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REVIEW ARTICLE

Investigating hierarchical critical periods in human neurodevelopment

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Identifying when periods of enhanced neurobiological plasticity occur throughout the human cortex is foundational to understanding when different neural circuits and the psychological processes that they support will be most impacted by adverse and enriching environments. Animal research has identified "critical periods" of plasticity that occur in primary cortices and enable profound environment-dependent sculpting of sensory function early in life. Recent evidence suggests that critical periods may additionally occur in the human brain during childhood and adolescence, where they are hypothesized to unfold hierarchically across sensorimotor and association cortical regions. In this article, we consider neural, environmental, and behavioral evidence for hierarchical critical periods in human development. We review neuroimaging studies that have characterized the development of in vivo correlates of critical period plasticity and synthesize research that has explored when lower-order and higher-order cortical regions exhibit differential environmental sensitivity. We outline how the field is well-positioned to further investigate the precise nature, timing, and consequences of putative critical periods and summarize approaches to making progress in this area. We end by describing the relevance of critical periods for understanding youth psychiatric risk and for informing age-specific environmental enrichment interventions capable of supporting healthy development by fostering resiliency.

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INTRODUCTION

The human cerebral cortex exhibits a multi-decade maturational time course during which it retains an innate capacity for environment-driven plasticity. During periods of developmentally enhanced plasticity, environmental inputs have a particularly large and lasting impact on the sculpting of neural circuits and the functions that they support, and thus on the sculpting of youths' neurodevelopmental trajectories. Demarcating when periods of maximal environment-driven plasticity occur is foundational to understanding when the youth brain will be most vulnerable to environmental disadvantage—as well as most amenable to environmental enrichment interventions designed to support healthy development and foster resiliency. Progress in the demarcation of plastic periods of environmental sensitivity can be made by applying neurobiologically-grounded frameworks for studying how the brain modulates the impact of the environment on neural circuits across developmental time.

Critical periods provide an essential framework for pairing research on the neurobiology of developmental plasticity with studies of environmental sensitivity [1–7]. Critical periods are age-constrained windows of enhanced neurobiological plasticity during which environmental inputs have a pronounced impact on the cortical circuits that encode them and on long-term behavioral functioning. Critical periods of environment-driven plasticity have primarily been studied in sensory systems of non-human animals; animal research has shown that the timing and expression of these periods are regulated by a conserved set of neurobiological mechanisms [2, 8, 9]. Importantly, accumulating evidence indicates that homologous neurobiological mechanisms manifest developmentally in the human brain, where they are expressed earliest in primary cortices with sensory and motor functions and latest in association cortices that support cognitive and socioemotional processing [1, 7, 10]. This neurobiological evidence has led to the hypothesis that critical periods akin to those seen in animal sensory systems occur in the human brain—and occur sequentially in sensorimotor and association regions [1, 2, 5, 7, 11–13]. Elucidating whether regionally-specific periods of human brain plasticity reflect archetypal critical periods has vital implications for understanding when environmental insults and interventions will have a particularly lasting impact on different brain circuits and psychological processes. However, confirmation of the existence of critical periods requires not only the demonstration of a unique period of brain plasticity, but also corroboration that plasticity results in a temporally constrained window in which both the brain and behavior exhibit heightened sensitivity to environmental inputs. Accordingly, the study of human critical periods requires the integration of neural, environmental, and behavioral perspectives.

In this review, we consider child and adolescent critical periods of environment-driven plasticity in humans from these three

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Box 1. Critical and sensitive periods

The terms "critical" period and "sensitive" period have both been used to describe time-limited windows of development when neural circuits exhibit transiently greater malleability by the environment and experience. Though occasionally used interchangeably in the literature, these two terms have been distinguished by the presumed functional form of the plastic window and by their precise application in different fields. The term critical period was originally used to describe a strictly timed period of development with an abrupt offset and loss of plasticity wherein the environment induced irreversible changes to circuit architecture and behavior. The term sensitive period, on the other hand, has been employed to characterize similar periods that have a gradual rather than an abrupt offset, that allow for continued rather than a total loss of plasticity, and that result in the environment having a particularly strong but not immutable effect on circuit functioning [11,19,23,234–238]. Despite the rigid original conceptualization of critical periods, it has been shown that the precise timing and length of critical periods are modifiable by the environment and that hallmarks of critical period plasticity can be induced or reversed in adulthood—even in primary visual, auditory, and somatosensory cortex. The critical period for ocular dominance plasticity in V1, for example, can be delayed by dark rearing [65,239], extended through late development by environmental enrichment [240], or reactivated in adulthood by environmental manipulations [241–243]. In addition, it is now recognized that different forms of restructuring and adaptation occur in circuits outside of their developmental critical periods, in line with continued (but often mechanistically distinct forms of) lifelong plasticity [19,20,24,243,244]. Accordingly, the boundary between critical and sensitive periods based only on their functional form is blurred.

A potentially stronger distinction between critical and sensitive periods arises from their varied use across fields. The term critical period has most commonly (although not exclusively [24,245]) been employed to describe windows of environment-driven plasticity in the cortex that are regulated by a set of core neurobiological mechanisms. The term sensitive period has been used more broadly, being applied to describe non-cortical, behavioral, or biological phenomenon that are most impacted during specific times in development. For example, the term sensitive period has been used to describe the vulnerability of a fetus to teratogens during the first trimester of pregnancy [246], developmental stages when caregiver attachment and parenting style most shape corticolimbic circuitry [184,247], a period of enhanced sensitivity to the sociocultural environment in adolescence [248], and windows when microbiota or specific nutrients impact neurodevelopment [249,250]. While these are certainly valid uses of the concept of sensitive time periods of development, they are distinct from the canonical critical periods considered here.

In this work, we use the term critical period to provide an account of developmental plasticity and environmental sensitivity that is *neurobiologically-grounded, cortical-centric*, and that depends on the *core critical period mechanisms* elucidated in animal studies. The use of this term conveys the central hypothesis that the human brain exhibits not just general periods of higher environmentally sensitivity—but critical periods that parallel those defined in animal models and that emerge from shared developmental biology and evolutionary history. Importantly, the term critical period does not imply that the onset and offset of these periods cannot be gradual or that the duration of the periods themselves is not quite protracted in humans, particularly within evolutionarily-expanded [129] association cortices. Furthermore, this term does not indicate that neural and behavioral plasticity (and associated opportunities for learning or recovery) cannot occur outside of a critical period—but instead that the responsivity of this plasticity to the environment is less extensive or relies on a different type of biological change. Finally, the use of the term critical period need not rule out the unexplored possibility that the same circuit may exhibit more than one critical period over human's highly extended developmental time course.

perspectives (see Box 1 for a discussion of "critical" and "sensitive" periods). We focus on childhood and adolescence given that neurodevelopment in infancy is characterized by distinct environmental demands and developmental processes (e.g., synaptogenesis and exuberant growth in infancy versus pruning and architectural refinement during youth). Hence, while the infant brain is highly malleable and sensitive to environmental inputs [14–17], the developmental processes that build the foundations of circuitry in infancy differ from those that refine, specialize, and consolidate mature circuits during childhood and adolescence. In what follows, we first provide examples of classic critical periods in animal sensory systems, describing established neurobiological mechanisms that prime, open, and close windows of environment-driven plasticity. We then extend this developmental phenomenon to murine (mouse and rat) association cortex: by integrating data from diverse studies, we describe a potential adolescent critical period in murine medial prefrontal cortex (PFC). Next, we review research pertinent to the study of mechanistically defined critical periods in humans. We examine both neuroimaging research that has characterized the development of in vivo correlates of critical period biology and research that has explored when different brain regions and psychological processes exhibit enhanced environmental sensitivity.

Taken together, existing literature provides compelling evidence that periods of developmental plasticity and environmental receptivity unfold in time along the human cortex's sensorimotor-association axis, suggestive of *hierarchically organized critical periods in humans*. Additional research is needed, however, to better elucidate the presence, timing, and behavioral consequences of human critical periods, especially within higher-order association cortex. We therefore end by describing future research approaches for studying critical periods, highlighting how continued work in this domain can inform efforts to reduce psychiatric risk by enriching youths' environments during periods of adaptive cortical plasticity.

CRITICAL PERIODS OF PLASTICITY IN ANIMAL MODELS

Neurobiological critical periods of environment-driven plasticity are defined windows in development during which particular environmental inputs have a pronounced impact on specific brain circuits and long-term behavioral functioning. Critical periods have predominantly been studied in primary sensory cortices in animal models, where they naturally occur during short (days to weeks) developmental windows. Notably, the initial conceptualization of a critical period postulated that a circuit would not restructure in response to environmental inputs beyond its critical window [18]. It is now understood that environment-driven change occurs in sensory (and other) systems outside of critical periods, although such changes tend to be smaller in magnitude, rely on a different set of (potentially compensatory) mechanisms, and require more potent or protracted environmental exposures (see also Box 1) [19–22]. Critical periods thus differ qualitatively and mechanistically from other forms of plasticity (e.g., early corticogenesis, adult homeostatic plasticity, learning and memory) [23, 24] and are thought to represent one of the optimal, but not the only, age windows for neural adaptation to and encoding of experience. In the following section, we first describe the nature of archetypal critical periods in murine sensory systems, focusing on the biological mechanisms that differentiate critical periods from other forms of lifespan brain plasticity. We then summarize extensive data that identifies a possible critical period of environment-driven plasticity in murine association cortex, which occurs during adolescence following peak plasticity in sensory cortex.

Archetypal critical periods in primary sensory cortex

Critical periods in primary cortices occur when a shift in circuit-relevant environmental inputs trigger a time-limited plasticity response in a biologically primed circuit. In animal systems, sensory critical periods are thus typically delineated by altering, enriching, or removing sensory inputs from the environment, and studying the differential effects of the environmental manipulation on cortical architecture and function at different ages. Such manipulations have shown, for example, that whisker trimming in mice during a critical period in barrel (i.e., somatosensory) cortex between postnatal days (P) 10 to 14 permanently alters layer 2/3 neuron receptive fields and degrades sensory tuning [25, 26]. Exposure to pure tones of a specific frequency during a critical period in primary auditory cortex from P12 to P16 dramatically shifts A1's tonotopic map to over-represent the tone and alters auditory frequency discrimination [27, 28]. Similarly, restricting visual input to one eye during a critical period in primary visual cortex that spans P21 to P30–35 results in marked and

largely permanent ocular dominance shifts in V1 and lower visual acuity [29, 30].

