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REVIEW

Modulation of Aversive Memory by Adult Hippocampal Neurogenesis

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Abstract Adult hippocampal neurogenesis (AHN) occurs in humans and every other mammalian species examined. Evidence that AHN is stimulated by a variety of treatments and behaviors with anxiolytic properties has sparked interest in harnessing AHN to treat anxiety disorders. However, relatively little is known about the mechanisms through which AHN modulates fear and anxiety. In this review, we consider evidence that AHN modulates fear and anxiety by altering the processing of and memory for traumatic experiences. Based on studies of the role of AHN in Pavlovian fear conditioning, we conclude that AHN modulates the consequences of aversive experience by influencing 1) the efficiency of hippocampus-dependent memory acquisition; 2) generalization of hippocampal fear memories; 3) long-term retention of hippocampal aversive memories; and 4) the nonassociative effects of acute aversive experience. The preclinical literature suggests that stimulation of AHN is likely to have therapeutically relevant consequences, including reduced generalization and long-term retention of aversive memories. However, the literature also identifies four caveats that must be addressed if AHN-based therapies are to achieve therapeutic benefits without significant side effects.

Keywords Adult neurogenesis · Hippocampus · Anxiety · Fear · Depression · Dentate gyrus · Rodent · Behavior · Phobia

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Introduction

Neurons are born in the dentate gyrus (DG) of the hippocampal formation throughout the life of virtually all mammalian species studied to date, including rodents [1], new- [2, 3] and old-world [2, 4] primates, and humans [5, 6]. The rate of adult hippocampal neurogenesis (AHN) is substantial. In the young rat, it is estimated that 9000 cells are born each day in the DG [1]. The majority of these cells differentiate into granule cells, the only neuronal cell produced in the adult hippocampus [7]. The probability of an adult-born neuron surviving for the long term varies greatly depending on the behavioral status of the animal, but under standard laboratory conditions the number of granule cells added each month is equal to 6% of the mature granule cell population [1]. Although the rate of AHN appears to be somewhat lower in primates than in rodents, the more protracted maturational time-course of primate neurogenesis (meaning that primate newborn neurons stay younger for longer) [8] may mean that the functional impact of AHN could be similar in primates and rodents [6].

Given its substantial rate and its conservation across mammalian species from mice to humans despite the metabolic costs, it is likely that neurogenesis contributes to hippocampal circuits in a functionally significant way. Indeed, evidence from human patients and rodent models suggests that AHN is important to mental health. Behaviors associated with cognitive and emotional fitness, such as physical [9] and cognitive [10, 11] exercise or interacting with an enriched environment [12–15], stimulate AHN. Conversely, chronic stress [16–18] and aging [19–21] are associated with reduced AHN. Studies in both human patients and rodents suggest that depression is also associated with reduced neurogenesis [22, 23], whereas antidepressant treatments from multiple different classes stimulate neurogenesis through effects on both the progenitor

population and the survival rate of the newborn neurons [24–27]. Blocking neurogenesis abrogates some of the behavioral effects of antidepressant drugs in animal models [17, 28–30], which has led to the theory that antidepressant treatments act, at least in part, by stimulating AHN [26, 31].

Although a large literature has emerged suggesting that modulation of AHN contributes to both the etiology and treatment of mood and anxiety disorders [32–35], the psychological and neural mechanisms of this contribution are poorly understood. One view that has gained traction in recent years is that adult-born neurons influence mood and anxiety by affecting the processing of aversive experiences, including how these experiences are remembered, and when and how aversive memories are retrieved. This view comports well with evidence that neurogenesis-dependent effects of antidepressant treatments are very sensitively detected in tasks that place animals in aversive or anxiogenic situations [17, 36]. Moreover, there is now extensive direct evidence that AHN modulates memory for traumatic events. In this paper, we will focus on this growing body of evidence. Specifically, we will critically review recent work suggesting that alterations to AHN modify the long-term effects of traumatic experience, including the strength and persistence of Pavlovian conditioned fear, the specificity of fear memory, and the nonassociative learning resulting from aversive experiences. It is our view that this literature provides fundamental insights into the mechanisms through which AHN is likely to affect the risk for and treatment of anxiety disorders such as posttraumatic stress disorder (PTSD), phobias, and generalized anxiety. Furthermore, the work identifies potential opportunities and challenges associated with developing therapeutics that target AHN.

