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Sensitive periods in human development: charting a course for the future

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Sensitive periods neurobiologically encode environmental experiences to facilitate plasticity and learning in human development. Knowledge of human sensitive periods has largely come from methods developed in animal models and remains limited in many domains. We provide a framework and suite of approaches to study these phenomena in humans to stimulate progress in understanding human sensitive periods. To do so, we evaluate how current research approaches can shed light on different aspects of human sensitive period processes. These approaches comprise environmental manipulations like deprivation and substitution paradigms, pharmacological manipulations, and computational modeling. Finally, we propose three novel approaches rooted in human neuroscience—including impoverished environments, enriched environmental interventions, and individual differences in stress—to motivate future research on sensitive period mechanisms.

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The brain requires input from the environment to develop normally. Environmental experiences have lasting effects on brain function and behavior, particularly when they occur during sensitive periods of development. Sensitive periods involve experience-expectant learning processes that shape development of sensation and perception as well as affective and cognitive processes [1,2]. However, to date, knowledge about sensitive periods comes largely from sensory research in animal models using environmental deprivation paradigms [2]. In these models, animals are deprived of a specific environmental experience (e.g. visual inputs) at various ages to assess when that experience is required for a particular capacity to develop normally. Research on sensitive periods in human development has translated this environmental deprivation approach from animal models to contexts of naturally occurring deprivation, such as infants born with cataracts that block visual inputs [3]. While this approach has revealed insights about human sensitive periods in some domains, it has produced little progress in many others.

Our goal is to stimulate progress in research on sensitive periods by providing a framework for conceptualizing and studying these phenomena in humans. To do so, we first review observable criteria for sensitive period phenomena that differentiate them from other learning mechanisms in human development. Next, we evaluate the strengths and limitations of the deprivation paradigm for learning about sensitive periods in humans. We then highlight alternative paradigms and emerging approaches that may be applied more broadly to examine sensitive period phenomena in human development. Finally, we advocate for several new approaches rooted in human neuroscience that address open questions about sensitive periods and may stimulate future mechanistic research in both animal models and humans.

Sensitive periods as learning mechanisms

Sensitive periods are developmental learning mechanisms that neurobiologically encode particular, expectable environmental experiences (Box 1) [4]. These types of experiences are ubiquitous, variable, and necessary to foster adaptive development across a variety of capacities, and range from sensory inputs like visual contrasts to complex cognitive and affective experiences like language and responsive caregivers [5]. Understanding of the neurobiological mechanisms underlying this sensitive period learning comes largely from animal models, benefiting from experimental control and neurobiological precision not historically possible in human neuroscience. These approaches have revealed how sensitive periods are instantiated in the brain at molecular to neural circuit levels (Figure 1; see Ref. [6] for a review).

Sensitive periods have multiple characteristics that distinguish them from other learning processes. First, they encompass periods of heightened neuroplasticity that involve substantial, rapid changes to brain function [6]. Second, sensitive periods tune neural responsiveness to specific types of environmental inputs, after which