A wealth of molecular, cellular, and activity-dependent factors regulate the timing and expression of sensory cortex critical periods by acting in a synergistic, sequential manner to *prime, open, and close* windows of environment-driven circuit remodeling [2, 3, 5, 7]. Critically, while plasticity-regulating biological factors are highly diverse (and thus not all included in this review), they share a common feature: they have a direct or downstream effect on the local excitation/ inhibition (E/I) ratio and the development of parvalbumin-positive (PV) inhibitory interneurons. The developmental strengthening of PV interneuron activity is central to both critical period opening and closing and is thus considered a central mechanism controlling when cortical circuits rewire in response to external inputs. In particular, an initial increase in perisomatic innervation of pyramidal neurons by PV cells—and a consequent strengthening of inhibitory γ-aminobutyric acid (GABA) activity at $GABA_A$ receptors—opens critical periods in sensory cortices [29, 31–33]. Critical periods then terminate when PV cells fully mature and high-frequency inhibitory firing is stabilized and maintained [22, 29, 34, 35]. Correspondingly, while experimentally enhancing PV interneuron activity or $GABA_A$ activation in juvenile cortex facilitates the onset of critical period plasticity [29, 31], silencing PV interneurons and reducing $GABA_A$ signaling in adult cortex reinstates environment-driven plasticity [22, 35, 36].

While an early increase in inhibitory signaling officially *opens* a developmental phase of environment-driven cortical refinement, this increase lies downstream from changes in excitatory synaptic connectivity and activity that *prime* circuits for plasticity by stimulating PV interneurons to develop. Specifically, the developmental increase in PV outputs appears to occur downstream from an increase in excitatory inputs onto PV cells [37] that is coupled to a potentiation of high-amplitude, synchronous excitatory activity [32, 38–42]. A potentiation of the strength and synchrony of excitatory cortical activity [42–45] arises from at least two key anatomical sources in juvenile circuits. First, the high interconnectivity of immature excitatory neurons, which emerges from an initial over-proliferation of dendrites, spines, and synapses [46], results in these neurons producing strong intrinsically-generated excitatory activity in the face of initially weak inhibition [43, 45, 47]. Second, there is an environment-driven increase in excitatory glutamatergic activity relayed to the cortex by thalamic axons as they strengthen their cortical connectivity in response to newly salient environmental inputs (e.g., visual input after eye opening) [48, 49]. Increases in the strength of excitatory drive onto PV interneurons from cortical [38, 50] and thalamic [40, 48, 51] inputs can directly promote their development and thus critical period plasticity. Furthermore, synchronized circuit activity initiates activity-dependent pathways that modify neural cell adhesion molecules on PV interneurons [31] and release proteins that promote PV neurons to develop (e.g., BDNF, Otx2) [52, 53], thereby additionally indirectly inducing plasticity [54]. Consequently, patterned increases in local excitatory activity capable of dysregulating the local E/I balance to drive a homeostatic increase in inhibition may serve as a prerequisite for critical period initiation.

Once a critical period is opened, both PV interneurons and pyramidal cells become exquisitely receptive to extrinsic inputs and thus serve as the main substrates for environment-driven refinement. Neuronal refinement is enabled when proteolytic enzymes activated by GABAergic transmission degrade the extracellular matrix and cell adhesion proteins [2, 55], allowing for structural plasticity. For pyramidal neurons, structural plasticity can be achieved through the pruning of exuberant glutamatergic dendritic spines and synapses, which often occurs in a Hebbian fashion and is mediated by complement proteins and proteases [56–59]. Additional forms of pyramidal plasticity include an increase in dendritic spine motility [26, 59] and the unsilencing of previously silent excitatory synapses (i.e., synapses lacking AMPA receptors) [60]. Ultimately, structural plasticity at pyramidal and PV neurons reduces spontaneous excitatory post-synaptic potentials in subpopulations of neurons and enhances high-frequency PV inhibitory firing [2]. These functional changes result in a continued developmental reduction in the E/I ratio [1–3] and help to increase excitatory-inhibitory coupling to re-establish circuit equilibrium and local E/I balance [61]. Furthermore, these functional changes lead to a stereotyped desynchronization and sparsification of intrinsic neuronal activity [43, 47, 62] that is hypothesized to shift the dominant source of circuit activity from intrinsically-generated to evoked, thereby enhancing the evoked-to-intrinsic signal to noise ratio (SNR) of activity in mature circuits [62].

As the critical period nears an end, neuronal adaptation to the environment slows due to the accumulation of molecular limiters of (or "brakes" on) neuronal plasticity that *close* critical periods. Key closers of critical periods of plasticity include SynCAM1, perineuronal nets, and myelin. SynCAM1 is a synaptic adhesion molecule that forms at thalamic-PV synapses and stabilizes thalamocortical connectivity [63, 64]. Perineuronal nets are extracellular matrix components that form around PV interneurons and alter their biochemical and electrical environment in a manner that reduces plasticity [6, 39, 40, 65]. Myelin is a lipid-rich sheath that forms in the cortex around the axons of both PV interneurons [66, 67] and pyramidal neurons [66]. At the closing of critical periods [9, 68], myelin-associated inhibitor proteins (e.g., Nogo, MAG, OMgp) interact with the Nogo receptor on neurons to inhibit continued neurite outgrowth, spine motility, and activity-dependent synaptic plasticity [9, 69–71]. These three plasticity brakes thus help to close the critical period by ensuring that PV interneurons stabilize both their functional outputs and their structural contacts with thalamocortical inputs and pyramidal cells [3, 40, 63, 64, 68]. An additional brake on critical period plasticity is offered by Lynx1 [72], a protein that binds to nicotinic acetylcholine receptors expressed at both thalamocortical inputs onto pyramidal neurons and in parvalbumin interneurons [72–74]. Increased expression of Lynx1 decreases acetylcholine neurotransmission [72] and functionally limits further structural plasticity of pyramidal cells [75], potentially by suppressing excitatory thalamic drive [73, 74] and adjusting the cortical E/I balance [72]. Experimental manipulations that reduce SynCAM1 expression, destabilize thalamocortical connectivity, degrade perineuronal nets, limit myelin formation, or inhibit the expression of Lynx1 all prevent the normative closure of critical periods of plasticity [40, 63, 68, 72, 76].

An adolescent critical period in association cortex

As detailed above, extensive research conducted in primary sensory cortices has uncovered the cascade of neurobiological change that orchestrates a circuit's critical period of environment-driven plasticity. Specifically, critical periods involve the successive development of mechanistic regulators that prime, open, and close windows of plasticity, including the development of thalamocortical inputs, excitatory activity, PV interneuron signaling, pyramidal neuron connectivity, intracortical myelin, and perineuronal nets (Fig. 1Ai). Moreover, refinements in these mechanistic regulators of critical periods give rise to stereotypical functional changes in plastic circuits, resulting in three functional signatures of ongoing plasticity: a decline in the E/I ratio, a potentiation and then reduction of synchronous intrinsic cortical activity, and an enhancement in the evoked-to-intrinsic SNR (Fig. 1Bi). Remarkably, recent studies have shown that mechanistic regulators and functional signatures associated with early critical periods of plasticity in sensory cortices are expressed later in cortical development in the murine medial PFC, suggestive of an *adolescent neurobiological critical period in association cortex*.

