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Current Opinion in Behavioral Sciences

Nested sensitive periods: how plasticity across the microbiota-gut-brain axis interacts to affect the development of learning and memory

Bridget Callaghan

There is a growing appreciation for the range of sensitive periods which occur across the brain. These sensitive periods give rise to sensory outcomes, as well as complex higher-order cognitive functions like learning and memory. More recently, an understanding that sensitive periods of development occur outside of the central nervous system (e.g. in the gastrointestinal microbiota) has emerged. Less well understood is how these peripheral sensitive periods may interact with those operating centrally to influence complex behavior. The goal of this paper is to put forward the view that sensitive periods of development occur across the entirety of the microbiota-gut-brain (MGB) axis, and that these nested sensitive periods may interact to influence learning and memory outcomes. Adopting this framework should promote a 'new wave' of thinking in the field which appreciates the complex central and peripheral forces acting on behavior, and uses that understanding to innovate therapies and interventions for disordered learning and memory systems.

Address
Department of Psychology, The University of California, Los Angeles, United States

Corresponding author: Callaghan, Bridget (bcallaghan@ucla.edu)

Current Opinion in Behavioral Sciences 2020, **36**:xx–yy

This review comes from a themed issue on **Sensitive and critical periods**

Edited by **Willem Frankenhuis** and **Catherine Hartley**

https://doi.org/10.1016/j.cobeha.2020.07.011

Introduction

Discrete windows of time exist in development when the biology and behavior of an individual is especially sensitive to the shaping effects of environmental stimuli. Such windows of enhanced plasticity occur in mammals across numerous biological systems and are commonly known as 'sensitive periods' in humans. The occurrence of a sensitive period is thought to involve a trade-off between exploration and exploitation within neural circuits, whereby biology can sample the environment to create an individualized adapted circuit within the sensitive period, before then stabilizing that circuitry and enhancing its efficiency in adulthood [1]. Although sensitive period mechanisms have been studied most intensively within sensory systems (e.g. primary visual cortex [2]), work in the last decade has demonstrated that stages of heightened developmental plasticity also occur for learning and memory behaviors [3,4•,5–7], and specifically within the limbic circuits (amygdala, hippocampus, and prefrontal cortex) that support those behaviors [8–12].

The idea that early environments can program the development of learning and memory has captured the attention of psychology and psychiatry largely because of its clear clinical implications. For one, environmental shaping of learning and memory help to explain how certain early conditions (e.g. parental deprivation) come to be associated with complex behavioral syndromes (e.g. psychopathology), in part through programming effects on the development of learning and memory systems, which are the basic building blocks of emotional behavior and personality. In addition, the identification of molecular mechanisms underlying heightened plasticity during sensitive periods highlights how one could manipulate such biological affordances to dramatically alter learning and memory behaviors which are no longer adaptive, even after the period of plasticity is closed (i.e. the potential to reopen sensitive periods in adulthood through manipulating molecular pathways) [13]. Perhaps the most significant clinical contribution of this work though, is that it has underscored the critical importance of early intervention, in which the heightened plasticity inherent in the sensitive period can be used to reprogram learning and memory trajectories. Nevertheless, beyond the blanket (but important) suggestion that early intervention for emotional and cognitive functioning should yield more dramatic and lasting treatment effects, the full potential for sensitive period research to revolutionize clinical treatment for cognitive and emotional functioning has not yet been realized.