Box 1 Defining sensitive periods

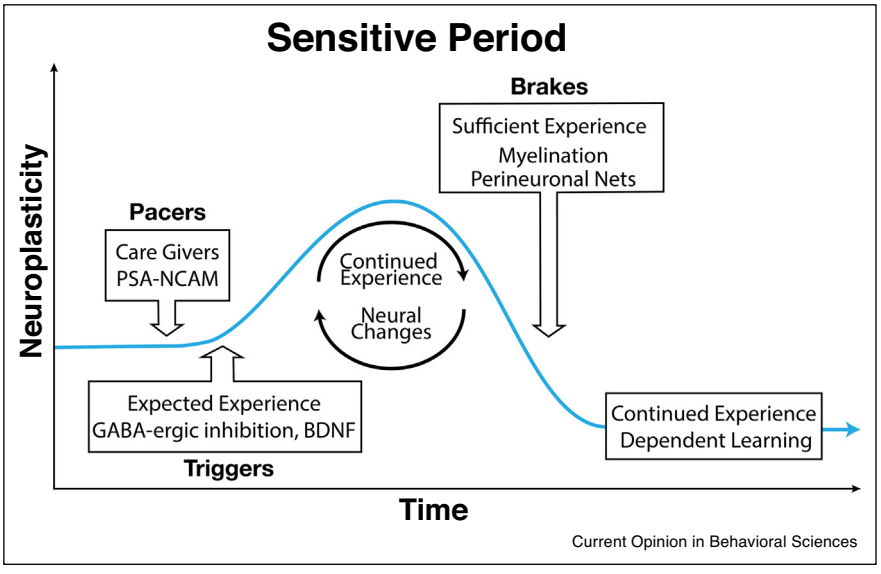
We define sensitive periods as developmental windows of experience-expectant learning mechanisms. Although the term sensitive period is also commonly used to refer to the *ages* when environmental experiences have their most lasting biological impact, we discourage use of this definition for several reasons. First, other forms of learning and plasticity also vary with age, rendering this definition non-specific to sensitive period phenomena. Moreover, it misrepresents the core nature of sensitive periods: sensitive periods do not refer primarily to measures of age but to neurobiological mechanisms in the developing brain. Lastly, sensitive period timing is not fixed but instead influenced by multiple experiential and biological factors, and this malleability in timing is difficult to reconcile with definitions of sensitive periods based on age. Instead, we argue that sensitive periods reflect developmental windows when the brain is prepared to neurobiologically encode particular, expectable environmental experiences. These periods are characterized by heightened plasticity in response to expectable experiences that produce changes in brain structure and function that persist once the sensitive period has ended. Residual plasticity after sensitive period closure enables environmental experience to continue modifying brain structure and function, though to a lesser degree. This residual plasticity also differentiates sensitive periods from other experience-expectant learning mechanisms without plasticity post-closure like critical periods.

additional tuning is diminished and requires extensive exposure. Indeed, exposure to the expected environmental experience is required to initiate sensitive periods [6]. Third, they occur for specific brain circuits only during specific windows of development, although their timing is itself malleable [2]. Fourth, sensitive periods are consolidated by factors that actively repress plasticity to protect the experience-modified circuitry and produce enduring effects on brain function and behavior [2,6]. Experimental approaches to probe sensitive periods require attention to each of these core features.