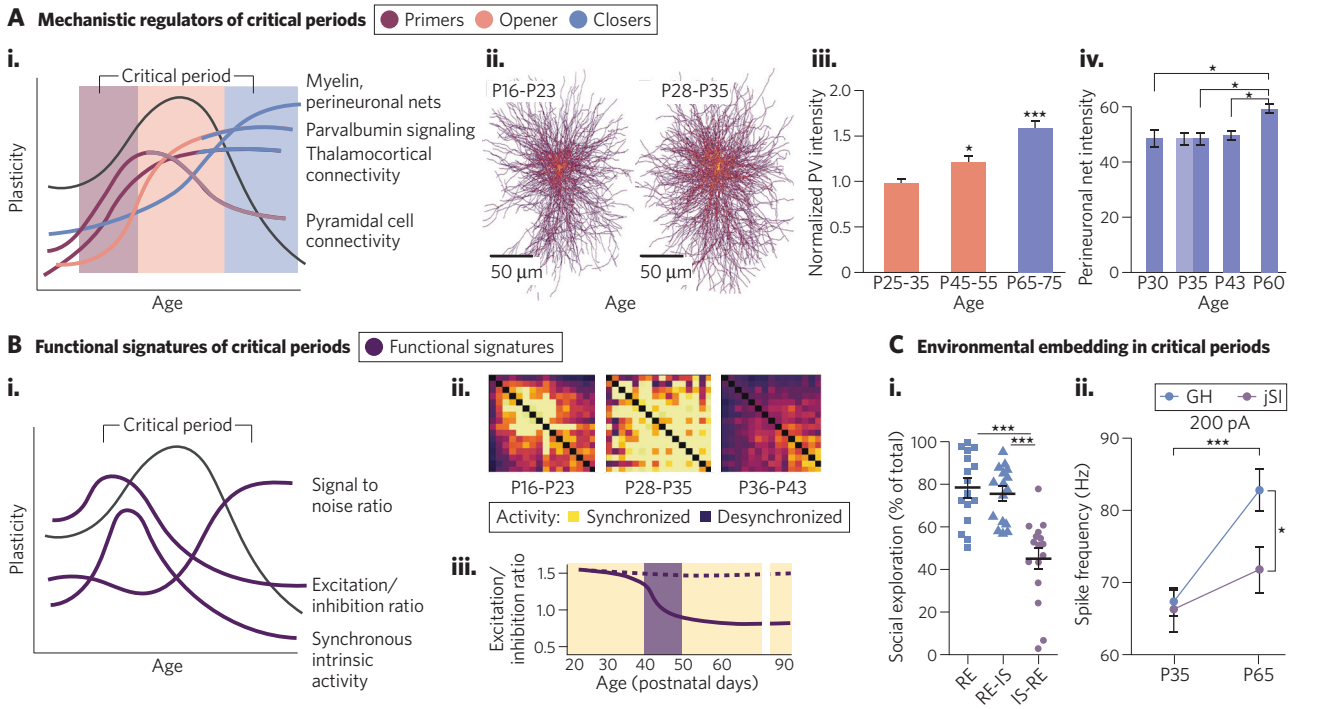

Fig. 1 An adolescent critical period of plasticity in murine association cortex. A Mechanistic regulators of critical period plasticity identified in primary sensory cortex are expressed in the murine prefrontal association cortex during adolescence. **i** Critical periods are regulated by the development of neurobiological mechanisms that prime circuits for, open, and close periods of environment-driven plasticity. The schematic shows expected trajectories of age-related change for key priming (pink), opening (peach), and closing (blue) processes throughout the critical period; panels **ii–iv** utilize the same color legend**. ii**. From pre-adolescence (P16–P23) to early adolescence (P28–P35), the murine medial PFC exhibits an increase in pyramidal cell dendritic arborization and spine density. This increase in morphological complexity and connectivity is reflected in the heatmaps of layer 2/3 pyramidal neuron dendrites shown here. Adapted from Pöpplau et al. [77]. **iii** The mean fluorescence intensity of parvalbumin (PV) increases in the murine medial PFC from early (P25–35) to late (P45–P55) adolescence and continues rising into adulthood (P65–P75). Adapted from Caballero et al. [82]. **iv** Perineuronal net fluorescence intensity increases significantly from middle (P43) to late (P60) adolescence in the murine medial PFC. Adapted from Drzewiecki et al. [91]. **B** Functional signatures of critical period plasticity identified in primary sensory cortex are also expressed in the murine prefrontal association cortex during adolescence. **i** A schematic depicting developmental change in three functional signatures of plasticity throughout the critical period. **ii** Synchronous intrinsic activity increases from pre-adolescence (P16-P23) to early adolescence (P28-P35) in the murine medial PFC and is subsequently suppressed (P36-P43), in line with changes in the patterning of population neural activity seen in periods of plasticity. The plots represent correlation matrices of spike-time tiling coefficients across medial PFC areas quantified at 100 ms latency; higher correlations (yellow) are indicative of stronger temporal synchrony in neuronal activity. Adapted from Pöpplau et al. [77]. **iii** The excitation/inhibition ratio of synaptic activity robustly decreases in the murine medial PFC during adolescence (P40–P50; solid line) until achieving synaptic balance in adulthood, unless PV expression is disrupted (dotted line). Adapted from Caballero et al. [90]. **C** The social environment impacts medial PFC-dependent behaviors and plasticity processes during adolescence. **i.** Mice socially isolated during early adolescence from P21–P35 and then returned to a regular environment (IS-RE) exhibit lower levels of sociability in early adulthood than mice raised in a regular environment (RE) and those exposed to social isolation exclusively after P35 (RE-IS). Sociability was indexed by exploration during a social interaction task. Adapted from Makinodan et al. [98]. **ii** Compared to group-housed (GH) mice, mice socially isolated during early adolescence from P21 to P35 and then returned to a regular environment (jSI) exhibit attenuated developmental increases in PV interneuron spike frequency from mid-adolescence (P35) to adulthood (P60), suggestive of reduced initiation of plasticity. Adapted from Bicks et al. [85].

In murine species, adolescence occurs approximately between weaning (P21) and adulthood (P60) and has been coarsely divided into early adolescent (~P21–P35, prepubertal), mid-adolescent (~P35–P45), and late adolescent (~P45–P60) stages (although stage definitions vary slightly across species and studies). Emerging research has demonstrated that primers, openers, and closers of critical periods are expressed in the (dorsal) prelimbic and (ventral) infralimbic divisions of the medial PFC in this age range, beginning with changes in excitatory activity and thalamocortical connectivity that *prime* the cortex for plasticity. From pre-adolescent (P16–P23) to early adolescent (P28–35) stages, pyramidal neurons in the mouse medial PFC exhibit an increase in dendritic branching complexity and firing rate (Fig. 1Aii) [77, 78]. These anatomical and functional changes enhance local excitatory connectivity and activity and result in an early adolescent potentiation of synchronous, intrinsic circuit activity (from P16 to P35; Fig. 1Bii) [77]. Studies have additionally shown that axonal projections from the thalamus to the medial PFC progressively increase throughout adolescence (P16–P60) [79] and contribute to an increase in cortical excitatory tone [80, 81]. Concurrent with the rise in excitatory cortical and thalamocortical connectivity, there is a marked increase in the frequency of spontaneous excitatory post-synaptic currents recorded in PV interneurons [82, 83]. Collectively, these data are consistent with a cortex that has been primed for plasticity through an enhancement of excitatory drive onto PV cells and a dysregulation of the local E/I balance.

Following an initial shift in the E/I balance towards excitation, PV interneurons—the central *openers* of critical periods—undergo marked developmental change in the medial PFC likely sufficient to initiate a period of heightened local plasticity. More explicitly, from early to late adolescence, there is an increase in PV interneuron density (from P21 to P35) [84], PV protein florescence intensity (from P25–35 to P45–55; Fig. 1Aiii) [82], PV cell spike

Box 2. Studying hallmarks of critical period plasticity with human neuroimaging

A range of methodological approaches has been applied to MRI and EEG data with the aim of studying plasticity-related neurobiology in youth. Here, we describe key approaches used by studies included in the main text, grouped by mechanistic regulators and functional signatures of plasticity. Although there is not a precise mapping between the measures derived from non-invasive imaging and the molecular and cellular processes that characterize critical periods, these approaches begin to bridge the gap between mechanistic studies in animals and macroscale studies in humans.

Mechanistic regulators of plasticity (primers, openers, closers)

Thalamocortical connectivity

a. Diffusion imaging of thalamocortical connection strength: Diffusion MRI can be applied to identify structural connections between the thalamus and cortex and to characterize developmental change in microstructural measures of connectivity strength [105–107]. While delineating connections between the thalamus and localized regions of cortex is difficult, a recent study created and anatomically validated a tractography atlas of thalamic connections with over 200 regions of cortex that can be readily applied to new data [105].

Pyramidal cell connectivity

b. Magnetic resonance spectroscopic imaging of glutamate concentration: Although MRI signals are not specific to any single cell type, MR spectroscopy can quantify regional levels of glutamate, a chemical used by cortical pyramidal neurons as an excitatory neurotransmitter and metabolite [108,113–115]. Notably, spectroscopic imaging at 7T facilitates the simultaneous sampling of neurochemicals in multiple brain regions and the differentiation of glutamate from glutamine [113].

Inhibitory signaling

c. Hurst exponent as a measure of inhibitory strength: The Hurst exponent is a signal dynamics-based measure sensitive to the long-term predictability of a timeseries that can been estimated using a variety of methods (e.g., rescaled range, detrended fluctuation analysis, discrete wavelet transform). Computational modeling and chemogenetic perturbations suggest that relative increases in synaptic inhibition may increase Hurst in fMRI data [251].

d. Pharmacological fMRI of GABA-linked functional signatures: Increases in inhibitory signaling have also been indirectly studied by acquiring fMRI data after individuals receive a pharmacological agent that potentiates GABA signaling. One study employing this approach demonstrated that functional connectivity patterns were reliably distinguishable between sessions where participants received a placebo versus a positive allosteric modulator of the $GABA_A$ receptor [112].

Cortical myelin

e. Contrast-based and quantitative imaging of myelin: Myelin located within the cerebral cortex can be imaged using both contrast-based measures (e.g., T1w/T2w ratio and gray-white contrast) and quantitative measures (e.g., R1, R2*, magnetization transfer, myelin water fraction, quantitative susceptibility mapping), the latter of which have been more extensively validated through histology [252–254]. Quantitative measures have the advantage of higher reliability and generally higher sensitivity to myelin, whereas contrast-based measures have the advantage of being obtainable from conventional structural acquisitions.

Functional signatures of plasticity

Synchronous intrinsic activity

f. Resting-state fluctuation amplitude as a marker of synchronous intrinsic activity: Changes in the prevalence and synchrony of intrinsic neural activity modulate the amplitude of fMRI activity [255,256], which can be quantified from the low-frequency fMRI power spectrum. Increases in the amplitude of intrinsic fluctuations in fMRI activity transiently occur when experimentally inducing cortical plasticity [191,257].

Excitation/inhibition ratio and balance

g. Computational models of the E/I ratio from fMRI: Biophysically-plausible circuit models with interacting excitatory and inhibitory populations can be fit to functional connectivity data to derive computational measures of the regional E/I ratio [117,118]. These computational readouts have been shown to be sensitive to pharmacological perturbations of E/I [117]; however, optimization of model parameters is still an active area of exploration [118].

h. Magnetic resonance spectroscopy of glutamate and GABA relationships: The simultaneous measurement of both glutamate and GABA is achievable with ^{1}HMRS, especially when collected at ultra-high field (e.g., 7T). Relationships between glutamate and GABA can be investigated by examining glutamate/GABA directly (a measure of ratio) [113,258] or by using a regression analysis to determine the population-level balance between glutamate and GABA and individual-level deviations from it (a measure of balance) [108,119].

i. Aperiodic activity as an index of E/I balance: The slope of the aperiodic power spectrum, which measures how quickly aperiodic (i.e., non-oscillatory) power decays with increasing frequency, is impacted by the temporal dynamics of excitatory and inhibitory neural activity [259,260]. Disrupting the normative balance of E/I through diverse pharmacological perturbations tends to steepen the slope [261], whereas a flattening of the slope has been linked to a higher balance between glutamate and GABA [119].

Signal to noise ratio

j. EEG power readouts of the evoked-to-intrinsic SNR: SNR can be studied during task states by isolating evoked and intrinsic aspects of EEG activity. For example, changes in EEG power that are time-locked to the presentation of a stimulus can be compared to background power to calculate SNR [123].

frequency (from P35 to P60) [85], and the strength of PV-mediated inhibitory drive onto pyramidal cells [77, 86, 87]. As inhibitory signaling is enhanced, the previously potentiated firing rate of pyramidal neurons decreases, and glutamatergic dendritic branches and spines undergo a period of pruning (from ~P35 to P55) [77, 78, 88, 89]. Adolescence in murines is thus distinguished by the developmental strengthening of high-frequency PV interneuron activity and a consequent reorganization of pyramidal cell connectivity in the medial PFC. Moreover, developmental change in PV and pyramidal cells results in an eventual reduction in synchronous intrinsic activity (P35 to P55; Fig. 1Bii) [77] and a decrease in the E/I ratio (P35–P50; Fig. 1Biii) [87, 90]: two functional signatures of progressing critical period plasticity. Finally, neurobiological processes that *close* critical periods by limiting plasticity also unfold in the murine medial PFC during adolescence. Significant increases in medial PFC perineuronal net density and staining intensity occur (P30–P60; Fig. 1Aiv) [84, 91–93], coincide with frontal increases in Lynx 1 expression [94], and are followed by the stabilization of axonal inputs from the thalamus to the medial PFC (P60) [79, 80]. PV interneurons are also myelinated throughout adolescence; adolescent myelination is necessary for PV cells to maintain their high-frequency firing in adulthood [95]. Hence, by the end of adolescence, the medial PFC exhibits maturation of its thalamic axonal connectivity, increased expression of myelin, Lynx1, and perineuronal nets, and the structural consolidation of PV cells, consistent with a closure of plasticity.

In addition to data showing that the prefrontal association cortex displays neurobiological hallmarks of critical periods throughout adolescence, studies have found that prefrontal circuit connectivity is established in this developmental stage. For example, chemogenetically inhibiting PV interneurons in the medial PFC during juvenile and adolescent stages (P14–P50), yet not during adulthood, results in persistent impairments in inhibitory drive onto excitatory pyramidal neurons [96]. Moreover, chemogenetically inhibiting thalamic inputs to the medial PFC [80] or PFC top-down cortical projections [97] during adolescence, but not adulthood, causes long-lasting excitatory deficits in the PFC. Adolescence is thus a key window for the functional integration of plasticity-regulating PV cells into surrounding circuitry and for the construction of both local and long-range PFC connectivity.

