.61, *p* = 0.218).

Clinical High Risk Individuals Tend to Have Higher GluCEST Than Those with Psychotic Disorders

To our knowledge, there are currently no published 7.0T ^{1}HMRS studies of individuals at clinical high risk for psychosis. However, a meta-analysis of lower field strength ^{1}HMRS studies did find significantly higher Glx (glutamate + glutamine) concentrations within the anterior cingulate/medial prefrontal cortex in high risk individuals compared to controls, but no significant group differences within the thalamus (Merritt et al., 2016). GluCEST data collected from those at clinical high risk for psychosis (N = 12) for the current study again mirrored this pattern of previous findings (anterior cingulate cortex: clinical high risk group mean z-score = 0.39, $F_{1,23}$ = 1.31, p = 0.265; thalamus: clinical high risk group mean z-score = -0.02, $F_{1,23}$ = 0.086, p = 0.772). Notably, the GluCEST contrast was higher in individuals at clinical high risk for psychosis than in those with a diagnosed psychotic disorder in both the anterior cingulate cortex and the thalamus.

Altogether, these regional analyses of specific diagnostic groups align well with the extant 7.0T ^{1}HMRS literature. Furthermore, the results underscore the possibility that reward sensitivity and patient diagnosis may be differentially associated with glutamate availability in distinct brain areas. Nevertheless, given the small sample size of each clinical diagnostic group and known neurobiological heterogeneity within diagnostic categories (Satterthwaite et al., 2020), these diagnostic group-based GluCEST analyses must be considered preliminary.

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CHAPTER 5: CONCLUSIONS, CONTRIBUTIONS, AND FUTURE DIRECTIONS

The human cortex undergoes prolonged and asynchronous postnatal neurodevelopment, allowing it to be continuously shaped by interactions between intrinsic developmental programs and external environments through late childhood and adolescence. This thesis sought to introduce and evaluate a conceptual framework for understanding central tenets of child and adolescent cortical development, including its protracted and heterochronous nature, its capacity to be sculpted by children's neighborhood environments, and its ability to confer either resilience to or risk for psychiatric illness. The proposed framework contends that the spatiotemporal unfolding of cortical development, the cortical embedding of environmental influences, and the cortical enrichment of psychopathology-associated phenotypes conform to a large-scale axis of cortical organization: the sensorimotor-association axis. Leveraging maps of cortical organization, animal-to-human translation, large developmental samples, biologically-informed multi-modal neuroimaging, environmental geocoding, and assessments of reward responsiveness, I found substantial empirical support for this framework (Sydnor et al., 2023, 2021a, 2021b; Sydnor and Satterthwaite 2023).

Synthesis of the present findings

A spatiotemporal model of child and adolescent cortical developmental plasticity

A central aim of this thesis was to introduce a comprehensive model of how neurodevelopmental plasticity spatially and temporally progresses across the human cortex during childhood and adolescence. The proposed model was grounded in the following three ideas: ontogeny mirrors phylogeny, temporal developmental variability engenders spatial feature variability, and sensory and association cortices exhibit asynchronous development. The model of cortical development thus suggests that development unfolds along the S-A axis: an evolutionarily-sculpted, dominant axis of spatial feature variability that captures a cortical continuum between sensorimotor and association cortices. Integrating organizational trends across studies, spatial scales, and species, this thesis first derives an archetypal sensorimotor-to-association cortical axis that—despite the immense complexity of the human cortex—consistently emerges as a large-scale organization motif. Next, harnessing non-invasive neuroimaging measures posited to be sensitive to developmental plasticity, it provides evidence for an S-A axis model of cortical development. In this developmental model, reductions in plasticity during childhood and adolescence cascade along the S-A axis. Plasticity is lost earliest in cortices that enable sensation, perception, and action. Plastic windows close later in cortices that subserve sensory integration, language, and attention. Finally, plasticity wanes last in cortices involved in cognitive and emotional control, social learning, and reward processing. By demonstrating that developmental change conforms to the S-A axis during childhood and adolescence, this research underscores how alignment of developmental programs to neuroaxes is a core tenet of development and highlights the value of neurodevelopmental models informed by brain organization.