Experience deprivation approach to sensitive periods

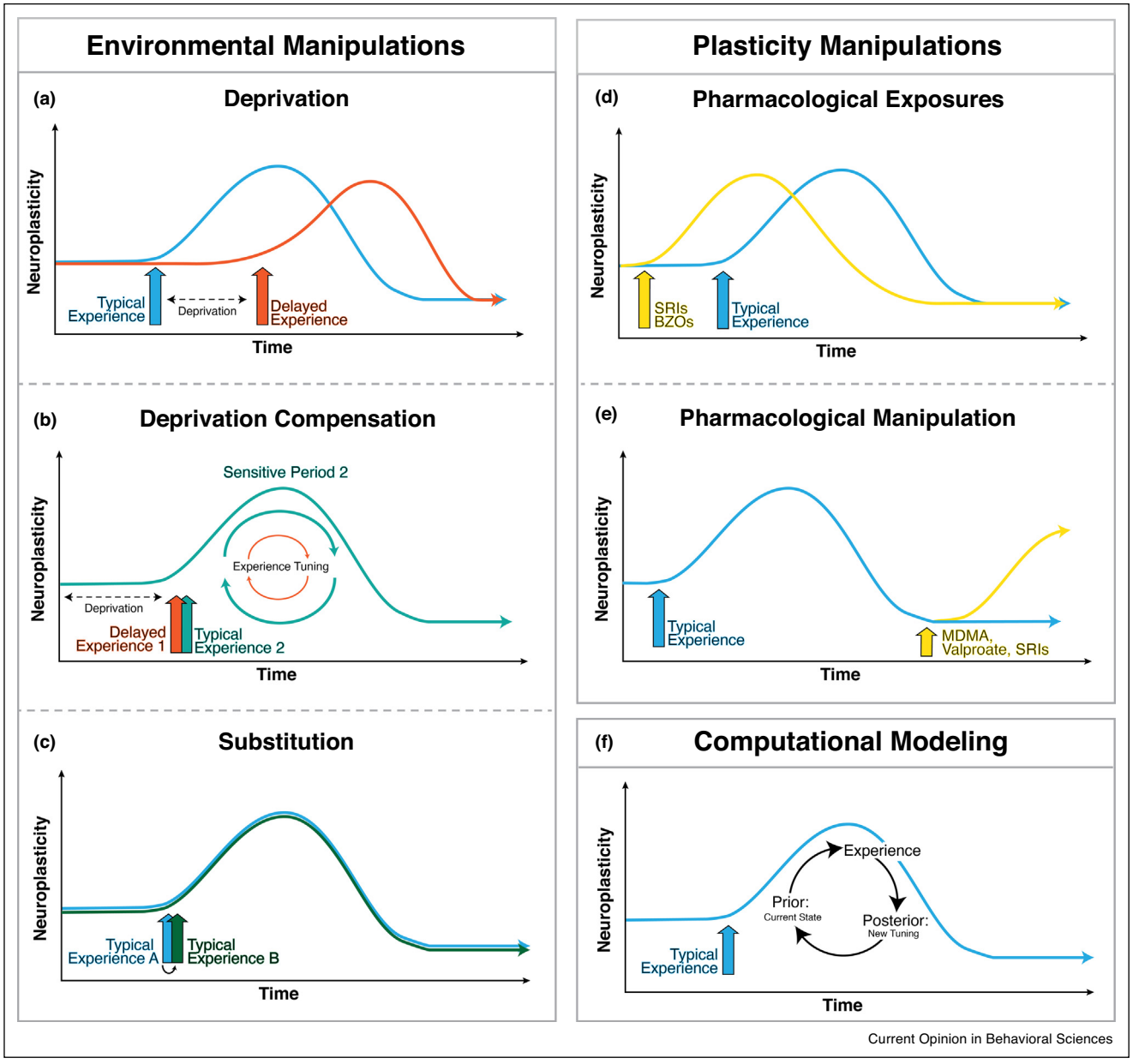
Sensitive periods encode specific environmental experiences. Exploiting variance in the timing of these expected inputs has produced insights into sensitive period plasticity. Experience deprivation paradigms constitute the earliest and most common approach to studying sensitive periods and compare how the absence of an expected experience at different points in development impacts brain or behavior [2] (Figure 2a). Seminal work by

Figure 1



Sensitive period mechanisms.
Sensitive periods are carefully orchestrated processes that unfold across levels from genes to behavior. Sensitive period initiation is regulated by molecular pacers and triggers. Pacers like polysialylated neuronal cell adhesion molecule (PSA-NCAM) inhibit sensitive period initiation to prevent precocious plasticity and maintain healthy developmental momentum. Conversely, environmental experience and molecular triggers [e.g. brain-derived neurotrophic factor (BDNF); gamma-Aminobutyric acid (GABA)] promote sensitive period initiation and increase neuroplasticity. The timing and quality of the expected experience also influence when the sensitive period occurs. Importantly, responsive caregivers may serve as both triggers for some sensitive periods (e.g. attachment), and pacers for other sensitive periods (stress responses). Once a sensitive period is successfully triggered, additional mechanisms facilitate rapid structural and functional reconfiguration and tuning to the expected experiential inputs. Dramatic synaptic and neural pruning occurs during sensitive periods to eliminate inefficient and unnecessary connections as circuit function becomes tuned by environmental experience. Continued exposure to expected experiences within the sensitive period is necessary to sculpt healthy brain function via these mechanisms. Sensitive periods are then closed to stabilize the experience-driven function. Sensitive period neuroplasticity is downregulated by a number of molecular and structural factors (e.g. peri-neuronal nets, myelination) that actively inhibit plasticity. After the sensitive period closes, limited residual plasticity enables continued modification through experience-dependent learning mechanisms available throughout the life course.