One explanation for the therapeutic limitations of the sensitive period approach to learning and memory (and associated mental health) is the continued focus (perhaps even over focus) on central nervous system biology, which is difficult to manipulate directly, particularly in childhood. However, more recent research in the field provides an intriguing potential solution — focusing on peripheral biology to affect both central nervous system functioning,

as well as learning and memory behavior. Specifically, it has been shown that peripheral circuits including the gastrointestinal system (gut) and the teeming mass of bacteria that reside there (the microbiota), may have their own sensitive periods of development [14–18] during which interactions with the central nervous system through the microbiota-gut-brain (MGB) axis can help to program learning and memory behavior [19–21]. The microbiota interacts with the central nervous system through a multitude of mutually inclusive pathways, including immune mediated, electrical (via the vagus nerve), and chemical (via metabolites entering the bloodstream; see Ref. [22] for a review of these mechanisms). Moreover, evidence suggests that during the sensitive period, the entirety of the MGB axis may be shaped by environmental conditions, particularly those well known to have a potent programming effect on learning and memory behavior (e.g. early adversity; [23•,24,25], see Figure 1). Finally, evidence is mounting which suggests that the microbiota itself might regulate the timing of sensitive periods across the body, acting as an environmental signal which can initiate the onset and offset of sensitive periods (i.e. by acting as a, so called, 'species expected stimulus' [23•,26]). As the peripheral nervous system and particularly the microbiota might be more easily manipulated than the brain (e.g. through probiotics, antibiotics, environmental, and nutritional interventions), this body of research has the potential to open new (and developmentally appropriate) avenues for manipulating behavior. In doing so, this work reveals the numerous, and perhaps unexpected, forces acting upon learning and memory across development.

Capitalizing on the recent developments in this dynamic field, here I review findings (particularly across the last 5 years) on sensitive periods of learning and memory. Although numerous sensitive periods for learning and memory exist [7,12,27,28], as case examples, I focus on the phenomena of infantile amnesia and relapse-resistant extinction seen in infant rats (postnatal day [P] 16-21), as well as neurobiological and behavioral parallels from the human literature (including the development of early associative memory). These developmentally unique behavioral signatures are accompanied by molecular markers in the brain which indicate heightened neural plasticity characteristic of sensitive periods, and different trajectories of these behaviors occur in response to specific early conditions (e.g. caregiver deprivation), highlighting the environments which the elevated neural plasticity responds to. First, I describe these developmentally unique behavioral signatures of learning and memory and their molecular markers, then I illustrate how such behaviors are affected by the early environment (namely caregiving stress), revealing the nature of the sensitive period. I then explore recent evidence which suggests that the MGB axis also exhibits developmentally unique functional and structural signatures, and is responsive to the same types of stress experiences which alter the early learning and memory system. Finally, I will discuss how MGB axis functioning, and more specifically microbiota manipulations, can influence learning and memory during the sensitive period. I end the paper by suggesting that understanding 'nested' sensitive periods (i.e. those occurring simultaneously within early learning and memory systems and the MGB axis) represents a 'new wave' of thinking in the field which should be considered in future efforts to understand complex higher order behaviors like learning and memory, as well as their environmental regulation.