Intrinsic activity as a functional marker and potential driver of developmental plasticity

To characterize heterochronicity in brain development, the present work explored changes in the amplitude of intrinsic functional activity as a potential marker of shifting circuit plasticity in the developing cortex. This approach was inspired by animal studies showing that when cortical regions are immature and malleable, intrinsic activity is both highly prevalent and spatially synchronized; as a result, electrophysiological, calcium, or electroencephalogram (EEG) recordings of this activity are characterized by high amplitude fluctuations. This approach was additionally supported by studies demonstrating that manipulating plasticity-regulating biological features in animals leads to changes in the amplitude of functional MRI activity. Finally, as demonstrated here, developmental changes in the amplitude of intrinsic functional MRI activity couple to the development of a structural MRI measure sensitive to intracortical myelin: a known restrictor of developmental plasticity. Hence, the present findings contribute to accumulating data suggesting that the amplitude of intrinsic fMRI activity could provide a non-invasive readout of changes in circuit plasticity in the human cortex (Fair and Yeo, 2020; Laumann and Snyder, 2021; Newbold et al., 2020).

In addition to providing insight into the unfolding of ongoing neurodevelopmental processes, the patterning of intrinsic activity itself has a profound impact on the developing brain. In early stages of development, intrinsic activity guides neuronal migration, impacts neuron survival (Blanquie et al., 2017), and helps to establish cortical topography (Ackman et al., 2012; Antón-Bolaños et al., 2019; Clause et al., 2014). As development continues, intrinsically generated neural activity influences circuit wiring, cortical growth (Benders et al., 2015), synaptic plasticity (Winnubst et al., 2015), and myelination (Gibson et al., 2014). Changes in intrinsic activity may therefore not only be an epiphenomenon of changes in circuit plasticity, but may additionally be a driver of this plasticity. Indeed, prior work has shown that large enhancements or alterations in cortical activity can induce a more plastic state, frequently through downstream effects on parvalbumin interneurons or perineuronal nets (Favuzzi et al., 2017; Lensjø et al., 2017; Newbold et al., 2020; Quast et al., 2023). Accordingly, it is possible that high amplitude, synchronized, rhythmic circuit activity may not only be a functional indicator of the plastic state of the cortex, but may also play an active role in enabling circuit plasticity (Reh et al., 2020).

Environmental influences on the hierarchical unfolding of developmental malleability

During brain maturation, environmental inputs can interact with neurodevelopmental plasticity to become cortically embedded. This thesis adds to a growing body of literature demonstrating relationships between the neighborhood-level environment and cortical properties in youth. **Chapter 3** uncovers across-cortex relationships between neighborhood socioeconomic conditions and the amplitude of intrinsic functional MRI activity, demonstrating how developmental trajectories of this measure vary across the environmental deprivation-enrichment spectrum.

The relationships observed between functional MRI activity amplitude and the neighborhood environment varied in nature across cortical regions. Specifically, relationships were opposite in direction in sensorimotor and association cortices, with individuals living in more socioeconomically disadvantaged neighborhoods showing a lower amplitude of functional MRI activity across the association cortex. This result aligns with previous studies documenting how poverty, low socioeconomic status, and severe environmental deprivation (institutionalized care) are associated with reductions in cortical electrical activity amplitude, as measured by EEG power (Cantiani et al., 2019; Marshall et al., 2004; Troller-Renfree et al., 2022). Notably, relationships between the neighborhood environment and functional MRI signal amplitude were additionally generally characterized by larger statistical effect sizes in the association cortex as compared to sensory cortex; effects were largest in inferior parietal, medial and lateral prefrontal, and precuneus association cortices. The temporally extended window of developmental refinement experienced by the association cortices may ensure that they remain responsive to—and are more impacted by—the environment through adolescence.