Figure 2



Current approaches to study human sensitive periods.
The suite of approaches currently available to study sensitive periods in human development include environmental manipulations, plasticity manipulations, and computational modeling. All of these approaches can be coupled with human neuroimaging to examine neurophysiological correlates of these manipulations. **(a)** The experience deprivation approach compares how the absence or delay of an expected experience at different ages impacts development. Deprivation of the expected experience will delay sensitive period timing relative to when the experience is typically present. **(b)** Deprivation paradigms may also inform the hierarchical nature of development. In the case of prolonged experience deprivation, the original sensitive period will close as the cortex gets appropriated for other functions. However, should that expected experience eventually occur (Delayed Experience 1), some of that functionality may be incorporated during later sensitive periods (Sensitive Period 2) through compensatory mechanisms. However, the tuning to the delayed experience will not be as robust as for the expected experience substrate at that time (Typical Experience 2). Cycling arrows indicate neural tuning to these experiences during the sensitive period. **(c)** Substitution paradigms manipulate the nature of expected experiences by switching between specific examples within the expected experience type. The substitution paradigm facilitates identification of typical sensitive period timing because it does not impact sensitive period opening or closure. **(d)** Pharmacological approaches use chemical compounds to alter sensitive period mechanisms. Pharmacological exposures in development like serotonin-reuptake inhibitors (SRIs) or benzodiazipines (BZOs) can accelerate sensitive period timing. **(e)** Pharmacological manipulations can also be used in adulthood to intentionally re-instantiate neuroplasticity after sensitive periods end. Drugs like valproate, SRIs, and 3,4-Methylenedioxymethamphetamine (MDMA) can disrupt sensitive period brake factors to increase neuroplasticity. **(f)** Computational modeling can

Hubel and Wiesel used this approach to identify a visual system sensitive period. They demonstrated that monocular visual deprivation—created by suturing one of the eyelids closed—leads to permanent changes in primary visual cortex and lasting visual impairments in the deprived eye, but only when the deprivation occurs during a specific window in the first months of life [7]. Visual deprivation at later ages produces no such brain or vision changes [7].

In humans, naturally occurring deprivation has been used to study sensitive periods. For example, infants born deaf or with dense cataracts that occlude visual inputs have revealed sensitive periods in auditory, language, and visual development [3,8]. Psychosocial deprivation associated with institutional rearing has also been used as a model for studying sensitive periods in humans [9]. For example, children raised in institutions typically lack a sensitive and responsive caregiver, a critical expectable experience and sensitive period input. Research examining variation in the timing of removal from institutions and placement into a family has revealed a sensitive period in the first two years of life for the development of a secure attachment to a caregiver [10].

Development is a progressive and hierarchical process. Capacities that emerge during earlier windows in development provide the scaffolding upon which subsequent competencies are built [11,12]. Deprivation paradigms can reveal how sensitive period mechanisms contribute to these contingencies in development. For example, in rodents an auditory sensitive period typically ends as the first visual sensitive period begins with eye-opening. Delayed eye-opening (i.e. visual deprivation) both delays the visual sensitive period opening and extends the earlier auditory sensitive period beyond the typical age of closure, suggesting auditory sensitive period closure is contingent on visual experience [13]. Deprivation paradigms in humans illustrate how plasticity in higher-order cortical areas may compensate for experience deprivation during earlier sensitive periods (Figure 2b). For example, cochlear implants to restore auditory input in children do not re-open earlier sensitive periods in primary auditory cortex for speech perception, but association cortical areas still experiencing plasticity can incorporate some of these lower-order auditory functions [14••]. Grey-matter and white-matter measures of regions affected by earlier auditory deprivation that typically facilitate speech perception do not predict speech development following implantation. Instead, associative auditory and frontal cortical regions that were not affected by the deprivation best predict speech development.