If adolescence is indeed a critical period in the murine medial PFC, then P21–P60 should be an age window wherein both PFC circuits and PFC-dependent behaviors are uniquely influenced by relevant environmental inputs. In contrast to straightforward approaches that alter the sensory environment to delineate critical periods in primary sensory cortex, the environmental manipulations most pertinent to studying critical periods in association regions are indeterminate. Nevertheless, manipulations of social experiences are predicted to be important and have been implemented to unveil that higher-order behaviors and circuits exhibit unique sensitivity to the social environment during adolescence. Social isolation in early adolescence (P21–P35) results in persistently decreased sociability and cognitive flexibility—long-term behavioral changes that are not seen when social isolation is introduced later (Fig. 1Ci) [85, 98]. Adolescent (P35) mice also exhibit experience-dependent changes in social dominance hierarchies, which are not observed in adulthood [99]. Significantly, it has been shown that adolescent social isolation attenuates normative developmental increases in PV interneuron spike frequency (Fig. 1Cii) [85] and myelination [98], suggestive of environment-driven changes in critical period plasticity that modulate sociocognitive abilities. Furthermore, post-adolescent reconfigurations of social dominance hierarchies are inhibited by Lynx1 expression, relating reductions in social sensitivity to critical period closing [72].

Considered together, neurobiological, environmental, and behavioral findings reveal an adolescent period of environment-driven plasticity in the murine PFC that has many of the distinguishing features of an archetypal critical period. Additional research is needed that tests the temporal specificity of putative critical period-like plasticity to adolescence and that defines its environmental triggers, mechanistic regulators, and long-term behavioral consequences. Still, current research underscores that critical periods need not be exclusive to the sensory cortex. Rather, critical periods appear to be a conserved form of developmental plasticity that is leveraged throughout sensory and association regions [2, 24] to refine perceptual, cognitive, and social functioning during different stages of postnatal development. Animal models thus support the use of a critical period plasticity framework for investigating age-constrained windows of environment-driven plasticity across the human sensorimotor-association cortical hierarchy.

HIERARCHICAL PLASTICITY IN HUMAN DEVELOPMENT

The human brain undergoes a uniquely extended period of postnatal cortical development, exhibiting longer neoteny (the retention of juvenile characteristics) and greater developmental heterochronicity than other primate species [10, 100–103]. Protracted and asynchronous development may have evolved to allow functionally diverse regions to adapt to new environmental demands at different ages, resulting in the emergence of multiple critical periods of environment-driven plasticity. In this section, we examine current evidence for the existence of critical periods in humans by drawing on principles of these plastic periods

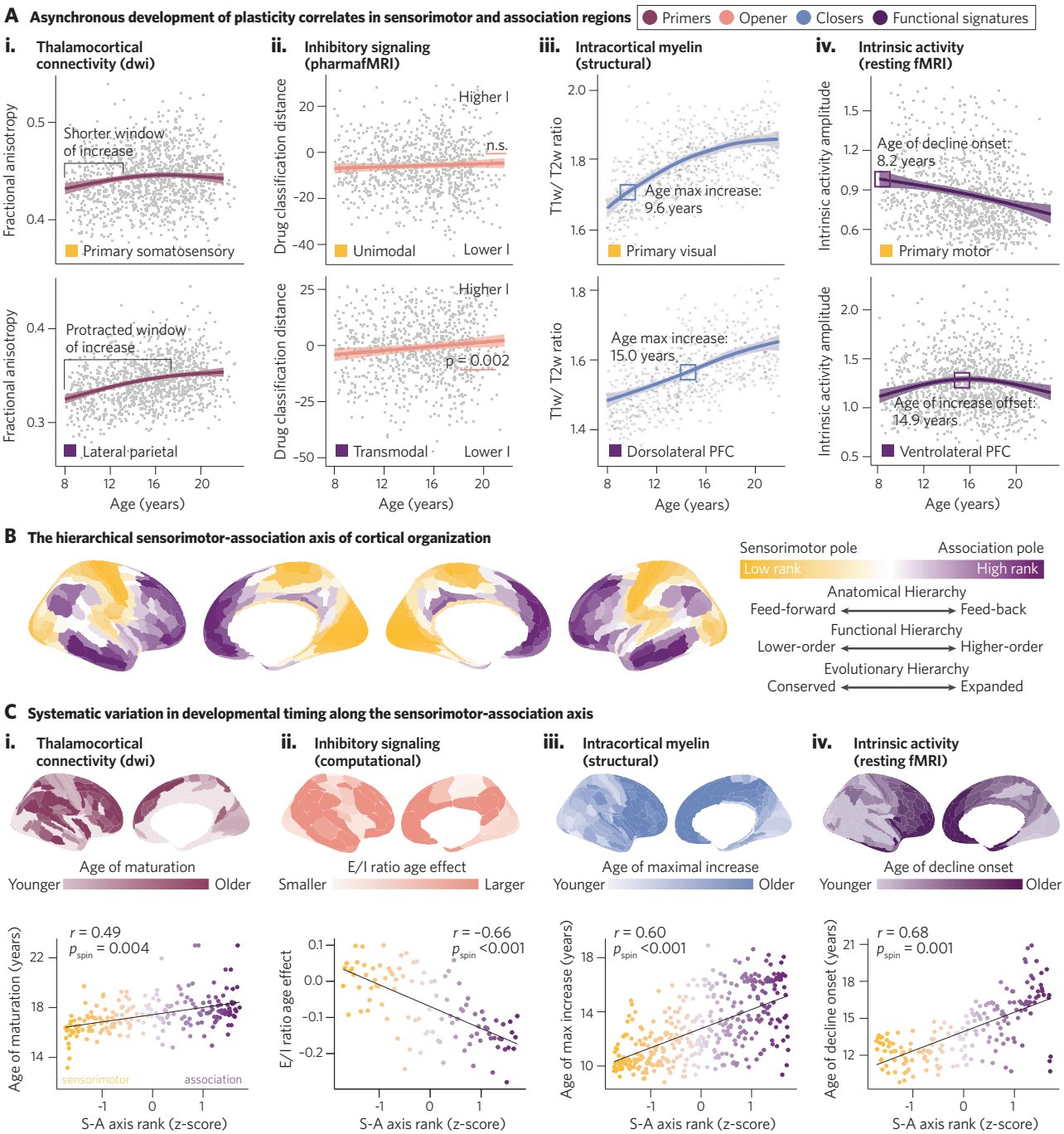

Fig. 2 Human neuroimaging uncovers a hierarchical axis of child and adolescent cortical plasticity. A Macroscale neuroimaging correlates of critical period plasticity exhibit temporally asynchronous development in sensorimotor cortices (top row) and association cortices (bottom row) during childhood and adolescence. Region-specific developmental trajectories are shown for exemplar sensorimotor and association regions for a primer (**i**), opener (**ii**), closer (**iii**), and functional signature (**iv**) of critical period plasticity. As compared to sensorimotor regions, association regions exhibit (**i**) larger and more protracted increases in thalamocortical structural connectivity (data from Sydnor et al. [105]), (**ii**) a greater enhancement in a pharmacological fMRI-based readout of inhibitory signaling (adapted from Larsen et al. [112]), (**iii**) a later age of maximal increase in the myelin-sensitive T1w/T2w ratio (adapted from Baum et al. [124]), and (**iv**) a unique, early adolescent increase in the amplitude of intrinsic fluctuations in resting-state fMRI activity (data from Sydnor et al. [110]). **B** The sensorimotor-association (S-A) axis is a dominant axis of organization that ranks all cortical regions along a continuous spatial dimension in the brain. The S-A axis aligns with the brain's anatomical [132], functional [131], and evolutionary [129,135] hierarchies and thus transitions from primary and unimodal regions (sensorimotor pole; yellow; low ranks) to modality-specific, multimodal, and finally to transmodal association regions (association pole; purple; high ranks). Moving spatially from the sensorimotor to the association pole of the axis, cortical regions transition from having greater feed-forward to feed-back connectivity, from supporting lower-order to higher-order psychological processes, and from being evolutionarily conserved to evolutionarily expanded. The S-A axis was derived in Sydnor et al. [10] by combining 10 brain maps of macrostructural, microstructural, functional, metabolic, transcriptomic and evolutionary cortical features that exhibit hierarchical spatial variation between sensorimotor and association regions. Cortical regions were first rank ordered from low (sensorimotor) to high (association) within each brain map in a data-driven manner. Rankings were then averaged across the 10 maps to derive an archetypal S-A axis. **C** Region-wise variability in the development of neuroimaging correlates of critical period plasticity systematically aligns with the S-A axis during youth. Brain maps display development-related summary statistics across all cortical regions for the plasticity correlates shown in (**A**). Plots portray correlations between developmental summary statistics and the S-A axis; the correlation value (*r*) and significance of the correlation derived from autocorrelation-preserving spin tests (p_{spin}) are shown with each plot. Regional ranks in the archetypal S-A axis (displayed in **B**) were z-scored for plotting. Negative z-scores represent the sensorimotor end of the axis and positive z-scores designate the association end. **i** The age at which a region's connection with the thalamus matures gets gradually older along the S-A axis, indicative of an older age at which the thalamus transitions from promoting to limiting plasticity. Adapted from Sydnor et al. and based on diffusion MRI indices of thalamocortical connectivity [105]). **ii** Biophysically-constrained computational models of cortical circuits applied to functional connectivity data reveal a greater decline in the excitation/inhibition (E/I) ratio at the association pole of the S-A axis during adolescence. Age effects represent pooled partial correlations between the computational E/I ratio and age derived from a meta-analysis of age effects calculated from models fit with different parameters. Data are from Saberi et al. [118]. **iii** The age at which cortical regions show a maximal increase in the T1w/T2w ratio gets older along the S-A axis, revealing delayed structural consolidation in higher-order regions. Adapted from Baum et al. [124]. **iv** Developmental reductions in the amplitude of intrinsic activity measured with resting-state fMRI are initiated at progressively older ages along the S-A axis, suggestive of cascading refinement in circuit plasticity. Data are from Sydnor et al. [110].

uncovered in animal research. We first review studies that have leveraged non-invasive neuroimaging to indirectly probe plasticity in the human brain. We next synthesize research examining age-varying impacts of the socioeconomic environment on sensorimotor and association cortical regions. Finally, we outline implications of hierarchical critical periods for refining psychological processing throughout youth.