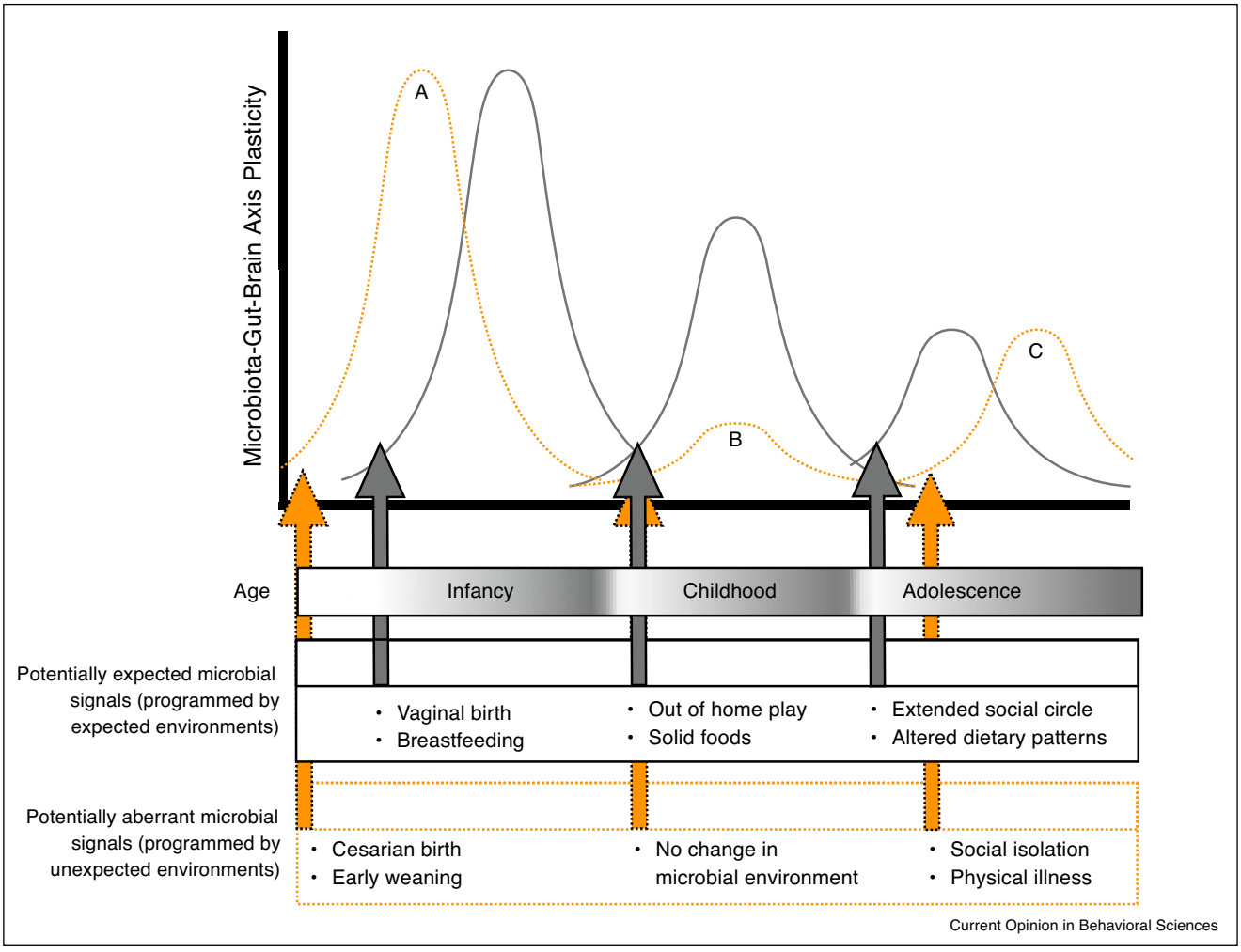
Sensitive periods of learning and memory

Behavioral signatures of a sensitive period in learning and memory

It has been known for decades that many mammalian species are faced with profound amnesia for their early experiences (infantile amnesia) [29]. While that observation is not new, the idea that this unique stage of behavioral development might represent a sensitive period in the maturation of the hippocampus was only recently suggested [29]. Evidence for that assertion was subsequently obtained by Travaglia *et al.* [4•] who showed that the transition from infantile amnesia to longer lasting adult-like retention for threat associations coincided with the development of several molecular markers in the hippocampus which had previously been shown to regulate the timing of sensitive periods within the visual cortex (e.g. activation of brain derived neurotrophic factor; BDNF). Moreover, in that study, manipulating those molecular markers in the hippocampus could bring about an early or delayed transition from infantile amnesia to adult-like memory retention. Importantly, infantile amnesia and its regulation by molecular markers of the sensitive period has also been shown to occur for hippocampus-dependent memories of non-aversive events [11], suggesting that this sensitive period of development within the hippocampus is not valence specific.