In contrast to the association cortices, primary and unimodal sensorimotor cortices displayed a higher amplitude of intrinsic functional MRI activity in youth raised in poorer socioeconomic environments. Speculatively, this pattern of results could denote that socioeconomic-linked deprivation manifests cortically as higher plasticity in sensorimotor cortices yet lower plasticity in association cortices in late childhood and adolescence. Murine studies have shown that reductions in plasticity in one cortical region can be triggered by enhancements in plasticity in the next region in a developmental sequence. For example, the onset of critical period plasticity in V1 controls the closure of the preceding critical period of plasticity in A1 through a V1-to-A1 anatomical projection (Mowery et al., 2016). The dependence of regional plasticity windows on a global developmental sequence advances a compelling theory: as developmental programs unfold along the S-A axis, insufficient enhancements of plasticity in association cortices could result in diminished reductions in plasticity in the sensory cortices to which they send feed-back structural connections. According to this theory, initially local environmental influences could ultimately affect the hierarchical unfolding of developmental malleability across the entire S-A axis.

The delineation of widespread and diverging effects of the environment along the S-A axis in the present work accords with this theory. Notably, the patterning of brain-environment associations along the S-A axis was not uniform throughout the entire age range studied, but was maximal in adolescence—coincident with when developmental change maximally differed along this same axis. Relationships between the environment and cortical properties therefore appear to be influenced by ongoing neurodevelopmental programs. These age-varying findings suggest that the effects of environmental enrichment or enhancement interventions on the developing brain will differ depending on a child's developmental state or stage.

A neurochemical contributor to diminished reward responsiveness in late development

Exposure to social and cognitive deprivation, environmental unpredictability, and environmental stressors has been connected to changes in reward-related behaviors and reductions in reward responsiveness (Dennison et al., 2019; McLaughlin and Gabard-Durnam, 2022; Risbrough et al., 2018; Sheridan et al., 2018; Stanton et al., 2019). Diminished reward responsiveness, in turn, is associated with poor psychological well-being, transdiagnostic psychiatric symptomatology, and suicidality (Bennik et al., 2014; Pelizza et al., 2020; Risbrough et al., 2018; Taubitz et al., 2015; Winer et al., 2017, 2016, 2014), classifying it as a possible intervention target for mental health prevention or treatment programs. This thesis takes a dimensional approach to studying reward responsiveness during the adolescent and post-adolescent period by examining a spectrum from severe reward deficits to high reward sensitivity across non-clinical and clinical samples. **Chapter 4** demonstrated that lower reward responsiveness is transdiagnostically associated with reduced levels of glutamate within (but not outside of) a reward network composed of prefrontal and cingulate transmodal association cortices and brainstem, thalamic, and striatal reward regions. It furthermore shows that glutamate availability within subcortical regions may particularly drive this association.

Given that reward regions in transmodal association cortex send glutamatergic inputs to reward processing subcortical nuclei, these findings may signify that diminished excitability and glutamatergic release from cortical-subcortical glutamatergic projections elicits reduced responding to rewards in late developmental stages. Reduced excitability of these projections could potentially arise due to lower neurite density and connectivity or a lower excitation: inhibition ratio in reward-related transmodal association cortex—phenotypes associated with a more mature cortex, a reduced level of plasticity, and greater environmental deprivation (Greifzu et al., 2014; Nichols et al., 2007; Sale et al., 2007; Tooley et al., 2021). Consequently, this work supports a neurodevelopmental account of reward deficits and mental illness risk that relates disruptions in reward network glutamatergic signaling to a reduction of transmodal association cortex plasticity. Considered together, **Chapters 2, 3,** and **4** of this thesis suggest that socioeconomic deprivation-related impacts on the hierarchical patterning of neurodevelopmental malleability along the S-A axis may confer risk for psychiatric vulnerability by blunting a programmed period of heightened transmodal cortex plasticity during adolescence.

