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Review

A critical period plasticity framework for the sensorimotor–association axis of cortical neurodevelopment

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To understand human brain development it is necessary to describe not only the spatiotemporal patterns of neurodevelopment but also the neurobiological mechanisms that underlie them. Human neuroimaging studies have provided evidence for a hierarchical sensorimotor-to-association (S–A) axis of cortical neurodevelopment. Understanding the biological mechanisms that underlie this program of development using traditional neuroimaging approaches has been challenging. Animal models have been used to identify periods of enhanced experience-dependent plasticity – 'critical periods' – that progress along cortical hierarchies and are governed by a conserved set of neurobiological mechanisms that promote and then restrict plasticity. In this review we hypothesize that the S–A axis of cortical development in humans is partly driven by the cascading maturation of critical period plasticity mechanisms. We then describe how recent advances in *in vivo* neuroimaging approaches provide a promising path toward testing this hypothesis by linking signals derived from non-invasive imaging to critical period mechanisms.

Highlights

Human neuroimaging studies have demonstrated that brain development progresses hierarchically along an S–A axis in which areas of association cortex are the last to mature.

Animal models delineate a hierarchical progression of critical periods of elevated experience-dependent plasticity across sensory systems which is governed by a conserved set of neurobiological mechanisms.

We propose that hierarchical development along the S–A axis in humans is driven by a cascade of critical periods that culminate in association cortices during adolescence.

We highlight advances in *in vivo* neuroimaging and computational approaches, including pharmacological functional magnetic resonance imaging (fMRI), chemogenetic fMRI, and biophysical modeling, that can provide insights into the development of critical period mechanisms along the S–A axis in humans.

The importance of a mechanistic framework describing spatiotemporal patterns of brain development

Understanding the spatial and temporal patterning of brain development during youth is essential for understanding both where and when the brain is most plastic during specific windows of development. These windows of developmental plasticity may represent periods of vulnerability as well as an opportunity for modifying the neurodevelopmental trajectory and developmental outcomes of an individual. Elucidating the neurobiological mechanisms that underlie such periods of elevated developmental plasticity is thus crucial for understanding how different environmental, experiential, and neurobiological factors interact to shape neurodevelopmental outcomes during windows of increased plasticity. Constructing a model that explains both the spatiotemporal patterning of developmental plasticity and the neurobiological mechanisms that drive it will be crucial for promoting healthy brain development and for designing neurobiologically informed interventions that can be optimally delivered at the time and place that they will be most effective in improving developmental outcomes.

In this review we present a mechanistic spatial and temporal framework for cortical development in which **critical period** (see Glossary) plasticity mechanisms progress along a hierarchical **sensorimotor–association (S–A) axis** of cortical neurodevelopment to drive experience-dependent maturation. Critical periods are an established form of developmental plasticity during which experience interacts with specific neurobiological factors to profoundly shape cortical circuits at a particular point in development [1]. We first highlight human neuroimaging studies

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that provide recent evidence for an S–A axis of cortical development. We then review data from animal models suggesting that critical period mechanisms unfold along a S–A cortical hierarchy. Finally, we outline several promising and emerging methodologies for investigating critical period mechanisms in humans, with a particular focus on methods for studying the development of inhibitory circuitry and the excitation/inhibition ratio.

Neurodevelopment unfolds hierarchically along a S–A cortical axis

The gross organization of the major structural pathways and network architecture of the brain is established early in development, within the first two years of life in humans [2–4]. However, cortical microstructure, neurochemistry, and function continue to be developmentally refined over the course of three decades [5–7]. During this time, neurodevelopment does not progress uniformly across the cerebral cortex, but rather unfolds asynchronously. Most strikingly, human developmental neuroimaging has characterized distinct temporal windows of development in sensory and association cortices. Studies of infancy and early childhood have shown that many aspects of cortical structure (e.g., gray matter microstructure [8–11]) and function (e.g., **functional connectivity** patterns [12,13]) are already more mature in primary sensory cortices than in association cortices after the first years of life [2,3]. This difference in maturational status between sensory and association cortices extends into and may even be enhanced in adolescence. Indeed, association cortex gray matter microstructure [14–17], white matter microstructure [18], myelination [19,20], cerebral perfusion [21], functional activation [22,23], and functional organization [24,25] continue to be refined through late adolescence [2,5,6,26]. Importantly, recent work has illustrated that rich variability in developmental timescales exists beyond this two-part sensory versus association cortex division. For example, the extent, timing, and patterning of intracortical myelin growth has been shown to differ between unimodal cortex, heteromodal cortex, and paralimbic association cortex [19,20]. Similarly, age-related changes in regional functional connectivity, as measured using resting state functional magnetic resonance imaging (fMRI), appear to follow the same developmental trend [13,25,27].

We recently proposed a model that accounts for this rich spatiotemporal variability in cortical development, which posits that maturational programs proceed across the cortex along a continuous and hierarchical axis of brain organization: the S–A axis [5]. This is an axis of cortical feature variation that spans in a graded manner from primary sensory and motor cortex to transmodal association cortex; every cortical region is ranked along this axis [5]. The S–A axis captures spatial heterogeneity in a large diversity of neurobiological features as well as hierarchical patterns of cortico-cortical anatomical and functional connectivity [5] (Figure 1A). Our model of hierarchical critical period development proposes that the S–A axis also captures variation in neurodevelopmental timescales, and thus organizes developmental chronology as well as features of brain structure and function [5].

Several recent studies have directly tested the hypothesis that cortical developmental programs align with the S–A axis. Our group investigated the development of two measures of cortical connectivity – functional connectivity and **structure–function coupling** – in youths aged 8–23 years [28,29]. These measures respectively index the strength of functional interactions between brain regions and the extent to which these interactions are constrained by direct white matter pathways, and provide complementary insight into how macroscale connectivity patterns support coordinated processing. We characterized local developmental trajectories for each measure using generalized additive models (GAMs), which are a powerful tool for modeling linear and nonlinear developmental effects (Box 1). We observed that both the magnitude and direction of age-dependent changes in functional connectivity and structure–function coupling varied according to the position of each cortical area along a functional gradient spanning unimodal to transmodal cortex, a homolog of the S–A axis (Figure 1B, left). As a result, higher-order association