Deprivation paradigms have facilitated seminal discoveries in animal models, but they have several notable limitations when applied to human development. First, deprivation in expected experiences can delay the timing of sensitive periods [15]. Without careful experimental control of deprivation timing, it can be difficult to extrapolate sensitive period timing observed in human deprivation to identify typical sensitive period timing (Figure 2a). Moreover, psychosocial deprivation conditions often involve both the absence of expected experiences and the presence of severe stress (i.e. parental deprivation is inherently stressful for young children) [16]. Stress can also impact sensitive period mechanisms (discussed below), making it difficult to isolate deprivation-specific effects. The deprivation approach may also prove difficult for probing sensitive periods for higher-order social, cognitive, and affective functions in humans, as these almost certainly require complex experience inputs (e.g. Refs. [17,18]). Thus, for many higher-order capacities, the specific required inputs remain unknown and are difficult to remove from the environment completely as required in the deprivation paradigm. Finally, from a generalization perspective, complete deprivation of experience is relatively rare in both human and animal development (outside of experimental manipulations). So, insights gleaned from these paradigms may not possess high external validity or generalize to the vast majority of experiences [16]. Given these limitations of the experience deprivation approach, there is a need for complementary paradigms to better understand sensitive periods in humans and better facilitate translation between animal model and human findings. Below we describe alternative approaches that may be applied more broadly than the deprivation paradigm to study human sensitive periods.

Alternative approaches to sensitive periods

Experience substitution

Whereas deprivation approaches manipulate the timing of expected experiences in development, substitution approaches manipulate the nature of these experiences. That is, substitution paradigms alter specific types of expected experiences (Figure 2c). For example, young birds learn to sing songs from adult tutors through a series of sensitive periods. The timing of these song-learning sensitive periods was recently corroborated in wild birds using pre-recorded songs that were broadcast through speakers as artificial tutors to sparrows at different ages in their natural habitat [19•]. Wild sparrows only learned the artificial tutor songs during two sensitive periods, and retained those songs into adulthood. In humans, international adoption provides a natural case of language

(Figure 2 Legend Continued) be used to simulate experience and plasticity manipulations. Here we illustrate one example in which computational modeling has generated predictions about how experience-driven tuning occurs during sensitive periods with the statistical framework of Bayesian learning, in which prior probabilities of neural activity in response to experience are updated over the course of the sensitive period as experience (i.e. evidence in the model) tunes posterior distributions of activity patterns.

experience substitution, as children cease exposure to their original language and are immersed in a different language. Research on these populations has shown that the neural imprint from exposure to the first language during sensitive periods is maintained after adoption without further exposure to that language [20,21]. Human studies have also manipulated some types of experience to identify sensitive periods. For example, varying the age at which infants encountered human and primate faces through picture book training has revealed a species-specific facial processing sensitive period in human infancy [22]. Recently, exposure to artificially generated auditory inputs in infancy has been used to study the effects of this exposure on language sensitive periods [23••].

Although less common than experience deprivation, experience substitution offers multiple advantages to probe sensitive periods. First, altering specific experiences within a class of expected experiences does not shift sensitive period timing like experience deprivation (Figure 2c). Moreover, age-localized exposure to different specific expected experiences may help localize sensitive periods. Varying exposure to specific songs across development has led to the identification of childhood sensitive period for anxiolytic signal acquisition in the medial prefrontal cortex across species [24]. Thus, substitution paradigms are well-suited to understand sensitive period timing. This approach may also facilitate progress in studying higher-order sensitive periods where deprivation of complex environmental inputs at different ages may not be possible. Instead, manipulating properties of expected experiences may help identify the required components of complex environmental experiences for a particular sensitive period. Substitution paradigms may prove instrumental for making progress in the emerging focus on higher-order social, cognitive, and affective sensitive periods.