A sensorimotor-association axis of developmental plasticity, environmental susceptibility, and psychiatric vulnerability

Developmental change in non-invasive functional and structural indicators of cortical plasticity spatially and temporally unfolds along the S-A axis. Youth raised in socioeconomically disadvantaged versus advantaged environments exhibit diverging neurodevelopmental trajectories across the S-A axis. Diminished reward responsiveness, a psychiatric risk factor, is linked to decreased glutamate levels in transmodal regions at the association end of the S-A axis. Together, this thesis reveals that progressing from the sensorimotor to the association pole of the S-A axis, cortical regions are plastic for longer throughout development, more influenced by the environment in late childhood and adolescence, and more associated with risk factors for psychiatric illness. The S-A axis thus emerges not only as a major axis of cortical organization, but also as an axis of developmental plasticity, environmental susceptibility, and psychiatric vulnerability.

Primary contributions and limitations

Contributions

The research presented in this thesis contributes the following primary conceptual advances. Building on extensive prior work (Burt et al., 2018; García-Cabezas et al., 2019; Hilgetag et al., 2019; Huntenburg et al., 2018; Margulies et al., 2016; Mesulam, 1998), it presents data in support of and derives an archetypal sensorimotor-association axis of cortical organization. This axis provides a framework for understanding the patterning of cortical feature variability as well as the progression and biobehavioral outcomes of cortical development. The S-A axis has now been explored in relationship to cortical contributions to cognition (Keller et al., 2022), childhood psychopathology (Kebets et al., 2023), predictive processing (Katsumi et al., 2022), epilepsy (Wagstyl et al., 2022), and psychedelic effects (Timmermann et al., 2023). Through proposing that developmental programs align with the S-A axis, it also offers a testable model of cortical development. This model has been evaluated and validated in independent studies examining the development of cortical microstructure and functional connectivity (Baum et al., 2022; Nielsen et al., 2022; Pines et al., 2022). In addition, by providing evidence that a major axis of cortical organization is also a primary axis of neurodevelopment, it illustrates how an understanding of brain organization can inspire new models of brain development, and how brain development in turn shapes cortical organization. This research also provides an example of how neurobiologically-grounded accounts of human neurodevelopment may be facilitated by translating mechanistic insights from causal animal studies to non-invasive human neuroimaging. Last, this thesis contributes to research examining how dimensions of environmental experience can influence developmental outcomes. In particular, it puts forth data in support of the theory that socioeconomic exposures may influence risk for psychiatric illness through experience-driven differences in plasticity in transmodal cortices integral to complex cognition and reward processing. These data indicate that policies that alleviate disparities in neighborhood-level disadvantage would have a large impact on healthy association cortex development through adolescence.

Limitations

The research presented in this thesis must also be considered in the context of the following primary limitations. The S-A axis model of cortical neurodevelopment proposed did not integrate subcortical structure development. Yet, subcortical-to-cortical inputs, in particular direct anatomic inputs from the thalamus and midbrain, have been shown to drive cortical plasticity during youth (Benoit et al., 2022; Larsen and Luna, 2018; Quast et al., 2023). Furthermore, non-cortical structures that execute heterogeneous functions, such as the striatum and cerebellum, display within-structure sensorimotor-to-association axes of organization (Guell et al., 2018; Haber, 2003; Liu et al., 2022). It is of significant interest to determine the extent to which S-A axes of neurodevelopment exist within subcortical structures (Liu et al., 2022) and how subcortical development interacts with the S-A axis of cortical development.