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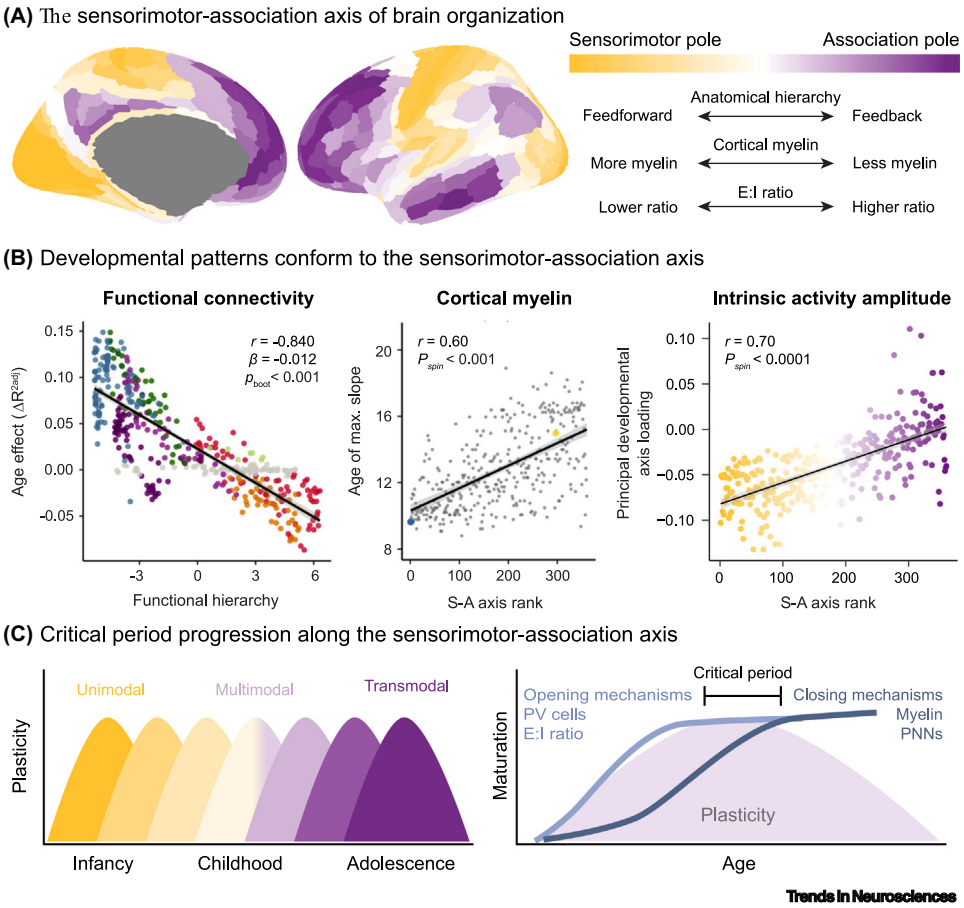

Figure 1. A critical period model for development along the sensorimotor–association (S–A axis). (A) (Left) The S–A axis is a large-scale axis of human brain organization that spans continuously from functionally-specific primary sensory and motor regions (sensorimotor pole; yellow) to modality-specific, multimodal, and then integrative transmodal association cortices (association pole; purple). (Right) The S–A axis captures spatial variation in circuit properties that are thought to influence the hierarchical cascading of developmental critical periods, including anatomical hierarchy position, intracortical myelin density, and excitatory (E) and inhibitory (I) circuit properties. (B) The S–A axis captures spatial and temporal variability in the development of functional and structural cortical properties. Functional connectivity: the magnitude and direction of age-related changes in between-network functional connectivity are largely explained by the position of a network in the cortical functional hierarchy, an fMRI-based homolog of the S–A axis. Each dot represents a single functional network. Positive and negative age effects indicate that the average connectivity of a network with other cortical areas increases with age (functional integration) or decreases with age (functional segregation), respectively. Cortical myelin: the age of maximal myelin growth progressively increases along the S–A axis, and regions nearer the association pole show a peak growth rate at later developmental stages. Each dot represents an individual cortical region. Cortical myelin content was proxied by the T1w/T2w ratio. Intrinsic activity amplitude: the principal axis of intrinsic activity amplitude development is strongly related to the S–A axis, revealing convergent spatial embedding of developmental and organizational axes. The principal developmental axis was obtained from a principal component analysis conducted on regional trajectories of fMRI fluctuation amplitude development; each dot represents an individual region. This developmental axis captured 87% of variance in regional maturational profiles. (C) A critical period plasticity model for the S–A axis of neurodevelopment provides mechanistic insight into hierarchically organized windows of neurodevelopmental plasticity. (Left) Windows of critical period plasticity are theorized to occur earliest, in infancy, at the sensorimotor pole of the S–A axis, and latest, in adolescence, at the association pole of the axis, with a gradient of developmental timing in between. (Right) Critical period mechanisms are hypothesized to underlie windows of developmental plasticity across the human cortex. Critical periods are initiated by opening mechanisms, including the initial strengthening of parvalbumin (PV) interneuron cell signaling and declines in the excitation/inhibition (E/I) ratio of a circuit. Critical periods are terminated by closing mechanisms, including the formation of cortical myelin and perineural nets (PNNs) which often form around PV cells. Panels A and B (right) are adapted, with permission, from [5]. Panel B (left) is adapted from [29] under license https://creativecommons.org/licenses/by/4.0/. Panel B (center) is adapted, with permission, from [31].

Glossary

Benzodiazepines: pharmacological agents that increase the effectiveness of endogenous GABA release through positive allosteric modulation.

Critical period: a period of developmental plasticity during which experience profoundly shapes brain development with long-lasting consequences for cortical circuit organization and behavior.

Designer receptors exclusively activated by designer drugs (DREADDs): engineered proteins that can be virally or transgenically expressed in the brain and later activated by a specific chemical actuator. This allows precise manipulation of neuronal activity in a particular set of cells at a particular time.

Excitation-to-inhibition (E/I) ratio: the relative balance of excitatory and inhibitory signaling strength within a cortical circuit. The E/I ratio is determined by multiple circuit properties, including the density and cell-type distribution of inhibitory interneurons, the density of excitatory pyramidal neurons, the size of pyramidal neuron dendritic arbors, the expression of inhibitory and excitatory neurotransmitter receptors, the number of inhibitory and excitatory synapses, and the level of recurrent excitation.

Functional connectivity: a functional magnetic resonance imaging (fMRI)-based measure that quantifies the statistical dependence between the functional time series of a pair of brain regions.

GAD65 knockout: GAD65 is one of two isoforms of the glutamic acid decarboxylase (GAD) enzyme necessary for the synthesis of the GABA neurotransmitter from glutamate. GAD65 knockout mice harbor a genetic deletion of the *Gad65* gene and have greatly reduced GABA release.

Parvalbumin-positive (PV) inhibitory interneurons: a class of fast-spiking interneurons that can powerfully inhibit excitatory and inhibitory neurons and synchronize local circuits.