Pharmacological manipulation

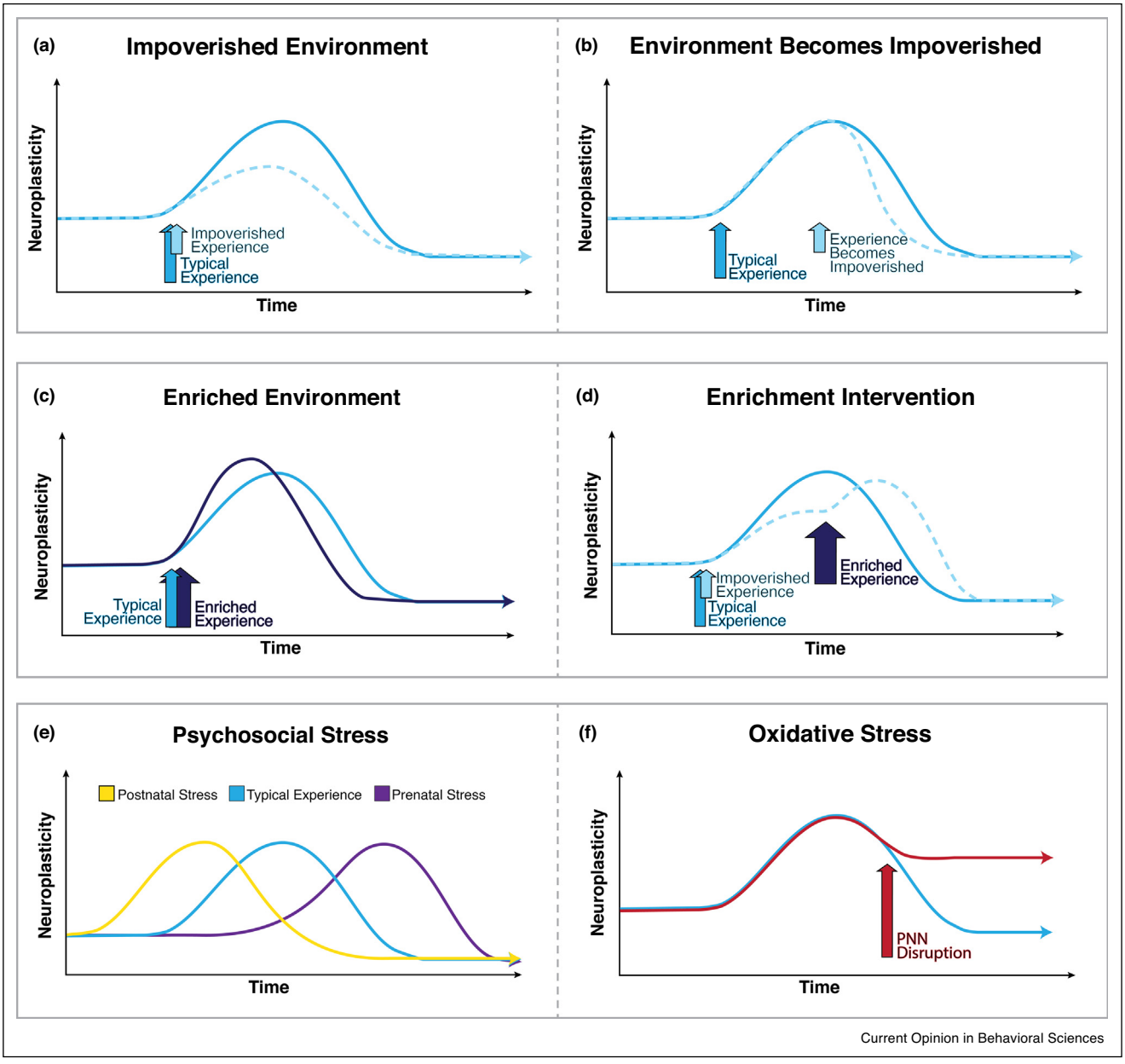
Pharmacological approaches use chemical compounds to alter sensitive period mechanisms. Pharmacological manipulations can shift sensitive period timing, prevent sensitive period initiation, and even reopen sensitive periods in animal models [6]. For example, precocious exposure to GABA-ergic anesthetics can trigger sensitive periods to open early in rodents (i.e. temporal acceleration) [6]. These drugs are used to sedate children, but have yet to be examined in the context of human sensitive periods. However, prenatal exposures to selective serotonin-reuptake inhibitors used to treat depression have similarly been shown to temporally accelerate sensitive period timing in language development [25]. Notably, such temporal acceleration of sensitive period timing may be adaptive in some contexts, but maladaptive in others. Understanding how pharmacological exposures in development impact sensitive periods is an emerging research direction with important basic and clinical science implications that can inform how altered sensitive period timing impacts development (Figure 2d).