Another putative sensitive period occurring around the same time as infantile amnesia is characterized by relapse-resistant safety (or extinction) learning. After being conditioned to fear threat-predictive cues, rats P16-21 can learn to inhibit their fear responding through a process of extinction (whereby the previously threat-predictive cue no longer signals an aversive outcome). Whereas adults will exhibit a range of relapse behaviors after such extinction learning (e.g. the renewal of threat responding when the context changes), P16-21 animals will not, exhibiting persistent fear reduction following extinction, which is relapse-resistant (for a review see Ref. [28]). It has been suggested that such extinction behaviors may represent a sensitive period of development in the amygdala and prefrontal cortex. Specifically, the transition from relapse-resistant to the more adult-

Figure 1



Graphical depiction of how the microbiota might act as an 'environmentally expected input' triggering periods of plasticity along the brain–gut axis. Solid lines and darker colors represent expected developmental gradients, which overlap with transitions in chronological age/stage of life. The box labelled 'Potentially expected microbial signals (programmed by expected environments)' highlights environmental factors that can influence the microbiota, and that might reasonably be expected to occur at different stages of human development (throughout our evolutionary history). These environmentally mediated shifts in the microbiota are hypothesized to trigger different phases of brain–gut axis plasticity. Dotted lines and orange colors represent altered developmental gradients which do not overlap with chronological age/stage of life. The box labelled 'Potentially aberrant microbial signals (programmed by unexpected environments)' highlights environmental factors that can influence the microbiota, and that might reasonably be expected to have been absent or infrequent at different stages of human development (throughout our evolutionary history). These aberrant microbial signals might trigger mistimed periods of plasticity in the brain–gut axis, either accelerated (A) or delayed (C), or might be insufficient to trigger a period of heightened plasticity in the brain–gut axis (B). Importantly, the fact that aberrant microbial signals can occur at all, represents the second concept that the microbiota itself is plastic and shaped by environmental cues.

like, relapse-prone, extinction is paralleled by the emergence of a more mature neural circuit which involves the prefrontal cortex [30], as well as by the appearance of molecular markers (perineuronal nets) in the amygdala [31•], which operate as a brake on sensitive period plasticity [2]. Interestingly, chemical removal of perineuronal nets from the amygdala in adulthood can reactivate the sensitive period of relapse-resistant extinction [31•]. Similar to those rodent findings, a developmental transition in safety learning circuitry has also been shown to occur in humans, whereby age is associated with the recruitment of a more mature, inverse pattern of connectivity between the amygdala and prefrontal cortex, which is also correlated with more mature emotion regulation behaviors [32–34]. Hence, similar to infantile amnesia, a strong developmental gradient can be seen for safety learning behaviors and neurobiology, and the appearance of such behaviors across development can be manipulated by altering molecular pathways which regulate developmental plasticity.

Taken together, these behaviors of infantile amnesia and relapse-resistant extinction appear to represent a phase of exploration of social-emotional learning, afforded by young animals living in the safe confines of the maternal nest, which occurs before threat responses such as avoidance are required for self preservation (exploitation) when animals develop and leave the nest [29]. Such behavioral exploration might enable the neural circuit to develop more flexible patterns of modulatory engagement, which then facilitate emotional self-regulation in adulthood (i.e. the exploitation phase of the neural circuit; [35]).

Effect of environmental stress on sensitive periods of learning and memory

The timing of the sensitive period for learning and memory is not only responsive to molecular manipulations. In fact, the early caregiving environment is a potent regulator of developmental trajectories for early memory and safety learning systems, highlighting which environments the heightened neural plasticity inherent to this sensitive period is responsive to. Specifically, P17 rat pups exposed to a stressful experience (like maternal separation) show an earlier transition into the adult-like longer lasting fear memory system [3,36], as well as an early transition into the more adult-like relapse-prone extinction system [5,37,38], precocious integration of the prefrontal cortex into the threat circuit [10], and accelerated maturation of the hippocampus [12]. Parallels also exist in humans; parent separation or divorce before a child's 8th birthday was associated with an earlier offset of infantile amnesia, as assessed through retrospectively reported earliest memories in adults [39]. Also, early stress, before 5-years of age, but not stress occurring later, was associated with hippocampal volume in early adolescence (9–13 years) [40]. Finally, insensitive parenting and early institutional care have both been associated with accelerated development of mature patterns of amygdala-prefrontal cortex connectivity [41,42], and a more mature profile of amygdala-prefrontal cortex-hippocampus connectivity during threat learning [43]. Together these findings support the idea that early adversities, particularly those that involve caregiving, are associated with the emergence of more mature behavioral and brain profiles [44•], suggesting an early termination of sensitive periods for learning and memory following stress.