Perineuronal nets (PNNs): components of the extracellular matrix that stabilize synaptic architecture. Perineuronal nets preferentially enwrap mature PV-positive interneurons.

Pharmacological functional MRI (ph-MRI): a technique in which a pharmacological compound is administered to participants and fMRI data are collected while the compound

Box 1. Using generalized additive models to characterize development

In many ways, development is a nonlinear process in which periods of relative change and stability unfold over time. To capture the broad array of potential nonlinear neurodevelopmental trajectories that could occur, it is useful to have statistical modeling tools that can flexibly capture different nonlinear functions. Generalized additive models (GAMs) are a class of regression models that can model a statistical relationship between a predictor (e.g., age) and an outcome (e.g., a measure of brain structure) as a smooth function. In the case of developmental modeling, the effect of age is commonly modeled using a penalized regression spline. The spline function can flexibly fit linear and nonlinear shapes while the penalty penalizes nonlinear complexity. The result is a regression model that can smoothly capture periods of nonlinear developmental change while avoiding overfitting. GAMs have advantages over the common approach of using polynomial regression terms because they are not restricted to the set of nonlinear fits available from polynomial regression, and they can be fit with a simple smooth term rather than a set of polynomial coefficients (which must be selected by the researcher). Furthermore, after fitting a GAM, the shape of the fit can be further interrogated to gain additional developmental insights. For example, the derivative of the smooth function, which quantifies the rate of change in the outcome measure given a change in age, can be evaluated to determine periods of significant age-related change. Other features of the developmental trajectory such as the age at the peak of the developmental curve, the age of maximum developmental change, and the age of maturation can be calculated along with 95% credible intervals. Calculating the derivative at specific ages across all cortical regions can also reveal how developmental change is spatially patterned across the cortex at different developmental stages [34]. Such approaches have been used to more precisely characterize developmental trajectories in human neuroimaging studies [105–107], including work mapping developmental programs of functional connectivity [29], myelination [19,31], and intrinsic BOLD signal fluctuation amplitude [34] across the S–A axis.

cortices exhibited the largest developmental increases in functional segregation and structure–function coupling. This work provided evidence that large-scale patterns of cortical functional development conform to the S–A axis.

In subsequent work from an independent group, the development of the **T1w/T2w ratio**, a measure shown to be sensitive to intracortical myelin content [30], was investigated along the S–A axis [31]. During brain development, cortical myelination can serve as a plasticity-restricting factor that limits the potential for further structural remodeling [32,33]. In a sample of youths aged 8–21 years, the magnitude and rate of age-related change in the T1w/T2w ratio differed systematically along the S–A axis, and developmental increases in T1w/T2w were largest and occurred most rapidly in cortices at the sensorimotor pole of the axis (Figure 1B, center). Furthermore, the age of peak developmental increase in the T1w/T2w ratio – potentially reflecting the age of maximal myelin growth rate – increased continuously along the S–A axis. These findings suggest that the S–A axis explains not only regional differences in the magnitude of developmental effects across the cortex but also variation in the timing of development of a structural marker of plasticity.

Most recently, we investigated whether developmental reductions in a potential functional marker of plasticity are also organized along the S–A axis [34]. Animal studies have revealed that, as sensory regions transition from plastic to mature and intrinsic (i.e., spontaneous or non-evoked), cortical activity transitions from widespread and synchronized – producing high amplitude neural recordings – to suppressed and sparse – producing low amplitude recordings [35,36]. Hence, development-linked reductions in intrinsic activity amplitude may provide a functional readout of local circuit plasticity. This readout can be studied non-invasively with fMRI: studies have shown that modulating biological regulators of plasticity and experimentally inducing plasticity indeed affect the amplitude of intrinsic fMRI recordings [37,38]. We therefore used GAMs to model spatially localized, age-related differences in the amplitude of fMRI fluctuations across the cortex. We found that the majority of spatiotemporal variance in regional developmental profiles for this functional measure was captured by a developmental axis that exhibited highly convergent spatial embedding with S–A axis (Figure 1B, right). Moreover, across cortical regions, the age at which the amplitude of intrinsic fMRI fluctuations began to decrease was closely linked to the age at which the T1w/T2w ratio maximally increased (as described in the preceding text [31]). This finding reflects a spatially correlated and temporally coupled pattern of cortical development for structural and functional markers of declining plasticity along the S–A axis [34].

is pharmacologically active in the brain. This allows researchers to understand how pharmacological manipulations influence fMRI signals.

Sensorimotor–association (S–A) axis: a dominant, macroscale axis of human brain organization that is hierarchically organized and rooted in evolution. This axis captures patterns of spatial variability in diverse cortical properties and has been shown to be present across data types and scales of measurement. The S–A axis spans from primary cortices supporting sensation and movement, to multimodal cortices supporting multisensory processing, language, and attention, and finally to transmodal association cortices supporting higher-order cognitive control and socioeomotional functions.

Structure–function coupling: the degree to which the functional connectivity of a brain area with other areas of the brain is statistically correlated with the magnitude of its structural connectivity (often measured using diffusion-weighted imaging).

T1w/T2w ratio: a myelin-sensitive measure derived by calculating the ratio of signal intensities from T1-weighted and T2-weighted MRI images.

Together, this series of studies demonstrates that the extent and timing of structural and functional brain development unfolds along the S–A axis throughout childhood and adolescence. This provides a concise framework for understanding how developmental plasticity spatiotemporally progresses, and provides insight into where and when the brain is most plastic throughout youth (Figure 1C, left). Understanding the precise patterning of plasticity is crucial for characterizing the manner in which experiences and interventions will most strongly impact on specific areas of the brain during particular developmental stages (Box 2). However, to understand how experience impacts on neurodevelopment, and what targets should be selected for neurobiologically informed interventions, the neural mechanisms that drive developmental plasticity must be identified. In the next section we propose that the observed spatiotemporal patterning of neurodevelopment along the S–A axis is driven by the hierarchically cascading maturation of critical period mechanisms.

Critical period plasticity mechanisms

Critical periods of brain development are windows of pronounced experience-dependent neuroplasticity during which experience shapes the brain with long-lasting (potentially permanent) consequences for brain function and behavior. A classic example of critical period plasticity is when the influx of synchronized visual input that occurs after eye opening begins a critical period of development for ocular dominance columns in primary visual cortex. A brief period of monocular deprivation during this early postnatal period (but not before or after) can permanently reduce visual cortex innervation for the closed eye [39]. A related term – 'sensitive periods' – has also been used to refer to temporally specific periods of experience-dependent development; during sensitive periods, behavioral outcomes are less permanent or the plastic window is less strict. Critical and sensitive periods thus differ in terms of degree but are not qualitatively different processes. For simplicity, we use the term 'critical period' going forward. Decades of work in animal models have shown that critical periods across brain systems are driven by a conserved set of neurobiological mechanisms that first promote and then restrict experience-dependent plasticity (reviewed

Box 2. How does experience shape critical period neurodevelopment?