Hierarchical development of neuroimaging correlates of plasticity

Studying critical periods during childhood and adolescence requires mapping out when individual cortical regions exhibit enhanced and diminished neurodevelopmental plasticity. However, investigating developmental plasticity in humans in vivo is challenging, as there is no direct measure of circuit plasticity that can be examined in the living human brain. A promising approach to address this challenge is to ground human work in decades of animal research by translating *neurobiological and functional hallmarks of critical period plasticity to non-invasive neuroimaging* applied to developing populations [1, 4, 5, 7, 104]. Studies employing this approach have shown that in vivo correlates of critical period plasticity are evident throughout the human brain, corroborating non-human data that developmental plasticity mechanisms are evolutionarily conserved across mammalian species [24]. Indeed, during childhood and adolescence, the human brain shows evidence for widespread developmental change in both mechanistic regulators and functional signatures of plasticity, including change in thalamocortical structural connectivity, excitatory connectivity, inhibitory signaling, intracortical myelination, the E/I ratio, intrinsic activity, and the evoked-to-intrinsic SNR (Box 2). When developmental change in these measures occurs, however, varies substantially across the cortex, and occurs earlier in sensorimotor than in association regions (Fig. 2A). Neuroimaging data thus suggest that childhood and adolescence may be characterized by heterochronous critical periods in lower-order and higher-order brain regions.

Throughout development, the human cortex exhibits changes in thalamocortical connectivity and markers of excitatory activity that are consistent with the *priming* of critical period plasticity. Beginning in infancy, thalamocortical structural connectivity steadily and continuously increases (Box 2a) [105–107]. From late childhood to mid-adolescence (~8–16 years), increases in thalamic connectivity are more pronounced in frontal and parietal association regions than in visual, somatosensory, and motor regions (Fig. 2Ai) [105, 107], suggesting that association cortices in particular are being primed for plasticity. Neurometabolite data obtained with proton magnetic resonance spectroscopy (^{1}HMRS) furthermore indicate that in late childhood and early adolescence (from ages 10–15 years), glutamate and GABA in the prefrontal association cortex are relatively imbalanced due to a disproportionately high level of glutamate (Boxs 2b, h) [108]; higher levels of ^{1}HMRS-measured glutamate may correspond to a higher level of excitatory neuronal activity [109]. Concordant with when association cortex exhibits high glutamate levels and increasing thalamic connectivity, functional imaging studies have shown that it displays a unique enhancement in synchronous intrinsic cortical activity (Box 2f). In fact, while intrinsic activity declines in amplitude in sensorimotor cortex throughout youth, it increases in association cortex until adolescence (until 13–18 years depending on the region) (Fig. 2Aiv) [110], which may be reflective of a potentiation of synchronous excitatory activity. The developing human cortex thus exhibits features that have been linked to the promotion of critical period plasticity in animal studies, with the association cortex exhibiting enhanced expression of plasticity primers in early adolescence.

Recent efforts have leveraged unconventional approaches to functional MRI (fMRI) acquisition and analysis to assess whether developmental increases in thalamocortical connectivity and intrinsic activity are followed by an increase in the strength of inhibitory signaling, the key *opener* of critical period plasticity. Such efforts suggest that the cortex may undergo multiple waves of inhibitory system maturation, including an early childhood wave that is widespread yet enhanced in sensorimotor cortex [111] and an adolescent wave that is more specific to higher-order association cortex [112]. A developmental increase in the fMRI-

Box 3. Intrinsic and extrinsic drivers of association cortex plasticity in adolescence

Neuroimaging data suggest that primers (thalamocortical connectivity, excitatory activity), a biological opener (inhibitory signaling), and an early functional signature (synchronous intrinsic activity) of critical period plasticity may be enhanced in association cortex during early adolescence. At present, it is not definitive whether these data are indicative of prolonged plasticity in the association cortex that is *maintained throughout* childhood and adolescence or an *adolescent-specific potentiation* of association cortex plasticity. While additional research is needed to distinguish between temporally protracted and temporally shifted periods of peak environment-driven association cortex plasticity, here we speculate on intrinsic and extrinsic changes that occur during adolescence that could lead to the emergence of the latter.

Critical periods of environment-driven plasticity in primary sensory cortices occur after newly available environmental information (e.g., sound, light) is relayed to the cortex by the thalamus, triggering a pronounced shift in the strength and patterning of cortical activity that stimulates the development of PV cells. In the human association cortex, a distinctive shift in the nature of local activity capable of eliciting the molecular cascade that defines critical periods may occur near the start of adolescence [110] due to the maturation of hierarchical corticocortical and thalamocortical connectivity. More explicitly, as sensorimotor regions mature and enhance the evoked-to-intrinsic SNR of their activity, they may send increasingly reliable and potent feed-forward information to association regions located higher in the cortical hierarchy. The increase in high-fidelity inputs to association regions may elicit a marked change in the strength of incoming activity, thereby helping to prime these circuits for peak plasticity [1,7]. The maturation of lower-order regions may also produce a shift in activity in association cortices via the thalamus, given that the thalamus is known to propagate activity via cortico-thalamo-cortical loops along hierarchically-organized processing streams [105,262,263]. The thalamus's dense bidirectional connectivity with all of the cortex and its central role in processing environmental inputs position it well to link evolving environmental demands to refinements in environment-driven cortical plasticity. Changes in the nature of youths' environmental exposures may also facilitate adolescent enhancements in association cortex plasticity. The onset of adolescence is characterized by a rise in independence coupled with a normative peak in environmental exploration and sensation seeking [176,177,193,264]. These behavioral traits expose adolescents to newly diverse and complex cognitive and social environments that may trigger environment-dependent increases in higher-order cortex plasticity [7], akin to how physical environmental information initiates sensory cortex plasticity. A link between social and cognitive environmental diversity and complexity and an increase in cortical plasticity has been extensively documented in murine studies. In rodents, environmental enrichment (the introduction of physical, cognitive, and social environmental stimulation) consistently leads to an enhancement of circuit plasticity through changes in critical period mechanisms, including changes in thalamocortical connectivity, PV interneuron activity, myelination, and perineuronal nets [36,265–267]. Moreover, the introduction of environmental enrichment has been shown to trigger the opening (and lengthen the time course) of critical periods in sensory cortex [22,240,241,268,269]. These key findings in animal models reveal a direct link between qualitative changes in environmental inputs and the onset of critical periods of environment-driven plasticity.

A biological incentive to seek out plasticity-inducing environmental experiences may arise from changes in the dopamine system that distinguish adolescence from other developmental periods [7,23]. For example, dopamine availability within the striatum continuously increases from late childhood to adulthood, whereas the density of striatal D2/D3 receptors peaks in adolescence [108,270–274]. This is hypothesized to engender an adolescent boost in dopamine sensitivity (e.g., through high receptor occupancy) that increases exploratory behaviors [176] and heightens motivational saliency. Dopaminergic innervation of the PFC also increases in adolescence [275] and may drive refinements in association cortex E/I balance [108] that modulate flexible engagement with diverse environments [176]. Finally, the onset of puberty may furthermore contribute to environmental exploration as sex hormones bind to receptors on mesocorticolimbic dopamine pathways and enhance adolescents' motivation for novel experiences [276–279]. Collectively, neural, experiential, and pubertal changes could facilitate the expression of plasticity-promoting processes throughout the association cortex during adolescence, opening unique periods of environment-driven plasticity.

based Hurst exponent (Box 2c), which is theorized to reflect an increase in inhibitory signaling, has been observed throughout the brain from ages 4–8 years old [111]. Early childhood increases in the Hurst exponent occur concomitantly with increases in PV mRNA expression, with slightly larger increases in both Hurst and PV mRNA localizing to sensorimotor cortex [111]. From ages 13–17 years, however, significant developmental increases in inhibitory signaling strength may be relatively restricted to the association cortex, suggestive of the late opening of a window of plasticity [112]. Specifically, a pharmacological fMRI study found that functional connectivity patterns associated with greater $GABA_A$ receptor inhibitory signaling (Box 2d) become increasingly dominant in association cortex—but not sensorimotor cortex—in this adolescent age range (Fig. 2Aii) [112]. As inhibitory tone putatively increases in the adolescent association cortex, there is a simultaneous reduction in PFC glutamate levels (Box 2b) [108, 113–116]. This developmental decline in glutamate availability is hypothesized to reflect the plasticity-linked pruning of excitatory pyramidal neuron dendritic and synaptic connectivity.

In the murine brain, critical period refinements in PV-mediated inhibition and pyramidal neuron connectivity result in an early reduction in the E/I ratio, followed by a suppression of synchronous intrinsic activity and enhancement of the evoked-to-intrinsic SNR. Neuroimaging studies have found that all three of these functional signatures manifest in the developing human brain. To probe developmental refinements in the cortical E/I ratio, advances in biophysically-constrained computational models of cortical circuits have been applied to functional connectivity data (Box 2g). These applications have provided evidence for child and adolescent reductions in the E/I ratio that differ in strength between sensorimotor and association cortices (although there are discrepancies in the patterning of reductions across studies [117, 118]). In prefrontal association cortex, developmental reductions in the E/I ratio temporally parallel increases in E/I balance (i.e., the coupling or correlation between E and I); E/I balance has been measured in vivo as the balance between glutamate and GABA neurotransmitters (Box 2h) [113] and neurotransmitter-linked changes in aperiodic neural activity (Box 2i) [119]. The youth brain also experiences developmental reductions in the amplitude of synchronous intrinsic activity (Box 2f). Reductions are larger and onset earlier (in childhood) in sensorimotor regions and are smaller and delayed (to mid-adolescence) in association regions [110]. Developmental declines in intrinsic activity co-occur with a spatial decorrelation in this activity, as measured by fMRI functional coupling on the millimeter scale [120–122]. Developmental declines in intrinsic activity are additionally followed by an increase in the evoked-to-intrinsic SNR of cortical activity, as revealed by EEG (Box 2j) [123].

As functional refinements decelerate, the human cortex displays two hallmarks of the *closing* of critical period plasticity: the stabilization of thalamocortical connectivity and the formation of intracortical myelin. The strength of thalamocortical structural connectivity stabilizes at younger ages in sensorimotor regions and at older ages in association regions [105], consistent with temporally ordered reductions in plasticity. Studies employing contrast-based and quantitative imaging measures of myelin (Box 2e) have additionally shown that association cortices myelinate less than sensorimotor cortices during youth (particularly within superficial layers), suggesting that higher-order cortex retains a greater capacity for plasticity [120, 124–127]. The maturational timeline of cortical myelination is also shifted in higher-order regions in a manner that aligns with a temporally delayed closure of plasticity: myelin shows both a maximal rate of growth and a maturational plateau at older ages in association as compared to sensorimotor regions (Fig. 2Aiii) [124–126, 128]. A delay in peak myelin formation from approximately 8–12 years in sensorimotor regions to 14–18 years in association regions has been directly linked to a delay in when association regions exhibit an initial reduction in intrinsic activity and the maturation of thalamic connectivity [105, 110]—revealing coupled development of multiple in vivo readouts of critical period-like plasticity.