Pharmacological manipulation can also be used to intentionally modify plasticity by re-opening sensitive periods [26] (Figure 2e). For example, MDMA reopens a striatal sensitive period for social reward learning in rodents [27•]. Work in humans aims to correct prior problems in sensitive period learning and facilitate recovery following brain injury (e.g. stroke) in clinical populations. In a proof-of-concept study, valproate (which inhibits a key sensitive period molecular 'brake') administered to healthy adults reopened an auditory sensitive period [28]. Fluoxetine, a treatment for depression, increases post-sensitive period plasticity in the visual cortex of both adult rodents [29] and human patients with amblyopia [30]. Although pharmacologically removing the brakes on sensitive period plasticity has potential to remediate a range of conditions, such manipulations also raise serious ethical questions [2]. Targeting specific circuitry also requires precision in pharmacological administration that is not yet available in humans.

Computational modeling

Computational models offer an alternative method of control over experience inputs and neural manipulations that provide a new frontier for research on sensitive period mechanisms. First, they can address questions beyond the scope of experimental data, for example by simulating evolutionary pressures on sensitive period mechanisms [31••]. Second, they enable efficient evaluation of multiple possible explanations for observed experimental data on sensitive period phenomena (e.g. Ref. [32]). Third, they provide a means to bridge the fine-grained knowledge of neural mechanisms in animal models with coarse-grained imaging capacities in humans to generate novel hypotheses about sensitive periods. For example, computational models of human neurophysiology in combination with empirical data in rodents have generated novel metrics reflecting sensitive period initiation that may scale to human neuroimaging [33]. Moreover, computational models have generated predictions about how experience-driven tuning occurs during sensitive periods with statistical frameworks (e.g. Bayesian learning) that have been successfully applied to data from animal models, and are testable with human neuroimaging data [34] (Figure 2f). Recent work even suggests that sensitive periods may occur in artificial intelligence systems learning from their environments in ways that parallel biological sensitive periods [35]. Future research building on this synergy between computational and experimental approaches to sensitive periods may, therefore, reveal both natural and artificial learning mechanisms. These computational approaches also come with limitations as abstracted, sparse representations of the complex biology underlying sensitive periods. For

Figure 3



Novel approaches to study sensitive periods.
We propose three novel approaches rooted in human neuroscience to generate progress in understanding sensitive periods across species: impoverished environments, enriched environmental interventions, and individual differences in stressors. **(a)** The impoverished environment approach manipulates environmental inputs such that they occur at the correct time but are sparse or poor quality in nature. Experiences that are impoverished throughout the sensitive period likely induce lower levels of plasticity and less learning. **(b)** Experiences that begin typically but become impoverished during a sensitive period may abbreviate sensitive period duration and impact learning as well. **(c)** Environmental enrichment approaches create more complex or higher-quality environments than those typically encountered. Work in animal models suggests that enrichment from birth accelerates sensitive period timing (both opening and closing), and increases neuroplasticity during the sensitive period relative to typical environments. **(d)** Environmental enrichment interventions are widely used in human development, but few studies have examined the effects of their timing in development via sensitive period mechanisms. Enrichment interventions in the context of adversity (impoverished experiences shown here) may rescue sensitive period plasticity and complex learning to some extent, but only if they occur during the sensitive period, not after. **(e)** Stressful experiences during development may influence sensitive period processes, such as altering their timing. Recent work in animal models suggests that adverse psychosocial stressors occurring prenatally delay sensitive period timing, while psychosocial stressors that occur postnatally accelerate sensitive period timing relative to typical development. **(f)** Stressor experiences that increase oxidative stress in the brain can also alter sensitive period closure. Oxidative stress disrupts the formation of perineuronal nets (PNNs), important brake factors that suppress sensitive period plasticity and protect experience-modified circuitry. Without these structural brakes, plasticity levels remain too elevated, learning is not appropriately consolidated, and the circuitry is vulnerable to future insult.

example, close attention must be paid to how well a model fits associated empirical data. Moreover, determining correspondence between model parameters and neuroimaging measures or underlying biology may be difficult or impossible in some cases.