The defining feature of a critical period is the increased ability of a biological system to change in response to experience. Neurodevelopmental critical periods are therefore times of opportunity to adapt to environmental demands and of vulnerability to adverse experiences. To better understand how experience shapes critical period plasticity throughout development, studies must account not only for the quantity and quality of experiences but also for the timing of experiences relative to the current state of plasticity in different regions.

The critical period model of S–A axis development posits that critical periods occur sequentially along the S–A axis, and predicts that sensorimotor regions will be particularly susceptible to early experiences, whereas associative regions remain susceptible to later experiences. Sensory deprivation experiments in rodents provide support for this model: ocular deprivation in infancy irreversibly disrupts normative visual cortical organization and decreases visual acuity, but these outcomes are not observed when deprivation occurs later in development [108,109]. By contrast, the development of the rodent prefrontal cortex is affected by environmental deprivation, environmental enrichment, and elevated stress when experienced in later developmental stages [110–112], suggesting a later or prolonged critical period. In humans, association system plasticity appears to be more prolonged, and cognitive and social deprivation during childhood or adolescence leads to differential development of association cortices [113]. Environments susceptible to conditions of low cognitive and psychosocial enrichment such as poverty [114,115] and institutionalization [116–118] are associated with structural and functional differences in association cortices and cognition.

In addition to shaping cortical development during critical periods, experience may also influence the neurobiological gating mechanisms that govern the timing of critical periods. Low-enrichment environments may accelerate neurodevelopment, and close critical periods earlier, whereas environments rich in novel, positive experiences have been shown to prolong the open state of the critical period, thus allowing the brain to further adapt to its environment [119]. Indeed, environmental enrichment may prolong critical periods by affecting PNNs and PV expression [120,121]. In a recent study [34], socioeconomic environmental deprivation was associated with a faster reduction in a functional marker of plasticity in association cortex, suggesting that the experiences of youths can shape the timing of the developmental plasticity of a cortical region. Moving forward, additional work will be necessary to understand precisely what types of experiences have the largest impact on different portions of the S–A axis during distinct developmental stages.

in [1,40]). Whereas critical period opening mechanisms allow the molding of cortical microcircuits to meet environmental demands, critical period braking mechanisms crystallize and limit further refinement of maturing circuits (Figure 1C, right).

The central feature of critical period development is the developmental strengthening and subsequent stabilization of inhibitory circuitry, particularly circuits involving **parvalbumin-positive (PV) inhibitory interneurons** [1]. The developmental strengthening of PV cells is a necessary critical period opening mechanism that is experience-dependent and facilitated by non-cell-autonomous factors [40–44]. In the case of ocular dominance plasticity, this occurs at eye opening when a change in coordinated, stimulus-evoked activity specifically triggers an increase in PV expression and the perisomatic innervation of $GABA_A\alpha1$ receptors by PV cells [45,46]. This, in turn, shifts the **excitation-to-inhibition (E/I)** ratio into a plasticity-permissive state in which spontaneous activity is suppressed and spike timing-dependent plasticity is facilitated [40,47,48]. The development of PV cells has been shown to be sufficient to trigger the activity-dependent opening of a critical period, and manipulating the timing and extent of either stimulus-evoked activity or PV development can change the timing of critical period onset [1]. For example, delaying PV maturation through experience deprivation can delay or diminish critical period-associated developmental processes and outcomes [42,46]. Similarly, the prevention of PV maturation in mice by **GAD65 knockout**, which eliminates a gene involved in synaptic GABA synthesis, prevents critical period opening [33,49]. Conversely, experimentally increasing inhibitory neurotransmission and promoting PV maturation through the administration of **benzodiazepines** in young animals can precociously trigger the opening of a critical period in immature cortex [49].

Once the opening of the critical period is triggered by the initial development of PV cells, a new set of mechanisms begin to stabilize cortical microcircuits by reducing the capability for future plasticity. These plasticity braking mechanisms, which are understood to close the critical period window, include the formation of both myelin and **perineuronal nets (PNNs)** which preferentially form on mature PV cells [32]. Although the formation of myelin is itself a plastic process [50,51], it serves as a critical period braking mechanism by restricting axonal branching and neurite outgrowth through myelin-mediated activation of the Nogo receptor [32,33]. Similarly, PNNs enwrap mature PV interneurons and limit further synaptic plasticity [52,53].

As PV cells begin to mature, the functional properties of cortical circuits evolve in a manner that facilitates experience-related sculpting. In particular, strengthening of inhibitory signaling facilitates spike timing-dependent plasticity, which further reduces excitation (E) via increased experience-dependent synaptic pruning, and results in a reduction of the local E/I ratio [1]. A decrease in the E:I ratio is thus a hallmark feature of critical period development [1,47,54]. As the E/I ratio declines, spontaneous activity is suppressed in favor of stimulus-evoked activity, producing an increase in the signal-to-noise ratio (SNR) of cortical circuits [47]. This allows stimulus-evoked activity – neural activity directly related to experience – to more effectively drive circuit plasticity. The formation of critical period braking factors furthermore ensures that these sculpted circuits produce a consistent and reliable output. The result of critical period neurodevelopment is thus an efficient circuit that has been sculpted by the environment of an individual and can reliably deliver high-fidelity output to downstream cortical areas.

A critical period framework for cortical neurodevelopment along the S–A axis

We hypothesize that the progression of cortical neurodevelopment along the S–A axis is mechanistically driven by a cascade of critical periods that progress hierarchically from sensory to association cortex and from infancy through adolescence. As each cortical area undergoes the critical period maturational process it begins to deliver reliable, high-fidelity outputs to areas

at the next level of the cortical hierarchy. This in turn engenders a shift in circuit dynamics that may be capable of triggering PV cell development [45–47] and thus a new wave of critical period opening in cortices further up the S–A axis. Evidence for this hierarchical critical period progression has already been documented across sensory systems in animal models. In visual and auditory systems, an influx of coordinated sensory stimulation triggers PV cell development and critical period opening in primary cortex (e.g., V1) [33,45], starting a cascade of PV cell development along the cortical hierarchy to higher-order sensory cortex (e.g., areas V2 to TE to 7a in primates) [55–58]. However, the extent to which this process extends to the association cortex and to the human brain – with its massively increased cortical surface and protracted, temporally variable development – has not been established [59,60]. Nevertheless, there is emerging evidence that critical period mechanisms, including PV maturation, myelination, and the formation of PNNs [44,61–64] (reviewed in [65]), are indeed developing in association cortices in animal models of peri-adolescence in a manner that facilitates higher-order cognition [66]. As such, it appears that, in the same way as early critical periods in sensory cortices support the development of sensory processing, the critical period development of the association cortices supports the maturation and refinement of higher-order cognitive abilities such as executive function and socioemotional processing [56,65,66]. However, translating these findings to human studies has been complicated by the limited ability to directly investigate specific critical period mechanisms using *in vivo* neuroimaging approaches. To move toward a mechanistic understanding of human development, there is a need to develop novel approaches to investigate critical period mechanisms across the cortex.