In sum, multi-modal neuroimaging studies have revealed that the human brain exhibits developmental change in indirect measures of primers, openers, closers, and functional signatures of critical periods, paralleling at the macroscale what has been documented in mechanistic research in animal models. These studies provide coherent brain-based data that are suggestive of critical periods that happen earlier in sensorimotor than in

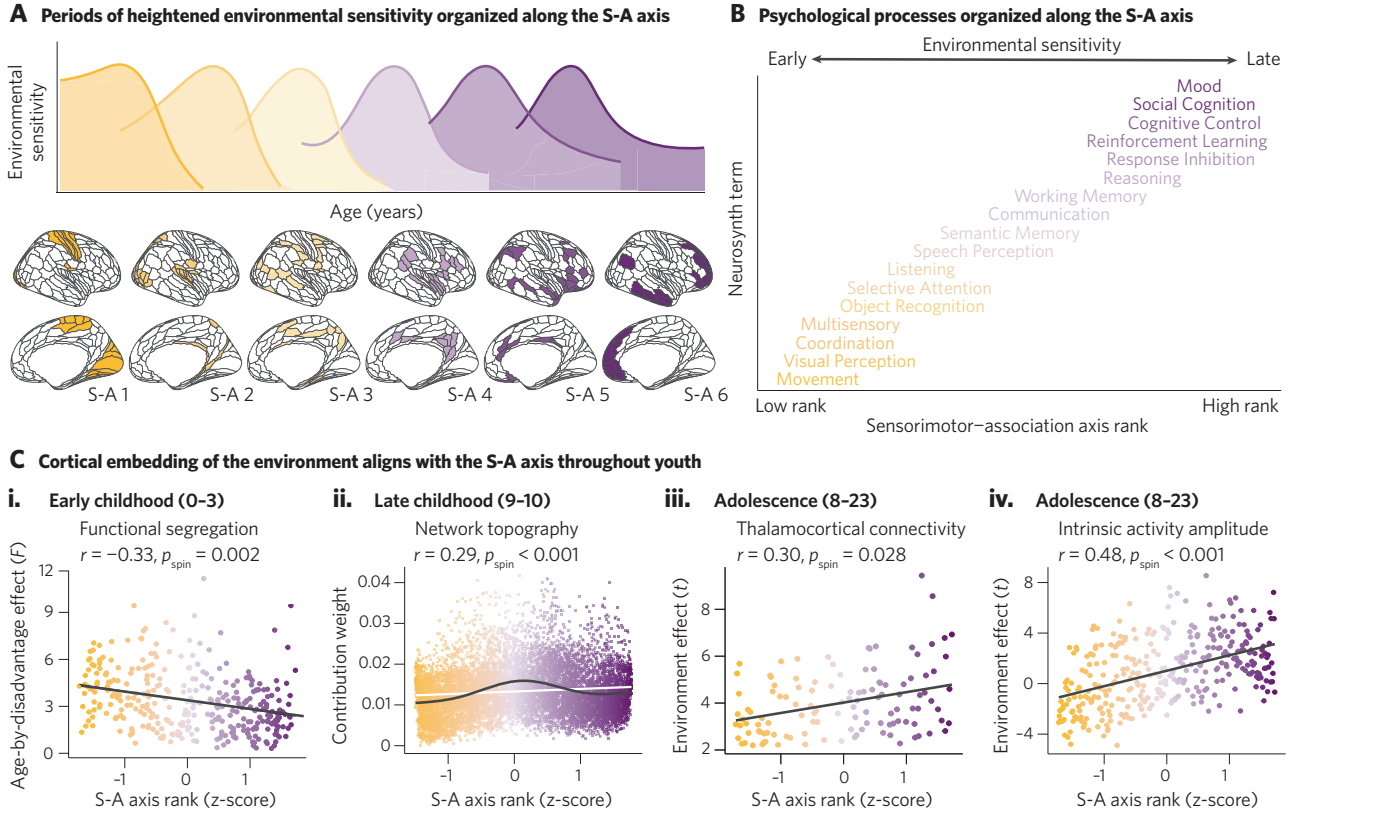

Fig. 3 Hierarchically-organized periods of heightened environmental sensitivity. A The hierarchical progression of critical periods is predicted to engender temporally shifted windows of heightened environmental sensitivity along the sensorimotor-association (S-A) axis. The diagram summarizes a hypothesized model wherein different sections of the S-A axis (here, represented in 6 equally sized bins) exhibit enhanced environmental sensitivity at different ages. In this model, the sensorimotor pole of the axis shows peak sensitivity to the environment at the youngest ages, while the association pole exhibits unique environmental receptivity latest in development. **B** The S-A axis captures a hierarchical spectrum of psychological processing. Transitioning spatially from the axis's sensorimotor to its association pole, cortical regions shift from supporting action, perception, and multisensory integration to attention, language, and executive functions, and finally to reinforcement learning, social cognition, and mood. The ordering of psychological processes along the S-A axis was empirically determined using Neurosynth-based functional decoding. The Neurosynth database was used to perform task-based functional MRI meta-analyses for each of the displayed psychological terms. Cortical regions with the highest meta-analytic activation scores were then identified for each term and their average S-A axis rank was calculated. Terms were plotted by average S-A rank for visualization. **C** The socioeconomic environment has a maximal effect on different portions of the S-A axis throughout development, lending empirical support to the proposed model of hierarchically timed environmental sensitivity shown in (**A**). Each plot depicts how the strength of brain-environment statistical effects (*y*-axis) varies along the S-A axis (*x*-axis) in a given developmental stage. From left to right, plots display the cortical patterning of environmental influences in early childhood, late childhood, and adolescence. Each plot contains the *r* value and p_{spin} significance value from a correlation relating statistical environment effects and S-A axis ranks. **i** In the first 3 years of life, associations between socioeconomic disadvantage and functional segregation are stronger nearer the sensorimotor pole of the S-A axis. The age-by-disadvantage effect value is an *F* statistic quantifying how much developmental trajectories of functional segregation varied according to the level of environmental disadvantage. Adapted from Tooley et al. [159]. **ii**. During late childhood, links between functional network topography and family income-to-needs ratio (INR) are strongest in the middle of the S-A axis. To study relationships between functional topography and family INR, Zhao et al. [157] predicted participants' INR from vertex-level measures of network topography and derived a prediction contribution weight per vertex; higher contribution weights are indicative of a stronger relationship between network features and family socioeconomic status. Adapted from Zhao et al. [157]. **iii**. From ages 8–23 years, associations between the neighborhood socioeconomic environment and the strength of thalamocortical structural connectivity are larger at the association pole of the S-A axis. Environment effects represent region-specific *t* values quantifying positive associations between more advantaged neighborhood environments and stronger thalamic connectivity, controlling for age. Reproduced from Sydnor et al. [105]. **iv**. From 8 to 23 years, associations between the neighborhood socioeconomic environment and the amplitude of intrinsic fMRI activity vary across the S-A axis and are largest at its association pole. Environment effects represent region-specific *t* values quantifying associations between the neighborhood environment and activity amplitude, controlling for age. Adapted from Sydnor et al. [110].

association cortex. Importantly, however, a categorical division between sensorimotor and association cortex does not capture the full spectrum of cortical variability in the development of imaging correlates of plasticity. Instead, this broad division in developmental timing has been shown to be embedded within a unifying and hierarchical *sensorimotor-association (S-A) axis of cortical developmental plasticity*.

The S-A axis is a large-scale spatial axis in the brain that embodies anatomical, functional, and evolutionary indices of hierarchical cortical organization (Fig. 2B) [10, 129–135]. Rather than assigning brain regions categorically into sensorimotor or association cortex, the S-A axis ranks all brain regions along a continuum according to their unique profile of features [10]. Accumulating data have empirically demonstrated that the S-A axis parsimoniously characterizes variability in age-dependent refinements in multiple imaging correlates of critical period biology—extending long-established knowledge on heterochronous development [136–138] to this dominant axis of brain

organization. During childhood and adolescence, the development of thalamocortical structural connectivity, the E/I ratio, intracortical myelin, and intrinsic cortical activity all unfold in a temporally ordered manner along the cortex's S-A axis [105, 110, 112, 117, 118, 124–126]. Transitioning spatially across the cortex from the sensorimotor to the associative pole of the axis, cortical regions exhibit an increase in the developmental age at which thalamocortical connections stabilize, the E/I ratio decreases, the myelin growth rate peaks, and the amplitude of intrinsic activity decreases (Fig. 2C). Neuroimaging data thus provide collective support for the hypothesis that the S-A axis captures a chronological progression of neurobiological critical periods that culminates in transmodal association cortex in adolescence (Box 3). Nevertheless, the defining feature of a critical period is heightened biobehavioral receptivity to circuit-relevant environmental inputs. Validation of hierarchical critical periods organized along the S-A axis thus requires evidence that windows of unique environmental sensitivity are shifted in time for increasingly higher-order cortical regions and the psychological processes that they subserve.

Hierarchical windows of environmental sensitivity

If the human cortex exhibits sequential critical periods of environment-driven cortical plasticity that unfold along the S-A axis, there should be evidence not only for hierarchical refinements in brain plasticity, but also evidence that the effects of the environment on the brain proceed in a hierarchical fashion over time. More explicitly, hierarchical critical periods predict that the human brain exhibits not only increasingly prolonged windows of *sustained* environmental sensitivity for more associative regions, but also *temporally shifted windows of heightened environmental sensitivity* that progress along the S-A axis (as depicted in a model in Fig. 3A). Temporally shifted windows of environmental receptivity should result in salient environmental inputs having a larger effect on sensorimotor cortices earlier in life and on association cortices later in development. Studies have empirically tested this prediction by investigating when different portions of the S-A axis exhibit the strongest relationships with youths' socioeconomic environmental circumstances. Given that variation in the socioeconomic environment is coupled to variation in physical, sensory, linguistic, cognitive, educational, and social environmental features [139–143], socioeconomic factors are highly relevant to understanding environment-driven cortical plasticity across the entirety of the functionally diverse S-A axis.

There is extensive evidence that from infancy to late adolescence, inter-individual differences in cortical properties are associated with variation in household and neighborhood socioeconomic circumstances [144–155]. Recent work examining hierarchical cortical variability in the strength of these associations has demonstrated that socioeconomic relationships are systematically patterned along the S-A axis throughout the course of development [105, 110, 156–158]. Consistent with the notion of hierarchical critical periods, studies have found that relationships between cortical properties and the socioeconomic environment are strongest at the sensorimotor pole of the axis during early childhood, in the middle of the axis during late childhood, and at the association pole of the axis during adolescence (Fig. 3C). More specifically, in the first 3 years of life, relationships between greater socioeconomic disadvantage and greater cortical functional segregation are significantly stronger in regions located closer to the S-A axis's sensorimotor pole, likely reflecting an early period of high plasticity in sensorimotor and language regions (Fig. 3Ci) [159]. Subsequently, in youth 9–10 years of age, links between socioeconomic circumstances and functional network topography (i.e., the cortical layout of network areas) are significantly stronger in association cortices, with maximal statistical effects now seen in the middle of the S-A axis (Fig. 3Cii) [157]. By adolescence (8–23 years), greater neighborhood socioeconomic disadvantage is associated with weaker thalamocortical connectivity and a lower amplitude of intrinsic fMRI activity, particularly for higher-order association regions [105, 110]. Consequently, in adolescence, socioeconomic effects diverge in strength in an ordered manner along the S-A axis and are strongest at its associative pole [105, 110]—suggestive of a late window of differential environment-driven plasticity in higher-order cortex (Fig. 3Ciii, Civ). Considered together with findings from developmental neuroimaging studies of plasticity, the hierarchical cortical embedding of socioeconomic-environmental influences provides additional support for the existence of hierarchical critical periods in human neurodevelopment.