Novel approaches to studying sensitive periods

Thus far, approaches to studying sensitive periods in humans have originated from methods used in animal models. Below, we propose three novel approaches rooted in human neuroscience to generate progress in understanding sensitive periods across species.

Impoverished environments

The impoverished environment approach manipulates environmental inputs such that they occur at the correct time but are sparse or poor quality in nature (Figure 3a,b). This approach targets the *quality* of experiential inputs and can provide information about sensitive period processes that complements knowledge from the deprivation and substitution approaches that manipulate the timing and type of these inputs. Moreover, this environmental context mirrors the adverse conditions most frequently experienced in human development (e.g. sparse language inputs, variable caregiving quality). A rich body of human research seeks to understand how such impoverished conditions influence brain and behavioral development [e.g. Refs. 31••,36–39], and examining effects on sensitive period mechanisms across species may provide key insights. For example, animal research controlling the timing and duration of impoverished inputs will be critical to isolate how the quality of experiential inputs influences specific sensitive period processes separate from the timing and type of input [40••].

Enriched environment interventions

The enriched environment approach also targets experiential input quality, to create more complex or higher-quality environments than those typically encountered. Work in animal models suggests that enrichment from birth accelerates sensitive period timing with adaptive consequences [41] (Figure 3c). However, there are few manipulations of environmental enrichment timing in animal models or in the context of prior adversity, though this paradigm may inform when interventions in humans might be maximally effective (Figure 3d). Many enrichment-based interventions target early human development [e.g. Refs. 42,43], but few have examined the effect of intervention timing on child outcomes. In the context of early life adversity, this approach can address how enriched environments introduced during versus after a sensitive period may rescue learning differently. Enrichment timing manipulations can also inform principles of hierarchical sensitive period learning by revealing how higher-order sensitive periods under enriched conditions may or may not compensate for effects of earlier impoverished sensitive period learning.

Stressors

Extensive research in human development examines how early life adversity influences brain and behavioral development. These exposures are diverse in their experiential components, with some reflecting the presence of threat (e.g. abuse), others reflecting social-cognitive deprivation (e.g. neglect), and many reflecting heterogeneous stressors (e.g. financial hardship). Not only do these different dimensions of adversity have distinct influences on neurocognitive development [37,44], but they also likely have divergent influences on sensitive period mechanisms. Although deprivation has frequently been used to study sensitive periods, adversity involving high levels of stress or threat has not. These exposures are not expectable experiences, and thus unlikely to be experiential substrates for sensitive periods. However, threatening or stressful experiences may influence sensitive period processes, such as altering their timing (Figure 3e) or the degree of associated neural plasticity (Figure 3f). For example, recent work in animal models suggests that stressors that occur before versus concurrent with sensitive periods can significantly impact sensitive period timing in different ways (Figure 3e; [45–47]). Moreover, early stressors have been shown in animal models to modulate neural responsivity during sensitive periods to expectable experience inputs like caregivers [48••]. In humans, trauma accelerates several aspects of neural development [49,50] in ways that may alter sensitive period timing. The conditions that render such accelerated timing adaptive or maladaptive in this context of adversity remain unclear in human development. Future research is needed to examine stressors as modulators of sensitive period processes in both animal and human studies.

Conclusion

Sensitive periods involve complex learning mechanisms, and studying these important developmental phenomena requires a suite of approaches. Though the environmental deprivation paradigm has dominated sensitive period research in animal models, its limitations in studies of human development suggest other approaches may lead to better understanding of human sensitive periods. We chart a course for the future study of human sensitive periods that includes existing approaches that can reveal different aspects of human sensitive period processes, as well as a set of novel approaches to address critical open questions in human neuroscience. These paradigm shifts will be essential to drive new progress in identifying human sensitive periods.

Conflict of interest statement

Nothing declared.

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