Approaches to investigating critical period mechanisms in humans

To formally test whether critical periods temporally progress along the S–A axis throughout youth, it is necessary to develop methodological approaches that can measure specific critical period neurobiological mechanisms in humans. A primary challenge is that there is often no clear mapping between cellular- or molecular-level neurobiology and the signals generated from non-invasive human neuroimaging tools such as fMRI. We outline here recent approaches that seek to overcome this difficulty by linking human neuroimaging measures to a hallmark feature of critical periods: the maturation of inhibitory neurotransmission and the resulting decrease in E/I ratio (Box 3 for advances in investigating myelin as a critical period braking mechanism). These approaches rely on innovative experimental designs, computational models, and animal-to-human translation to understand how changes in the E/I ratio of cortical circuits map onto fMRI signals. We focus on approaches for investigating E/I using fMRI owing to the widespread availability of this imaging approach, including in large-scale developmental neuroimaging datasets such as those generated by the Adolescent Brain Cognitive Development and the Lifespan Human Connectome Project Development studies, and its ability to investigate whole-brain patterns while maintaining relatively high spatial resolution. We note, however, that approaches using electrophysiological imaging such as electroencephalography (EEG) are also promising (Box 4). Applying insights from these approaches to the study of human neurodevelopment represents a promising avenue for future studies investigating critical period development in the human brain.

Pharmacological functional MRI

Pharmacological functional MRI (ph-fMRI) involves administering a pharmacological agent (drug) and acquiring fMRI data while the acute effects of the drug are present. This allows an empirical assessment of the effect of a drug on the fMRI signal. Ph-fMRI studies that use a drug to experimentally manipulate the E/I ratio can thus be used to empirically assess how manipulating the E/I ratio impacts on fMRI signals. We recently used a double-blind, placebo-controlled ph-fMRI study with an alprazolam drug challenge to generate an empirical model

Box 3. Approaches for studying myelin, a critical period braking factor, in humans

Two of the best-studied critical period closing mechanisms are the formation of perineuronal nets (PNN) and an increase in myelination [32,40]. There are currently no techniques available to investigate PNNs in the living human brain, and thus human studies on this topic have been limited to postmortem approaches [122]. Myelin, on the other hand, is a promising target for studies of critical period closure during human development.

A variety of quantitative techniques have been developed to specifically measure the effects of myelin on different aspects of the MRI signal *in vivo*. These approaches have previously been reviewed and compared in detail [123–126]. Briefly, popular approaches can be categorized as measuring (i) relaxometry, such as quantifying the effect of myelin on longitudinal (R1) or transverse relaxation rates (R2); (ii) the relative concentrations of water contained in myelin versus intra- and extracellular compartments, such as myelin water fraction (MWF); or (iii) the magnetization transfer between macromolecules and free water, such as the magnetization transfer ratio (MTR), inhomogeneous magnetization transfer (ihMT), and macromolecular proton fraction (MPF). These methods have all been shown to have good agreement with histological measures of myelin, although there are key limitations that should be acknowledged. Relaxometry-based methods and MWF may have reduced specificity in areas high in iron concentration [127], and MTR may have lower reproducibility than other measures [126]. These methods have been further combined with diffusion-weighted imaging to calculate the g-ratio, which reflects the ratio of the inner to the outer radius of the myelin sheath [123,128]. Each of these families of techniques have been used to demonstrate increases in myelin content during development [20,129,130].

Another approach that has recently grown in popularity is the T1w/T2w ratio. An advantage of this method is that it is derived from T1-weighted and T2-weighted images, which are commonly collected in standard MRI acquisition protocols. However, the T1w/T2w ratio is not a quantitative measure, and values can therefore vary based on scan parameters, and a tissue reference is needed [131]. Corrections for radiofrequency transmit field (B1+) biases should also be applied [132]. Further, although the T1w/T2w has proved to be useful in mapping intracortical myelin across the cerebral cortex, it suffers from limited sensitivity and specificity for myelin content in white matter and subcortical structures [127]. Despite its limitations, the T1w/T2w ratio has been successfully used to infer the development of intracortical myelin across the S–A axis [19,31].

linking the pharmacological reduction of the E/I ratio to patterns of fMRI functional connectivity [67]. The benzodiazepine alprazolam is a positive allosteric modulator of the $GABA_A$ receptor that enhances the strength of GABA-induced hyperpolarization, thus facilitating inhibition and reducing the E/I ratio. We trained a multivariate support vector machine (SVM) classifier to distinguish drug from placebo sessions – in other words, sessions with lower or higher E/I ratio, respectively – based on patterns of fMRI functional connectivity (Figure 2A, top). The model could not only significantly distinguish drug from placebo sessions in unseen individuals

Box 4. Investigating changes to E/I ratio using electrophysiology in humans

As PV interneurons develop and contribute to reductions in the local E/I ratio during critical periods, they produce changes in the electrical activity of local circuits. Notably, mature PV cells have greater amplitude, greater frequency, and lower decay time of inhibitory postsynaptic currents than immature cells, which together support mature high-frequency gamma oscillations [133]. This originally led to the hypothesis that gamma oscillatory power would increase during a critical period. Surprisingly, it has been demonstrated that high-frequency oscillatory power actually decreases during the transition from adolescence to adulthood in the prefrontal cortex of non-human primates and humans [134]. It was found that this pattern emerges because the developmental strengthening of inhibition increasingly suppresses spontaneous and task-irrelevant cells from being integrated into stimulus-evoked gamma rhythms. Greater spontaneous gamma power and less task-evoked enhancement of gamma rhythms have also been observed in more immature (as compared to mature) PV networks in mouse models [135]. As such, mature cortex with reduced E/I ratio has reduced overall gamma power – owing to more precise tuning of stimulus-evoked gamma activity.