Hierarchical critical periods and psychological processing

Neural and environmental manifestations of hierarchical critical periods should emerge concurrently with behavioral evidence that the environment has a more marked effect on different psychological processes at different stages of development. Namely, environmental inputs should have a particularly lasting impact on psychological processes supported by higher ranking regions of the S-A axis at sequentially later ages. Identifying the functions subserved by cortical regions that occupy different portions of the S-A axis can thus provide data-driven predictions regarding windows of enhanced environment-driven behavioral refinement. Functional decoding of the S-A axis reveals that it ranges from cortical regions that support sensation, action, and multisensory integration at its sensorimotor pole, to those supporting language, attention, and executive functions in the middle, to regions supporting reward, social, and emotional processing at its most associative pole (Fig. 3B). Below we consider whether sensory, language, and higher-order processes may be differentially malleable by the environment across developmental stages, as predicted by the hierarchical unfolding of critical periods along the S-A axis.

Behavioral data have provided evidence for the existence of time-limited periods of peak environmental impact on lower-order psychological processes that are consistent with hierarchical critical period predictions. The strongest evidence arises from studies showing that environment-driven sculpting of sensory and language abilities occurs in consecutive (though partially overlapping) periods of early development. Research on auditory and visual processing has resolved that sensory environmental inputs must be experienced during infancy or early childhood (prior to approximately 7 years of age) for relatively typical auditory frequency discrimination and visual acuity to be established. As a result, children born deaf who receive cochlear implants prior to age 7 years show typical or marginally impacted auditory skills, whereas youth implanted after age 7 show a large decrement in auditory functioning [160–163]. Similarly, treatment for reduced vision due to ocular pathology is significantly more effective at improving visual acuity if initiated prior to age 7 years; after this age treatment efficiency significantly declines [164–168]. In the domain of language processing, studies have determined that exposure to a first language during early and middle childhood is required for typical language syntactic understanding to be achieved. If first language exposure does not occur between the ages of 3–10, individuals appear unable to obtain syntactical proficiency in any language in adulthood [169–171]. These observations reveal that there are temporally constrained windows wherein the establishment of long-term behavioral functioning is profoundly impacted by the environment—and that these windows are shifted in time for psychological processes linked to adjacent portions of the S-A axis. Consequently, these observations provide behavioral indications of human critical periods and imply that similar periods may exist later in development for higher-order psychological functions.

In contrast to sensory and language processing, the study of critical periods for complex cognition is nascent: there is a relative dearth of studies that have comprehensively compared how

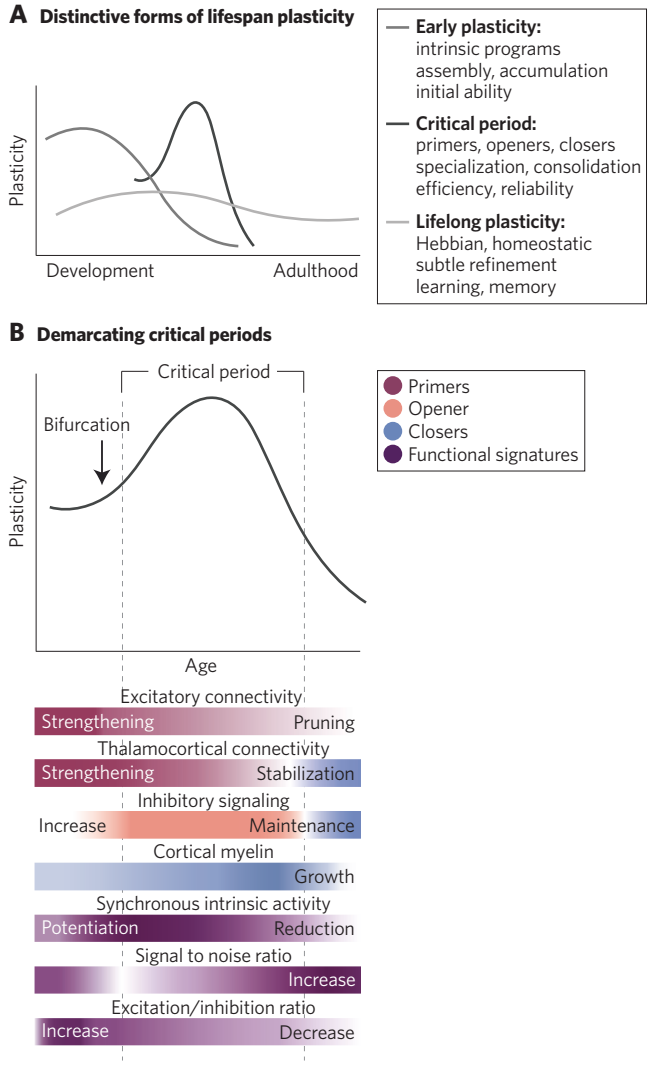

Fig. 4 Differentiating lifespan and critical period plasticity. **A** Distinct forms of cortical plasticity are hypothesized to operate over the human lifespan, including early developmental plasticity, critical period plasticity, and lifelong plasticity. Early developmental plasticity may be relatively more driven by intrinsic genetic and molecular programs that assemble circuits through accumulation processes to allow for the initial emergence of behavioral abilities. Critical periods of environment-driven plasticity are regulated by distinctive priming, opening, and closing mechanisms that specialize and consolidate circuits in a manner that may engender improvements in behavioral efficiency and reliability. Lifelong plasticity, which extends throughout adulthood, is dominated by Hebbian and homeostatic mechanisms that produce subtle refinements in circuits to facilitate continued learning and memory. **B** Future work can temporally delineate the onset and offset of a putative critical period in the human brain by integrating across developmental charts of imaging correlates of plasticity.

environmental exposures affect higher-order psychological processes across diverse developmental stages. Preliminary data with cross-age comparisons suggest that although higher-order processes significantly develop from infancy to adulthood, there could theoretically be windows in late childhood or adolescence when they are differentially impacted by certain environmental exposures. For example, cognitive training may improve components of executive functioning more in early than late adolescence [172–175], environmental novelty and unpredictability may impact reward learning more in middle adolescence than at younger and older developmental stages [176–181], and opportunities to practice empathy may support social cognition more in late adolescence than earlier in youth [182]. These very early data —while hypothesis-generating rather than conclusive—cohere with the notion of temporally delayed developmental windows wherein higher-order processes are relatively more malleable by the environment, as predicted by functional decoding of the S-A axis.

One outstanding question regarding the nature of hierarchical critical periods is how higher-order psychological processes can exhibit both significant developmental improvements throughout infancy, childhood, and adolescence *and* temporally delayed critical periods wherein they are differentially impacted by the environment. Here, we propose three empirically testable properties of critical periods that reconcile the existence of prolonged trajectories of behavioral change and time-limited critical periods. These properties converge on an understanding of critical periods as a near-final maturational form of circuit plasticity that can be distinguished neurally, behaviorally, and environmentally from both preceding forms of early developmental plasticity and subsequent adulthood plasticity (Fig. 4A). First, earlier forms of developmental cortical plasticity should be mechanistically distinct from critical period plasticity. In particular, early cortical plasticity may be relatively more driven by intrinsic genetic and molecular programs that function to build initial circuits through assembly and accumulation processes. Critical period plasticity, in contrast, is driven by extrinsic inputs and priming, opening, and closing mechanisms that serve to refine constructed circuits through processes of specialization and consolidation. Second, early cortical and critical period plasticity should support independent facets of psychological functioning. Early cortical plasticity that constructs initial circuits may be required for the initial emergence of behavioral abilities and improvements in the capacity to accurately engage them. Critical period plasticity, which specializes and consolidates circuits, may instead engender improvements in behavioral efficiency and reliability. Prolonged windows of developmental change for higher-order psychological processes may therefore be characterized not by a unitary process, but by earlier increases in accuracy and subsequent reductions in latency and variability that are facilitated by distinct types of plasticity.

Third, the embedding of environmental experience should differ during early developmental and critical period plasticity. There is an incredibly robust literature showing that environmental exposures consistently impact brain development from birth into adulthood [144–155]. Importantly, this literature is not incompatible with hierarchically-organized, time-limited periods when a potentiation of environment-driven plasticity occurs on top of an age-independent baseline of environmental receptivity. We posit that certain environmental exposures may have a differentially significant or lasting impact on higher-order psychological processing during a critical period as they will drive the specialization of a circuit immediately prior to its consolidation. Hence, while the cortex adapts to the environment over all of developmental time, environment-driven plasticity during the critical period will determine the final maturation form of a circuit; this final form may be more predictive of certain aspects of adult functioning. Studies that test these three properties will help to elucidate the behavioral consequences of critical period-like neurobiological plasticity in humans.

As reviewed in this section, neural, environmental, and behavioral data offer coherent support for hierarchical critical periods in human neurodevelopment that mechanistically mirror those first defined in other species. Yet, while extant evidence for critical periods that occur in both sensorimotor and association cortices is compelling, it is ultimately not conclusive. Behavioral and environmental studies provide robust demonstrations of critical period-like phenomenon for sensory and language

processing early in life, though it is not clear whether these periods arise due to developmental refinements in critical period neurobiology. In fact, many studies characterizing developmental change in imaging markers of plasticity have been conducted either with infants or with youth 8–10 years of age and older; therefore, periods of neurobiological plasticity are not well-characterized in earlier childhood. In contrast, neuroimaging studies reveal that macroscale correlates of critical period biology are expressed in the association cortex throughout youth, providing the foundation for adolescent critical period hypotheses [1, 7, 12]. While socioeconomic data additionally point to heightened environmental sensitivity in association circuits in late childhood and adolescence, investigations into age-varying impacts of the environment on higher-order psychological processes are sparse. Definitive confirmation of hierarchical critical periods in humans thus requires further research that examines when temporally-discrete periods of neurobiological plasticity and environmental sensitivity occur and how they impact long-term behavioral outcomes.