Sensitive periods of microbiota-gut-brain axis development

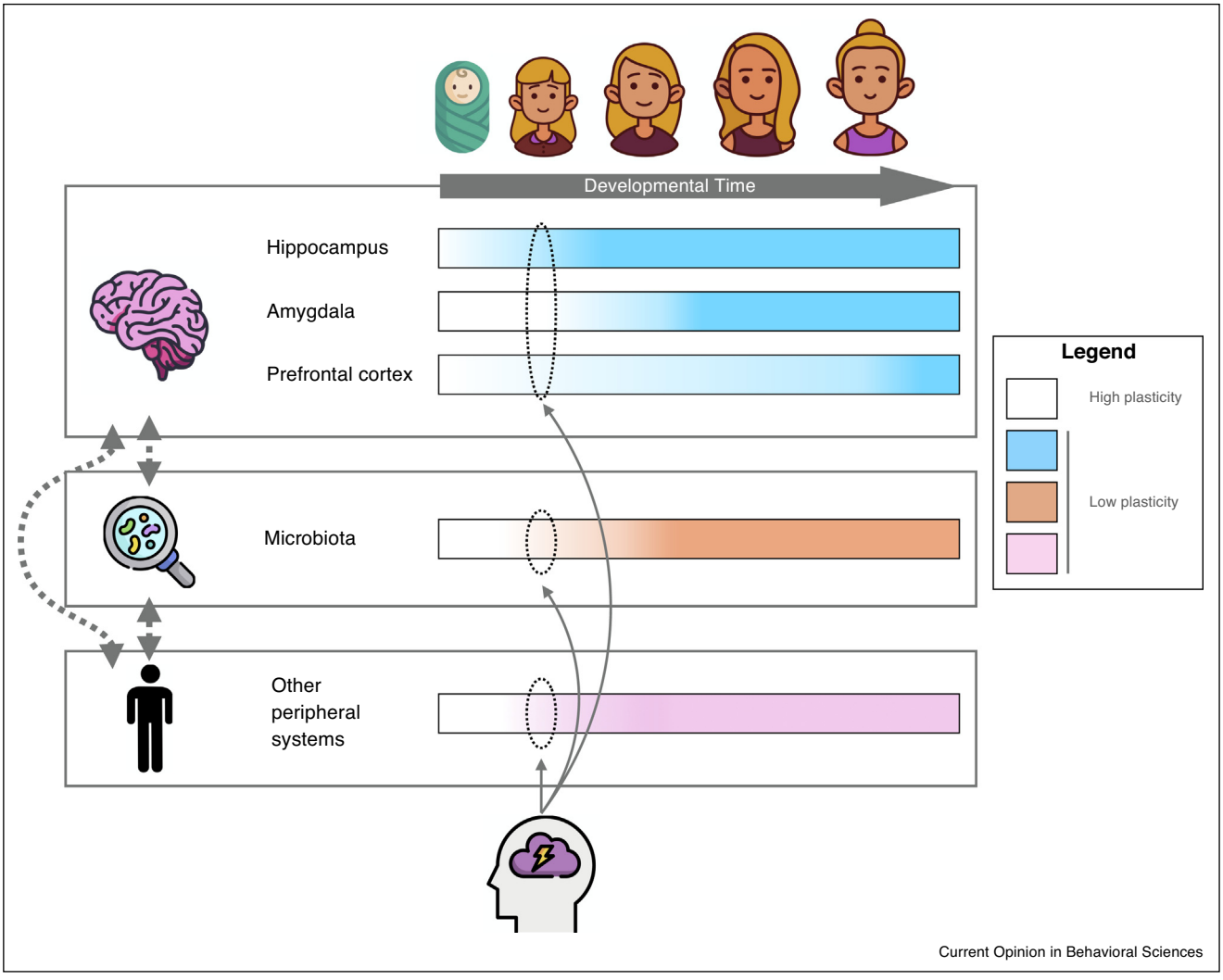
Biological signatures of a sensitive period in the MGB axis