The developmental reduction in high-frequency power can be captured by electrophysiological techniques such as EEG which measure electrical activity generated by neurons. Changes in oscillatory power at different frequencies can be measured in the power spectral density (PSD) of the electrophysiological signal, which represents signal power across the frequency spectrum. For brain activity, PSD conforms to a 1/frequency (1/*f*) power law such that power decreases as a function of frequency. The steepness of the 1/*f* slope is reflected by the 1/*f* exponent: a higher exponent reflects a steeper decline in power with increasing frequency. Manipulations that reduce the E/I ratio in neural network models, in chemogenetic mouse models, and in human electrocorticography convergently result in an increase in the 1/*f* exponent of the PSD [72,136,137]. This pattern is consistent with the developmental reductions in gamma power observed in animal models of development (which would steepen the 1/*f* slope). The 1/*f* exponent may therefore be a useful biomarker of E/I changes in developmental studies. In a test of this hypothesis, a recent study demonstrated that intracranial recordings in mice and EEG recordings in humans show a developmental increase in the 1/*f* exponent [136].

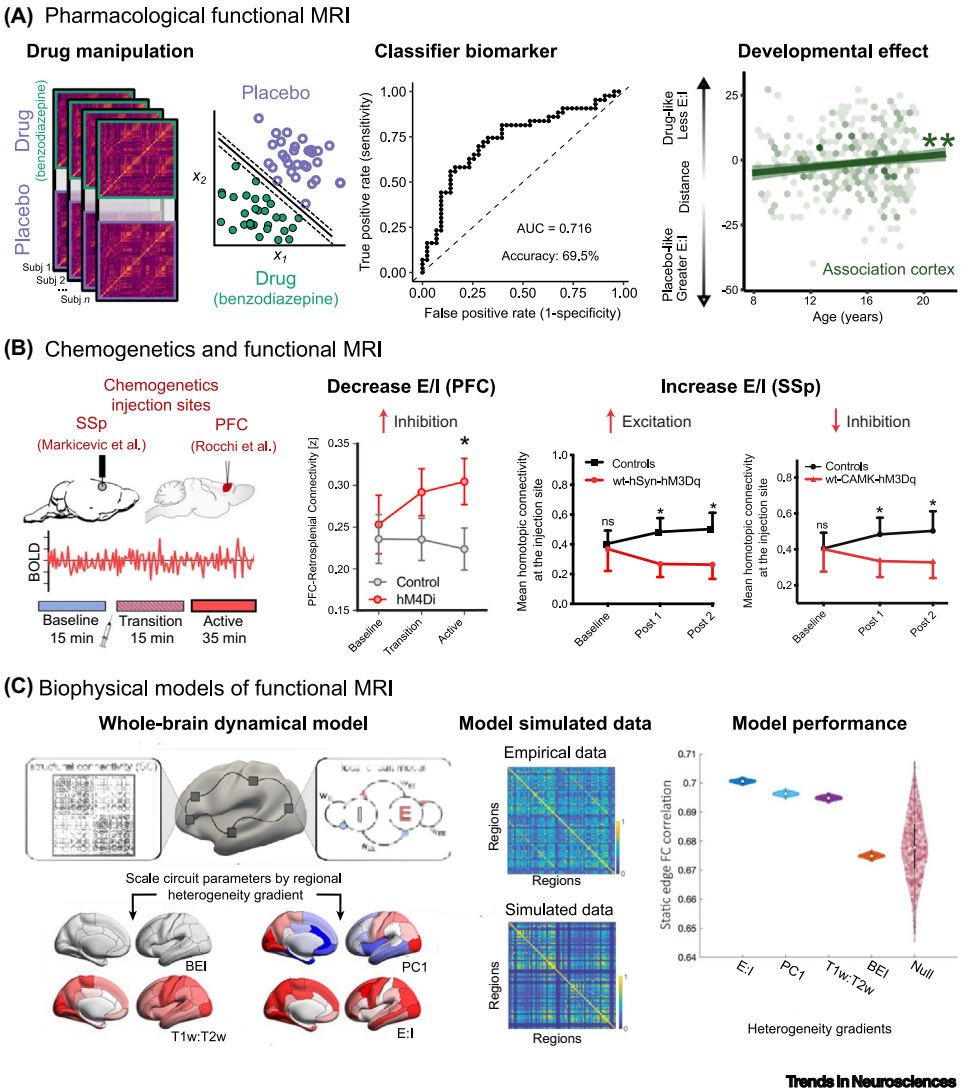

Figure 2. Approaches to investigating changes in the excitation/inhibition (E/I) ratio using functional magnetic resonance imaging (fMRI). (A) Pharmacological functional MRI: drugs can be used to manipulate the E/I ratio while fMRI data are recorded (drug manipulation) to measure the effect on the fMRI signal. Recent work used a benzodiazepine manipulation to train a machine-learning classifier to distinguish patterns of fMRI connectivity generated from drug (i.e., reduced E/I) from placebo scans (classifier biomarker). The trained and validated E/I biomarker was then used to discover evidence of declining E/I in the association cortex during youth (developmental effect). (B) Chemogenetic functional MRI: the E/I ratio can be precisely manipulated using designer receptor exclusively activated by designer drug (DREADD) animal fMRI studies. Recent work used DREADDs to chemogenetically manipulate the E/I ratio in somatosensory cortex (SSp) or prefrontal cortex (PFC) while recording fMRI data (left). Chemogenetically decreasing E/I by increasing inhibition results in increased fMRI connectivity to anatomically connected regions (e.g., retrosplenial cortex; center). Conversely, chemogenetically increasing E/I by either increasing excitation or reducing inhibition results in reduced fMRI connectivity to homotopic cortex (right). *P=0.039, two-sided t test between chemogenetic manipulation and control group mice. Data from Markicevic *et al.* [73] and Rocchi *et al.* [72]. (C) Biophysical models of functional MRI: biophysical models place a local circuit model in each region of cortex that has biologically plausible parameters that correspond to excitatory and inhibitory neuron populations. Communication between circuits is scaled by pairwise structural connectivity (left, top). A whole-brain dynamical model produces simulated activity that can be transformed to the simulated fMRI blood oxygen level-dependent (BOLD) signal. The whole-brain model can be further informed by spatial heterogeneity in the neurobiological properties of each cortical area (left, bottom). Simulated fMRI data can be used to construct a simulated fMRI connectivity matrix that can be compared to empirical fMRI

(Figure legend continued at the bottom of the next page.)

but the spatial pattern of functional nodes that contributed most to the SVM classifier also aligned with the spatial distribution of benzodiazepine-sensitive $GABA_A$ receptor subunits (α1, α2, α3, and α5), but not with benzodiazepine-insensitive $GABA_A$ subunits (α4 and α6) (Figure 2A, top). This suggested that our empirical model had learned to distinguish fMRI connectivity patterns generated by pharmacologically reducing E/I conditions using feature weights that conformed to known benzodiazepine pharmacology.