Primary limitations in the developmental investigation center on the scope of the research. In particular, the developmental investigation was conducted in a single, cross-sectional sample of youth ages 8 to 23 years old and could therefore be extended to additional samples, a broader age range, and longitudinal study designs. Extension of the present analyses to additional youth samples (i.e., samples acquired at different sites and comprised of populations with varying demographic or clinical compositions) is necessary to ensure generalizability of the results; notably, replication of the developmental results has been demonstrated in a second, independent sample (unpublished). It is additionally of interest to expand the developmental framework to infant, early childhood, and young adult populations. Continued insight into spatiotemporal axes of neurodevelopment during younger and older developmental stages will help to elucidate how plasticity is distributed across brain regions throughout humans' multidecade maturational course. Unlike this cross-sectional study, future investigations with longitudinal study designs could characterize within-individual developmental changes in non-invasive neuroimaging measures. A longitudinal approach could uncover temporal precedence between development of structural and functional metrics as well as the effects of the environment on the pace of an individual's development. The developmental investigation furthermore focused on one proposed non-invasive functional marker of plasticity and one non-invasive structural marker of declining plasticity. Incorporation of neuroimaging measures that can index additional developmental changes (e.g. changes in metabolism, local and global connectivity, pruning, and neurochemistry) in future work will help to provide a more in depth and mechanistic account of human cortical maturation.

Primary limitations in the environmental and clinical investigations arise from the aggregation of multiple constructs into a single neighborhood environment factor and a single reward responsiveness measure. The neighborhood environment factor was a composite measure of multiple indicators of neighborhood socioeconomic advantage. Yet many variables co-vary with neighborhood-level socioeconomic conditions, including material resource availability, cognitive and social enrichment, educational exposures, parenting behaviors, healthcare, chronic stress, psychological safety, and experiences of racism. The use of a composite measure precluded inference regarding which of these variables contributed to the brain-environment associations described in this research. Developing a nuanced understanding of how each of these variables affects brain development and developmental outcomes may ultimately help to inform interventions or policies that equitably support healthy child neurodevelopment across socioeconomic circumstances. Similarly, the reward responsiveness measure provided a single summary score that encompassed multiple reward-related processes. Reward responsiveness can be decomposed into multiple sub-domains including reward valuation, anticipatory pleasure, consummatory pleasure, motivation, and reward learning (Der-Avakian et al., 2016). These sub-domains may have differential associations with reward circuit signaling and mental illness risk, necessitating work that delineates multivariate yet specific associations between components of reward responsiveness, psychiatric symptomatology, and the development of transmodal reward regions across the environmental deprivation-enrichment spectrum.

Future directions: plasticity-informed environmental and psychiatric interventions during youth

This thesis introduces a model of when cortical regions that support distinct psychological functions exhibit enhanced and diminished plasticity during development, and of how this plasticity is impacted by the neighborhood environment and related to psychiatric risk. This model helps to provide a foundation for understanding when specific cortical regions are most malleable by extrinsic influences—and thus an understanding of when during development interventions are likely to have a more lasting impact on different brain areas and behaviors. The present research specifically supports that transmodal association cortices enhance their plasticity in early adolescence and may thereby be particularly amenable to environmental enrichment or mental health interventions during this developmental stage. Moving forward, the field should aim to construct mechanistic, developmentally-grounded, trial-tested guidelines concerning optimal developmental windows for specific interventions. Progress towards this aim requires a better appreciation of 1) the intrinsic mechanisms underlying protracted cortical plasticity in humans, 2) the extent to which the effects of interventions on development and developmental outcomes vary depending on the distribution of cortical plasticity, and 3) whether the timing of plastic periods can be extrinsically modulated to deliver interventions during desired developmental states. These three complementary lines of research will facilitate the creation of biologically-motivated interventions that incorporate basic principles of human development and are delivered while the brain is undergoing demarcated periods of malleability.