TESTING FOR CRITICAL PERIODS IN HUMANS

Future research directions

Comprehensive evidence for the presence of a critical period of environment-driven plasticity in the human brain must include two key components. First, there should be evidence for a specific developmental window during which the biological state of the cortex is prepared to facilitate and consolidate environment-driven plasticity as a result of the consecutive expression of primers, openers, and closers of critical periods. Second, there should be evidence that the effects of circuit-relevant environmental exposures on both the brain and behavior vary by age and are distinctive within the demarcated window of peak neurobiological plasticity. In this section, we describe approaches to identifying the timing of neurobiological periods of enhanced plasticity across the cortical hierarchy and to studying differential impacts of the environment across developmental time.

Integrated cascades of critical period processes

The identification of a critical period requires confirmation that there is a temporally restricted age window of neurobiological plasticity that is orchestrated by the development of evolutionarily conserved plasticity mechanisms. In murine models, critical periods last from a few days (S1, A1) to a week (V1) in sensory cortex up to putatively 1 month in association cortex (medial PFC)—occupying approximately 5–15% and 65% of developmental time, respectively. Yet, in human neuroimaging studies, developmental change in nearly all macroscale correlates of critical period biology unfolds very gradually, with significant change in individual measures persisting for decades. Evidence of gradual refinements in individual plasticity markers may appear inconsistent with the existence of developmentally confined critical periods. However, critical periods are not defined by developmental change in just one biological feature, but rather by synergistic and successive changes in many interdependent biological processes. Critical periods may therefore arise when gradual changes cumulatively lead to a *bifurcation in the developing system* that results in a relatively rapid potentiation and then final consolidation of environment-driven adaptation.

Transformative changes in biological systems termed "bifurcations" arise when small, continuous changes in system parameters result in a sudden, qualitative change in the behavior of the system as a whole [183]. Examples of neurobiological bifurcations include the sudden firing of an action potential following cumulative changes in ion concentrations or the rapid transition from wakefulness to an unconscious state following anesthesia-induced changes in neural activity. Understanding critical periods as the ultimate bifurcation in an otherwise slow, progressive developmental process aligns with the theory that these periods may occur in the years prior to when a cortical region approaches a final state of consolidation and maturation. In addition, understanding critical periods as bifurcations in a multidimensional process underscores how periods of peak neurobiological plasticity can be identified for a region of cortex by studying not just one measure in isolation—but concerted change in multiple neurobiological and functional hallmarks of plasticity. Putative critical periods of heightened plasticity may therefore be temporally demarcated in the human cortex by integrating across developmental charts of graded change in imaging correlates of plasticity (Fig. 4B).

As depicted in Fig. 4B, a critical period of plasticity should emerge after thalamocortical structural connectivity exhibits a maximal rate of increase and the amplitude of intrinsic activity approaches a developmental peak. In addition, it should take place while inhibitory signaling is significantly increasing, excitatory glutamatergic connections are being pruned, and the local E/I ratio is declining. Finally, a critical period of plasticity should close after intracortical myelin exhibits rapid growth, thalamocortical connectivity stabilizes, synchronous intrinsic activity robustly decreases, local E/I balance is re-established, and a high evoked-to-intrinsic SNR is achieved. Integrating across cascading age-related changes in these correlates of plasticity can help to narrow the temporal window of when individual cortical regions exhibit biological evidence for critical period plasticity. Furthermore, the temporal ordering of such windows can be characterized across the entire brain, allowing for their precise hierarchical embedding to be elucidated.

Natural experiments and enrichment interventions to study environmental sensitivity

The identification of a biological period of high plasticity provides highly suggestive but ultimately insufficient evidence to designate a specific time in development as a critical period of environment-driven plasticity. Similarly, observations that particular environmental exposures impact the brain or behavior within one developmental stage cannot, without comparison to other ages, be used to substantiate the existence of a critical period. What must be demonstrated is that the developmental period in which critical period biology is expressed coincides with a temporally limited window when environmental inputs have a maximally large or enduring effect on cortical circuits and the establishment of adult forms of psychological processing. Accordingly, key approaches to testing for the presence of critical periods will involve studying age-varying relationships between the environment, brain, and behavioral outcomes both within and outside of biologically defined periods of heightened cortical plasticity.

Age-dependent associations between the environment, brain, and behavior can be studied using both cross-sectional and longitudinal datasets by applying statistical approaches that model time-varying coefficients, including but not limited to varying coefficient generalized additive models, time-varying effect models, latent change score and growth curve models, marginal structural models, and structured life course modeling [110, 184–189]. These statistical approaches could be used, for example, to test the critical period hypothesis that cognitive enrichment introduced in adolescence will have the largest impact on how quickly and reliably one can engage executive processes. Statistical models that probe time-dependent relationships could furthermore be used to test the critical period hypothesis that engagement in social hobbies and activities [190] during adolescence will have an outsized impact on the consolidation of association cortex plasticity.

The expression and timing of hierarchical critical periods could additionally be investigated in humans through "natural" experiments, or experiments that leverage naturally occurring variation in youths' environmental inputs. Natural experiments of ocular

pathology and deafness have been used in the fields of visual and auditory development to identify when light and sound exposure have the largest effect on sensory processing outcomes. A similar approach could be applied to study environmental variation relevant to psychological functions that are supported by hierarchically diverse cortical regions. Natural experiments could include, for example, studies that examine the time-dependent impact of arm casting on fine motor abilities [191], of bilingualism on language ability [192], of exposure to geolocation-based environmental diversity on cognitive flexibility [193], or of COVID-related social isolation on social cognition [194].

Natural experiments would be complemented by large-scale efforts that deliver positive environmental enrichment programs to youth of varied ages [5] and examine their longitudinal impact on imaging correlates of plasticity and behavioral outcomes. After-school programs could be designed that enrich distinct aspects of experience, for example, by providing opportunities for musical instrument training (sensory enrichment), second language learning (language enrichment), academic tutoring (cognitive enrichment), outdoor exploration (novelty enrichment), or team-building activities (social enrichment). Each of these opportunities could be introduced independently to groups of youth spanning elementary to high school ages, allowing for relationships between enrichment, psychological functioning, and cortical circuit plasticity along the S-A axis to be interrogated over development.

CONCLUSIONS AND CLINICAL IMPLICATIONS

The developing brain is biologically primed to adapt to and encode its environment. Animal studies have uncovered that environmental adaptation is most enduring in the cortex during defined critical periods that emerge due to the development of mechanistic regulators of circuit plasticity. Research examining developmental plasticity in humans from neural, environmental, and behavioral perspectives has begun to support the hypothesis that critical periods of environment-driven plasticity occur in the human brain and are expressed throughout the cortex hierarchically. Additional research is needed, however, to understand whether both sensorimotor and association cortices exhibit archetypal critical periods similar to those originally defined in animal sensory systems, and to elucidate precisely when such periods occur. Progress in this field of research has the potential to identify discrete time points in development during which specific brain circuits and the functions that they subserve exhibit unique sensitivity to circuit-relevant environmental influences. Accordingly, progress in critical period research can inform efforts to support healthy development in youth through the delivery of environmental interventions that best align with their neurodevelopmental context.

Critical period research has implications not only for optimizing brain development in healthy youth but also for modifying risk-related developmental trajectories in youth experiencing symptoms of psychiatric illness. The foundational premise of a critical period is that the brain adapts its circuitry and function to the environmental inputs it most commonly encounters, producing behavioral phenotypes that are tuned by experience. If the brain encounters disadvantageous environmental inputs, then psychiatric symptoms may emerge not due to abnormal neurodevelopment—but due to a normative adaptation of the system to a more adverse environment. Transdiagnostic psychiatric symptoms, including executive dysfunction [195–198], altered reward learning [199–202], and alterations in social cognition [203–205] may arise, for example, from low cognitive stimulation, environments lacking novelty or diversity, or diminished sociocultural enrichment. Indeed, there is evidence that risk for versus resilience to psychiatric illness is related to these environmental characteristics, including to cognitive enrichment, extracurriculars, and academic opportunities [206–208]; environmental novelty [209] and predictability [210, 211]; and social support and school belongingness [206, 212–214]. Further underscoring the environmental antecedents of psychiatric risk, socioeconomic environmental disadvantage is a robust risk factor for transdiagnostic, youth-onset psychopathology [215, 216]. Conceptualizing psychiatric symptoms as an expected developmental plasticity response to under-resourced, stressful, or socioeconomically deprived environments may partially explain why 50–75% of lifetime psychiatric disorders onset by age 25 years [10, 217–219]. Furthermore, conceptualizing psychiatric symptoms in this manner indicates that there are societally constructed disparities in youth mental health due to *systematic inequities in environmental opportunity*.

There are at least two likely pathways through which environmental (in)opportunity influences psychological adaptability versus vulnerability to psychiatric illness; these pathways may be relevant to understanding psychopathology in different subsets of individuals. In some individuals, disadvantageous environments may alter circuit development during periods of normatively expressed critical period-like plasticity. In others, the environment may act directly on mechanistic regulators of plasticity to dysregulate the timing, length, or expression of a putative critical period itself. Indeed, post-mortem studies of humans with psychiatric conditions and studies of animal models of psychiatric disease have reported disrupted expression of primers, openers, and closers of critical period plasticity, particularly in association with mood and psychosis-spectrum symptomatology [104]. For example, cross-species studies have documented the following in (models of) depression and schizophrenia: reduced glutamatergic input from the thalamus to the PFC [220–222]; lower PV cell density, PV protein expression, and PV-mediated inhibition [223–228]; and decreased cortical myelination and perineuronal net density [227, 229–231]. In vivo studies in humans have provided additional context for these findings by uncovering that disrupted expression of plasticity markers emerges developmentally. Studies have reported weaker developmental strengthening of thalamic structural connectivity with the PFC in adolescents with psychosis-spectrum symptoms [106, 107] and a blunted developmental increase in association cortex inhibitory signaling in youth with high levels of mood symptomatology [112]. In line with this general pattern, reduced developmental growth of myelin within the PFC has been documented in adolescents with higher levels of compulsivity and impulsivity [232] and lower levels of resiliency [233]. Critical periods of plasticity may thereby have implications not only for understanding when environmental antecedents of psychiatric risk become cortically embedded, but also how they do so neurobiologically.

Complementary investigations support an account of youth-onset psychopathology wherein environmental *deprivation* increases psychiatric risk during periods of developmental malleability. Significantly, this account indicates that population-level psychiatric risk can be lowered by increasing access to opportunities for environmental *enrichment*. Future research on critical periods will help to uncover when different forms of enrichment are likely to have a maximal positive impact on the long-term sculpting of distinct brain circuits and behaviors—thereby helping to inform enrichment interventions that are tailored to age-specific periods of neurobiological and behavioral plasticity.

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Valerie J. Sydnor, Amar Ojha, and Angela Martinez performed literature reviews for material presented in the article. Valerie J. Sydnor, Bart Larsen, and Beatriz Luna conceived of the topic; Finnegan J. Calabro provided expert input. Valerie J. Sydnor wrote the original article and created the figures. All authors critically revised the article.

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