While age-related gradients in memory retention and safety learning mark the opening of a sensitive period in learning and memory systems, developmental gradients of microbiota structure and function help to identify a sensitive period of development within the microbiota-gut-brain (MGB) axis. Similarly to periods of flux in neural circuits suggesting the operation of a sensitive period of development in that brain circuit [45], stages of flux in the microbiota can be used as one signal that a sensitive period might be operating in the MGB axis. Indeed, tremendous shifts in bacterial diversity (both increases in diversity itself, as well as changing composition of specific taxa) occur up to approximately 4 years of age in humans [46,47], with environment playing a large role in the structural and functional composition of the community during that time (e.g. mode of birth and breastfeeding effects [48]). Although less research has examined how the microbiota develops across middle childhood and adolescence, there is suggestive evidence of continued structural and functional microbial change across those maturational stages [49,50]. Moreover, theories have emerged which suggest that ecological features specific to middle childhood and adolescence (e.g. large shifts in social networks as a result of school transitions, and diet changes due to increasing independence) would likely contribute to compositional flux in the microbiota at these developmental stages [51•]. Together this work identifies developmentally unique signatures of the microbiota, and stages of microbial flux, which are strongly suggestive of the operation of a sensitive period of development in the MGB axis (see Figure 1).

Effect of environmental stress on sensitive periods in the MGB axis

A second piece of evidence for a sensitive period in the MGB axis is that environmental perturbations strongly shape the microbiota during the putative window of enhanced developmental plasticity. For example, early caregiving adversities (parent-infant separation) which shape learning and memory trajectories and their associated neurobiology, also shape the composition (both decreased overall diversity as well as a change in abundance of several bacterial taxa) of the gastrointestinal microbiota in early life in monkeys [16], as well as in rats [52–54]. Interestingly, the maternal separation procedure, which is a popular model for psychosocial stress, is just as frequently used to model functional gastrointestinal disorders (like irritable bowel syndrome; IBS; see Ref. [55] for a review). In humans, few studies exist which specifically examine the effects of caregiving adversity on microbiota composition, however, at least three studies suggest that such effects may occur. In a small proof-of-concept study, I recently showed that microbiota diversity was lower in children and adolescents who had a history of institutional care, than in youth who had always been with their biological caregivers [25]. In another recent study, a significant association between functional taxonomic composition of the microbiota and parent-child relationship dysfunction was reported [56]. Finally, retrospective reports of childhood adversity in adults have been associated with differential taxa abundance in the gastrointestinal microbiota during pregnancy in females [14]. Together these non-human and human animal data strongly suggest that early experiences (particularly those in the caregiving environment) can shape the

Figure 2



Graphical depiction of the concept of 'nested sensitive periods'. Boxes represent different physiological systems across the body (from top to bottom: Central Nervous System, Microbiota, Other Peripheral Systems). Developmental time across a human lifespan is represented on the top x-axis. Within each system gradient colored boxes represent system plasticity. As can be seen in the legend, high plasticity is represented in white, low plasticity (or system stability) is represented in solid colors; different colors correspond to the different physiological systems. NB: the levels of plasticity for the different systems are approximations only, and are not intended to necessarily represent the true state of the system at a given developmental stage. The figure on the bottom x-axis represents an environmentally aberrant event (a violation of a species-expectation). The broken circles represent the effect of that event across the different physiological systems. The degree to which the event affects the physiological system would be, in part, determined by the level of plasticity in the system when the event occurred (i.e. if the sensitive period was open). The arrows on the left of the figure which connect the boxes represent the idea that the different sensitive periods can interact, which could lead to unique or amplified outcomes. That is, even if an event only affected one physiological system, the effect of that event may reverberate throughout the body.

development of the microbiota (and MGB axis), supporting the notion that the MGB axis has its own period of elevated developmental plasticity to environmental input (i.e. a sensitive period; see Figure 1).