Elucidating intrinsic mechanisms underlying protracted cortical plasticity

The S-A axis model of neurodevelopment provides an estimate as to when and where the cortex is most plastic throughout childhood and adolescence. This model furthermore posits that the sensory-to-associative sequence of development arises due to the hierarchical progression of plasticity-facilitating and plasticity-restricting neurobiological events. However, the precise nature of these events and the mechanisms enabling extended association cortex plasticity in humans remain undercharacterized. Characterization of intrinsic drivers and limiters of plasticity may help inform research into plasticity-targeted interventions, aid design of Fast-Fail clinical trials that survey effects of treatment on neuroimaging plasticity markers, or uncover biological readouts for guiding the administration of interventions during specific epochs of developmental plasticity (Sydnor and Satterthwaite, 2023).

Animal model findings offer inspiration for initial mechanisms to investigate in the human brain. As described, early strengthening of inhibitory signaling enables windows of heightened experience-dependent plasticity in non-human animals (Fagiolini and Hensch, 2000; Takesian and Hensch, 2013). The relative strength of cortical inhibition can be studied in humans using pharmacological functional MRI (Larsen et al., 2022), biophysical computational models of functional dynamics (Deco et al., 2021), or neurochemical imaging of GABA (Perica et al., 2022). Murine models have shown that structural inputs from the thalamus to the cortex significantly impact cortical circuit organization and plasticity by affecting spontaneous excitatory activity and parvalbumin interneurons (Benoit et al., 2022; Quast et al., 2023). Thalamocortical structural connectivity can be studied in vivo with diffusion MRI-derived tractography and microstructural modeling. Dopaminergic inputs from the ventral tegmental area to the cortex additionally serve to enhance plasticity in both sensory and association cortical areas (Bao et al., 2001; Larsen and Luna, 2018). Connectivity between this brainstem area and the cortex can be measured with functional connectivity (Boroshok et al., 2022) and dopamine can be studied in the pediatric brain through measurement of brain tissue iron (Larsen et al., 2020; Parr et al., 2023). Cortical plasticity is limited by the growth of intracortical myelin (Baum et al., 2022; McGee et al., 2005). Multiple MRI measures are thought to be sensitive to cortical myelin content, including the T1w/T2w ratio, the magnetization transfer ratio, and the R1 signal. Future studies could aim to validate these measures as relevant to plasticity by combining animal model neuroimaging with cellular or molecular manipulations, by inducing brain plasticity in humans through behavioral or neuromodulatory approaches, by examining whether the expression of proposed plasticity measures predicts learning capacity or training gains during youth, and by delineating how age-related changes in these measures relate to psychological or behavioral advancements.

Evaluating intervention efficacy by generalized developmental timing or person-specific estimates of developmental plasticity

Age-dependent changes in the distribution of cortical plasticity suggest that the same external inputs or experiences may exert differential influences on the developing brain, depending on developmental timing. The environmental analyses presented here provide support for this theory, as brain-environment associations were influenced by local and global developmental patterns. This demonstrated interdependence between ongoing neurodevelopmental refinement and extrinsic impacts on cortical maturation implies that the efficacy of youth interventions may also depend on a child’s current developmental stage. This calls for randomized trials that robustly evaluate whether the effects of environmental enrichment and psychiatric interventions on brain development and developmental outcomes differ according to an individual’s age or an individual’s developmentally plastic state (Luby et al., 2020; Park and Mackey, 2022). Important trials with this goal have been carried out, though they have generally focused on the earliest periods of brain development (Sheridan et al., 2022; Vanderwert et al., 2010). Moving forward, trials could deliver the same intervention to youth of different ages and examine whether the effects of the intervention on individual cortical regions and the behaviors they subserve vary as a result of age. Alternatively, the same intervention could be delivered to age-matched individuals that differ in their expression of neuroimaging biomarkers of cortical plasticity or maturation. Ultimately, this line of research may help to delineate optimal windows for interventions informed by either a general understanding of neurodevelopmental timing or by person-specific estimates of neurodevelopmental plasticity.