Having generated an fMRI model sensitive to changes in the E/I ratio, we next used this model to test a central prediction of the hierarchical critical period neurodevelopmental model – that a developmental reduction in the E/I ratio will occur selectively in association cortices during adolescence. Specifically, we first applied our empirical E/I model to an independent developmental sample and found that functional connectivity patterns became more 'drug-like' (i.e., more similar to patterns seen during alprazolam administration) between the ages of 12.9 and 16.7 years. Conceptually, this provides evidence for a developmental reduction in the E/I ratio across the brain in this age range. To localize where E/I ratio-linked changes in functional connectivity patterns were occurring during development, we next separately trained our SVM classifier on connections with association cortex and connections with sensory cortex, and then applied each model to the developmental dataset. We found that changes in functional connectivity indicative of age-related reductions in the E/I ratio were only observed for the association cortex model (Figure 2A, right). Together, these findings provide evidence for a developmental reduction of the E/I ratio that is specific to association cortex during adolescence.

This study provides one example of the utility of ph-fMRI data for investigating developmental changes in the E/I ratio. Future work can begin to determine the specificity of these findings for inhibitory modulation by developing ph-fMRI biomarker models of the E/I ratio that are based on different pharmacological manipulations of excitatory or inhibitory neuron populations. Importantly, this work more broadly demonstrates the potential of ph-fMRI data to generate fMRI biomarkers of other neurobiological targets which could then be applied to new datasets to gain fresh insights. In particular, other critical period regulating factors such as the nicotinic system [68] or pharmacological agents such as valproic acid that may reopen critical periods [61,69] may be useful targets for pharmacological fMRI studies.

Chemogenetic neuroimaging of animal models (chemo-fMRI)

Although ph-fMRI has the advantage of being readily applicable to human research, it is limited in its ability to spatially target specific brain circuits and by the specificity of the mechanism of action of available drugs. These limitations can be addressed in studies of animal models where more targeted experimental manipulations are possible. Recent work has demonstrated the effectiveness of chemogenetic manipulations using **designer receptor exclusively activated by designer drug (DREADD)** tools which allow viral or transgenic expression of a particular receptor at a particular location that can later be activated by the experimenter using a specific chemical actuator [70–72]. When paired with functional neuroimaging approaches like fMRI (i.e., chemogenetic fMRI or chemo-fMRI), DREADD experiments can reveal how precise changes in microcircuit activity influence fMRI signals and fMRI-derived measures that can be quantified in human participants [70,71].

connectivity matrices (middle). Recent work has demonstrated that a biophysical model informed by a spatial gradient of E/I gene expression captures the true patterns of fMRI connectivity better than chance or competing gradients of neurobiology. Biophysical models could now be used to investigate how E/I model parameters vary across development. Abbreviations: AUC, area under the curve; BEI, balanced E/I model; FC, functional connectivity; PC, principal component; Subj, subject. The top panel (A) is adapted, with permission, from [67]. The middle panel (B) is adapted from [72] under http://creativecommons.org/licenses/by/4.0/ and from [73]. The bottom panel (C) is adapted, with permission, from [80].

Two recent studies have used chemo-fMRI approaches with DREADDs to provide converging evidence for how differences in the E/I ratio influence patterns of fMRI functional connectivity [72,73]. In the first study, two DREADD experiments were performed that acutely increased the E/I ratio selectively in the somatosensory cortex of mice during a resting-state blood oxygen level-dependent (BOLD) fMRI scan [73]. Chemogenetically increasing the E/I ratio by either facilitating excitatory neurons or suppressing inhibitory PV interneurons led to reductions in both intra-regional connectivity (measured by fMRI regional homogeneity) and inter-regional functional connectivity to other nodes of the somatosensory network (Figure 2, middle). These findings were replicated and extended in a second study that chemogenetically manipulated the E/I ratio in mouse prefrontal cortex [72]. Again, chemogenetically increasing the E/I ratio, by either facilitating excitatory neurons or suppressing inhibitory PV interneurons, resulted in resting-state fMRI hypoconnectivity. Conversely, chemogenetically reducing the E/I ratio resulted in fMRI hyperconnectivity (Figure 2, middle). Notably, both studies found that E/I-related changes in fMRI connectivity were greatest for brain areas that were anatomically connected to the DREADD target, suggesting that local E/I changes preferentially impact on connectivity within an anatomical network. Together, these studies provide evidence that a the functional connectivity of a region to other nodes of its anatomical network is inversely related to its E/I ratio.

Future directions for this work could center on translating findings from chemogenetic manipulations in animal models to human studies to generate a directional hypothesis for the development of fMRI connectivity during critical period development in the human brain. Specifically, these chemo-fMRI findings suggest that, as the E/I ratio decreases at the opening of the critical period, fMRI connectivity within a maturing functional network should increase with age. Because chemo-fMRI effects were greatest for parts of the network that share direct anatomical connections [72,73], future studies of functional network development may see stronger effects if analyses are constrained to regions within functional networks that share anatomical connections.

Biophysical computational models

An emerging body of work has used biophysically plausible computational modeling of cortical microcircuits to understand how changes in excitatory and inhibitory activity impact on large-scale patterns of BOLD functional connectivity and dynamics. These computational biophysical models place a local circuit model in each cortical region that simulates population-level activity of excitatory and inhibitory neurons based on biologically interpretable parameters (Figure 2, bottom). These parameters include the strength of recurrent excitatory-to-excitatory, excitatory-to-inhibitory, and inhibitory-to-excitatory connections (overviewed in [74,75]). Each regional microcircuit also receives long-range input from other regions that is scaled by the strength of its pairwise structural connectivity, which is usually based on a structural connectivity matrix generated from diffusion-weighted MRI data. Population-level circuit activity is then used to simulate the BOLD signal using a hemodynamic response model such as the Balloon-Windkessel model [76]. Simulated BOLD data from each cortical region can be used to construct a functional connectivity matrix which is typically compared to an empirical connectivity matrix to optimize model parameters or to determine the accuracy of the simulations. The resulting model parameters can provide insight into how E/I population dynamics are associated with empirical BOLD fMRI signals.