Trauma, Fear, and Anxiety

Traumatic experiences cause long-lasting changes in thought and behavior. These changes can be adaptive, such as when one learns to avoid a dangerous person or place. But changes can also be maladaptive. Anxiety disorders are among the most prevalent psychological disorders, affecting almost 18% of the US adult population [37]. Symptoms are frequently precipitated or exacerbated by a traumatic or intensely stressful experience [38, 39]. For instance, agoraphobia—fear of public spaces—can, in some cases, be traced to the experience of a panic attack in a public space [40]. Many patients with social phobia report having experienced severe teasing during childhood [41]. PTSD was diagnosed in as many as 17% of US soldiers returning from combat in Iraq and Afghanistan [42]. These cases illustrate the importance of understanding the mechanisms through which traumatic experiences influence the brain and behavior.

One way in which traumatic experiences cause long-lasting changes in behavior is through Pavlovian conditioning. The aversive event serves as an unconditioned stimulus (US), and other cues present during the event become conditioned stimuli (CSs). By virtue of their association with the traumatic event, the CSs acquire the ability to evoke aversive psychological states such as fear and anxiety. As we will discuss further below, although Pavlovian conditioning is not the only mechanism through which traumatic experiences cause long-lasting behavioral effects, it can account for a wide range of clinical phenomena [38, 39].

From an ethological perspective, fear and anxiety are viewed as representing defensive responses that prepare an animal for an expected threat. According to one prominent theory, fear and anxiety are unique responses that are adapted to threats differing in physical or temporal imminence [43, 44]. Proximal threats, such as a predator that has come into view, evoke active defensive behaviors—such as freezing or attempts to escape—that are typically characterized as reflecting fear [45]. Less imminent threats, such as when a predator is expected but not observed, cause the suppression of nonaversive behaviors, such as foraging or pursuing a mate—behaviors that, if continued, would increase the likelihood of encountering a predator. In rodents, anxiety-like behavior is often operationalized as the suppression of nonaversive behaviors. For instance, standard tests of anxiety-like behavior, such as the open field, elevated plus, or light/dark box all assess the conflict between remaining in an enclosed, safe space versus exploring an unfamiliar environment that might contain food or a mate. Fear and anxiety can be evoked by stimuli with innate threat value (e.g., predator odors or sounds), as well as by CSs that acquire threat value after having been paired with aversive events [46, 47].

The mechanisms through which fear and anxiety responses are learned have been investigated extensively in rodents using Pavlovian fear conditioning. In fear conditioning, an animal receives pairings of a neutral stimulus and an aversive stimulus (the US)—usually an electrical footshock. As a result, the neutral stimulus becomes a CS with the ability to elicit fear responses on its own. For instance, after receiving a few trials in which a tone co-terminates with footshock, rodents will exhibit fear behaviors such as freezing upon hearing the tone by itself. Human patients with anxiety disorders exhibit abnormalities when trained in laboratory-based fear conditioning paradigms [48–53], supporting the idea that these tasks capture clinically relevant learning mechanisms.

The neural mechanisms of fear conditioning include both cortical and subcortical contributions. Key sites of plasticity are the basolateral nuclei of the amgydala, which integrate pain (US) and neutral sensory (CS) inputs [54]. Associative plasticity in these nuclei appears to endow the CS with the ability to evoke fear and anxiety-like conditioned responses. Conditioned responses are mediated through projections from

the basolateral amygdala to the central nucleus of the amygdala (CeA) and the bed nucleus of the stria terminalis (BNST), which, in turn, activate a host of behavioral and physiological responses through projections to various subcortical targets. The projections to CeA and BNST have been hypothesized to differentially mediate defensive responses to CSs predicting immediate versus delayed threats [55], perhaps meaning that CeA controls fear, whereas BNST controls anxiety [56, 57]. When the CS in fear conditioning is a discrete unimodal cue, such as the sounding of a tone or the illumination of a light bulb, these subcortical mechanisms appear sufficient to support fear conditioning. However, when the CS is a more complex multimodal cue, cortical mechanisms, and particularly the hippocampus, are often required [58, 59].