MGB axis shaping of learning and memory

A variety of studies have now examined how alterations to bacteria during sensitive periods of development can influence learning and memory outcomes. For example, in adult rodents, early microbiota depletion (through growing up germ-free or being treated with chronic antibiotics) impaired extinction learning, which could be rescued by colonization with a diverse microbiota in infancy, but not when colonization occurred after weaning [57]. In infant rats, it was shown that probiotic treatments could reverse the effects of maternal separation on accelerated memory development [36,58], and prevent those effects of stress being transmitted across

generations [59]. Moreover, probiotics could reverse the accelerated development of neural circuits underlying adult-like fear and extinction behaviors in young maternally separated rats [10,36]. Although very little human data exists on how the MGB axis relates to learning and memory, one study has shown that microbiota diversity was associated with cognitive functioning in infancy [60]. Together these data are suggestive of a sensitive period during which microbiota diversity can influence the development of fear and safety learning and cognitive functioning more broadly.

In addition to the behavioral effects reported above, the microbiota has also been shown to influence the development of neural systems which underlie learning and memory in a manner consistent with sensitive periods. For example, germ free mice display alterations in the brain transcriptome (including in the hippocampus and prefrontal cortex) relative to mice raised in specific pathogen free (SPF) conditions [61]. Importantly, colonization of germ-free animals with the bacteria from SPF animals prevented these transcriptomic changes only if the colonization occurred early in life, supporting the notion that there is a sensitive period for the effects of microbial presence on brain function. Similarly, microbiota alterations (germ-free and antibiotic treatment) during the sensitive period in rodents have also been shown to program structural and functional development within amygdala, prefrontal cortex, and hippocampus (see Ref. [62•] for a review).

A new wave of sensitive period research

As seen in the examples discussed above, evidence is accumulating to suggest that the microbiota not only has its own unique sensitive period, during which time it can be shaped by early environments (including adversity), but that it may also act as a regulator of sensitive periods within learning and memory systems. Indeed, a theory was recently put forward which suggests that the microbiota may be best thought of as a species-expected environmental input required for development [23•]. In other words, similar to the way that light is an expected input which guides neuronal development in the young visual cortex [2], and parental care is an expected input for the development of learning and memory systems [63] and the microbiota [64], the microbiota itself appears to be an expected input for the development of the entire MGB axis, as well as for the development of learning and memory systems (as we have seen here). This is an important idea as it suggests that several biological systems (both central and peripheral) may exert independent and interactive effects on the maturation of learning and memory, and moreover, that the stage of development of the MGB axis is a critical consideration when attempting to understand learning and memory behavior (see Figure 2). Indeed, the growing appreciation that there are 'nested sensitive periods' (i.e. occurring simultaneously within central and peripheral circuits) could occasion a 'new wave' of thinking in the field. Recognizing the complex forces acting on learning and memory behavior, this 'new wave' of research would favor investigations designed to understand complexity (which include mapping multiple biological systems and their interacting temporal dynamics across many stages of development). Such a focus will not only enhance our understanding of the complex mechanisms underlying our behavior, but may also catalyze a therapeutic breakthrough, expanding treatment and intervention targets to those that exist outside of our central nervous system.

Funding

Funding for this work was provided by grants from the National Institutes of Mental Health, and the Brain Behavior Research Foundation.

Conflict of interest statement

Nothing declared.

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