Extrinsically manipulating plasticity during development

Although brain development is expected to follow a similar, programmed sequence in all individuals, the rate at which this sequence unfolds—and thus the rate at which plasticity is diminished over development—varies across individuals. Hence, the timing of regional windows of plasticity is itself plastic (Gabard-Durnam and McLaughlin, 2020). The fact that the unfolding of developmental plasticity is, to some extent, adaptable indicates that interventions could potentially be delivered while extrinsically enhancing (or diminishing) cortical plasticity in a careful and judicious manner (Sydnor and Satterthwaite, 2023). This approach would necessitate extensive additional research in animal models and humans on the spatial specificity, duration, and potential advantageous and detrimental downstream consequences of extrinsically modulating plasticity.

Potential investigatory approaches could focus on psychotropic administration, neuromodulation, modifiable lifestyle factors, or environmental enrichment. Animal studies have shown that GABA receptor agonists can trigger increases in cortical plasticity in juvenile animals (Fagiolini and Hensch, 2000; Hensch, 2018), whereas drugs that reduce GABAergic neurotransmission can reinstate plasticity in adult animals (Harauzov et al., 2010); pharmacological manipulation of inhibitory signaling thus bidirectionally changes plasticity, dependent on age. The effect of GABA signaling on developmental plasticity could be studied in humans by examining plasticity markers or developmental trajectories in children who were versus were not exposed to anesthetic agents, or in adolescents who have versus have not taken benzodiazepines. Selective serotonin-reuptake inhibitors (SSRIs) (Guirado et al., 2014; Maya Vetencourt et al., 2008) and valproate (Silingardi et al., 2010; Yang et al., 2012) have been shown to reopen windows of plasticity in mature murines through downstream effects on BDNF and histone deacetylases, respectively. Supporting that these agents also induce a more plastic brain state in humans, the SSRI fluoxetine was shown to enhance visual function improvements induced by training in humans with amblyopia (Sharif et al., 2019) and valproate was found to reopen a critical period for learning of absolute pitch in adults (Gervain et al., 2013). Naturalistic "intervention" studies with individuals who take SSRIs or valproate for medical reasons could be employed to directly explore the effects of these psychotropics on cortical maturation or plasticity. Outside of psychotropics, neuromodulatory techniques like transcranial magnetic stimulation (TMS) are thought to influence neural plasticity and have the advantage of being targetable to specific brain regions or circuits (Sydnor et al., 2022). The effects of brief exposure to non-invasive brain stimulation on short-term changes in cortical neurochemistry, connectivity, or intrinsic activity could be studied to better understand associations between specific stimulation paradigms and markers of plasticity. During development, circadian clock genes help to control the timing of region-specific windows of plasticity (Kobayashi et al., 2015), giving rise to circadian hypotheses of developmental plasticity. The impact of circadian rhythms and sleep on cortical plasticity during development could be studied in large youth samples with sleep tracking data available. Finally, extensive work in animal models has directly shown that environmental enrichment can enhance plasticity (Gabard-Durnam and McLaughlin, 2020); human neuroimaging studies—including the present findings—provide convergent data. Future studies could examine the effects of environmental enrichment programs, for example cognitive enrichment in the household, resource provision or community center support in the neighborhood, or anti-poverty measures at the city level, on within-individual changes in developmental plasticity and developmental outcomes.

Supporting healthy brain development by aligning interventions with each child's neurodevelopmental context

The research avenues described above will help to motivate clinical research on environmentally and biologically informed interventions, identify sensitive periods of developmental plasticity wherein these interventions may have a particularly large and sustained impact on the brain, and reveal how periods of plasticity may themselves be extrinsically modulated to facilitate alignment between intervention timing and developmental state. This plasticity-sensitive approach to fostering healthy brain development holds potential for preventing developmental insults from becoming permanently cortically embedded through delivery of interventions that best align with each child's specific neurodevelopmental context.

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