Recent work has demonstrated that the performance of biophysical circuit models most closely matches neurobiological systems when the model construction is informed by known E/I gradients. For example, allowing circuit properties to vary along a gradient that is associated with gene expression patterns for excitatory and inhibitory neuron cell types [77] significantly improves the accuracy of simulated BOLD dynamics relative to a homogenous model [78,79] or to models informed by competing indices of cortical hierarchy [80] (Figure 2, bottom). Similarly, when the biophysical

model parameters for each cortical area are tuned in a data-driven fashion rather than being informed by neurobiology, a hierarchical gradient is produced that recapitulates the E/I gradient used to inform *a priori* models [81]. Together, these studies demonstrate that biophysical models can simulate fMRI data that match empirical data based on biologically plausible parameters that align with E/I neurobiology.

Moving forward, these biophysical models can be used to determine whether observed differences in empirical fMRI data that occur over development are consistent with differences in the E/I ratio. For example, one could manipulate the excitatory or inhibitory model parameters at different regions of the S–A axis to produce fMRI data that simulate hypothesized developmental changes in E/I, and evaluate their alignment with empirical developmental fMRI data. A related approach would be to fit biophysical models to empirical fMRI data from different developmental stages and investigate how the model parameters that best fit each dataset vary across developmental epochs. Researchers could then test the hypothesis that parameters reflecting inhibitory signaling would increase with age, leading to a reduced E/I ratio.

Methodological considerations for ph-fMRI, chemo-fMRI, and biophysical fMRI models

There may be new challenges or limitations to applying the three methodological approaches described in the preceding text to pediatric imaging samples. One significant challenge in developmental neuroimaging is the presence of signal artifacts related to head motion, which influence many aspects of fMRI signal [82,83]. It is crucial that work applying these approaches to developmental samples uses rigorous, field-standard motion correction and exclusion procedures to minimize the contribution of motion artifacts to developmental effects [84]. Furthermore, studies constructing biophysical models and chemo-fMRI models have to date only been performed in adult human and animal samples. Future work should carefully evaluate whether the methodology developed in adult samples is valid for studies of pediatric brains.

Concluding remarks and future perspectives

We have outlined a critical period model for the S–A axis of cortical development. This framework provides a cohesive basis for understanding the patterns and underlying mechanisms that drive spatiotemporal gradients of developmental plasticity across the cortex. As discussed in earlier sections, there is compelling evidence for this developmental model that spans both human studies and animal models of development. Moreover, emerging approaches now offer the opportunity to further probe critical period mechanisms and their temporal unfolding along the S–A axis in humans using pediatric neuroimaging techniques. Nevertheless, as highlighted in the following section, many open questions and exciting future directions remain (see also Outstanding questions).

The degree to which genetic and environmental factors interact to modulate critical period mechanisms in the human brain will be an important area of future study. As critical periods allow experience to interact with neurobiology to shape long-term outcomes, an important extension of the proposed model would be to characterize how the nature and timing of experience – such as environmental enrichment, adversity, or stress (Box 2) – influence developmental plasticity through critical period mechanisms [85]. In addition, a growing body of work has shown that some interindividual variability in cortical structure and function is heritable and that genetic contributions may fluctuate over development and across the cortex [2,3,86–91]. The mechanisms that drive critical period opening, closing, and expression have been shown to be regulated by gene expression [33,40,92]; nevertheless, the degree to which critical period mechanisms are influenced by genetic differences remains to be explored. Notably, the *CLOCK* gene has been implicated in influencing critical period timing and has several polymorphisms in the population [93]. Another interesting target

Outstanding questions

Brain development in humans appears to progress hierarchically along an S–A axis, where areas of association cortex are latest to mature. How does hierarchical neurodevelopment support cognitive development during youth?

How do individual differences in the timing and expression of critical period plasticity along the S–A axis relate to individual differences in cognitive performance?

What factors influence individual differences in the pacing of development along the S–A axis? How do environmental or experiential factors such as socioeconomic status, trauma, stress, psychotropic use, and puberty influence the timing and expression of plasticity?

How do differences in genetics influence the timing and expression of critical period plasticity? How are these effects further modulated by gene–environment interactions?

How does the precise timing and nature of experience impact on patterns of neurodevelopment? Are these effects mediated by critical period mechanisms?

Can we identify distinct 'critical' experiences for distinct developmental epochs? What experiences most strongly shape cortical circuits in association cortex during later developmental stages?

Can we identify person-specific, non-invasive markers of critical period opening and closing along the S–A axis during youth?

What is the role of critical period mechanisms in the emergence of psychopathology during youth?

What is the role of biological sex in shaping patterns of development and underlying mechanisms following puberty?

may be the critical period trigger, Otx2, whose gene *OTX2* has multiple polymorphisms that have also been implicated in schizophrenia and bipolar disorder [94].

The pronounced developmental plasticity that is afforded during a critical period creates a window of opportunity for healthy and adaptive sculpting of the brain to its environment; however, it may also confer vulnerability to atypical development and the emergence of psychopathology [65,85,95,96]. Our critical period plasticity framework for the S–A axis of development predicts that youth-onset psychopathology may be linked to variation in the expression of critical period regulating mechanisms and altered cortical sculpting along the S–A axis. Recent work looking both broadly across mental disorders and at specific disorders such as major depressive disorder (MDD), autism spectrum disorder (ASD), and pediatric bipolar disorder has revealed that they are linked to atypical cortical organization along the S–A axis [27,97–99]. Studies investigating the neurobiological mechanisms underlying conditions such as MDD, psychosis spectrum disorder, and ASD have also implicated critical period mechanisms such as atypical E/I ratio, PV inhibitory dysfunction, and PNN degeneration [92,95,96,100–103]. Together, this work suggests that the emergence of neuropsychiatric disorders during youth may be linked to alterations in the S–A axis that may in part be driven by critical period mechanisms. Future work should investigate whether developmental differences in critical period plasticity at different phases of development are linked to the emergence of psychiatric symptoms during youth and begin to identify neurobiologically informed therapeutic targets [104].

The critical period plasticity framework for hierarchical cortical development along the S–A axis has substantial implications for understanding not only when and where but also how neurodevelopmental plasticity unfolds across the cortex. The approaches outlined here represent a promising and exciting path toward achieving this aim, and highlight the importance of interdisciplinary collaborations that bridge across methods, model systems, and levels of analysis. Moving toward a mechanistic understanding of human neurodevelopment will pave the way to understanding how spatiotemporal windows of neurodevelopmental plasticity are shaped by complex interactions between environment, genetics, and biology to foster healthy development or create vulnerability to psychopathology.

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Declaration of interests

The authors declare no conflicts of interest.

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