The hippocampal contribution is evidenced in 2 common variations of fear conditioning: context and trace fear conditioning. Contextual fear conditioning (CFC) occurs when a physical environment or a context serves as a CS. The hippocampus is believed to be required for generating a "conjunctive" memory representation of the context—that is, a memory representation conjoining unimodal features within the context, as well as their relations to each other [60, 61]. The hippocampus thus generates a contextual CS representation, which acquires emotional valence via hippocampal projections to the basolateral amygdala. The hippocampus contributes to both acquisition and recall of CFC [62, 63], with some exceptions (discussed below). CFC can be acquired very rapidly; a single-trial context-shock pairing can produce fear memory lasting for many months, leading some to propose CFC as a model of episodic memory [64, 65]. The other common form of hippocampus-dependent fear conditioning, trace conditioning, occurs when a temporal gap ("trace interval") is interposed between the offset of the CS and onset of the US. Hippocampal lesions impair both the acquisition and expression of trace fear conditioning, possibly because the hippocampus is required for maintaining a memory trace of the CS during the trace interval [66–70], although other explanations have been proposed [71, 72].

AHN Contributes to Hippocampus-dependent Forms of Fear Conditioning

The first evidence linking AHN to traumatic memory came from studies in rodents in which ablation of AHN was reported to impair performance in context and trace fear conditioning. Both findings were initially obtained using rather nonspecific ablation methods such as low-dose X-irradiation or systemic administration of antimitotic drugs [73–77], but they have since been replicated using more precise interventions. Our laboratory recently developed a transgenic mouse in which immature neurons can be inducibly ablated in the adult mouse brain [78]. This method affords the ability to arrest adult neurogenesis (in both the hippocampus and subventricular zone) without impairing the production of glia or the survival of terminally differentiated neurons and glia. Using this system, we found that neurogenesis-arrested mice acquired less fear of the trace-trained tone than did control mice, confirming that suppression of adult neurogenesis impairs acquisition of trace fear conditioning. Other recent studies demonstrated that highly specific optogenetic silencing of adult-born hippocampal neurons impairs acquisition [79] and expression [80] of CFC. The recent work suggests that impairments in trace and contextual fear conditioning after neurogenesis ablation are related to the loss of adult neurogenesis rather than to side effects of the ablation methods.

However, the requirement of adult neurogenesis in these tasks is not absolute. The literature contains numerous reports in which suppression of neurogenesis was not associated with impaired trace conditioning [81, 82] or CFC [77, 83–85]. Indeed, a recent meta-analysis [86] revealed significant heterogeneity among 37 published studies on the effects of neurogenesis ablation in CFC. Across studies, the effect of neurogenesis ablation approached but failed to reach statistical significance. This lack of consistency suggests (pessimistically) that the effect of neurogenesis ablation on CFC could be spurious or (more optimistically) that the effect is subject to modulation by procedural factors.

In fact, the meta-analysis did not account for procedural factors likely to modulate the effect of neurogenesis ablation on CFC. For instance, one factor likely to be of importance is the extent of training. Although CFC is typically considered to be a hippocampus-dependent task, it has long been known that CFC can be acquired in the absence of a functioning hippocampus [60, 63, 87]. When the hippocampus is lesioned prior to CFC training, animals often acquire normal levels of contextual fear, presumably because extra-hippocampal learning mechanisms can compensate. However, extra-hippocampal learning mechanisms appear to be less suited to rapid learning than the hippocampus. When CFC training involves only a single trial (i.e., a single context- shock pairing), both pre- and post-training lesions impair CFC, whereas multiple-trial CFC is sensitive to post-training but not pre-training hippocampal lesions [88]. These findings suggest that the hippocampus is the default learning mechanism for CFC, but CFC can, nonetheless, be acquired in the absence of a functioning hippocampus if sufficient training is provided.

The neurogenesis-dependence of CFC may be governed by similar principles. Using low-dose irradiation to arrest adult neurogenesis in hippocampus, Drew et al. [75] demonstrated that pretraining ablation of neurogenesis impairs single- but not multiple-shock CFC. The differences between single- and multiple-shock CFC were not attributable to the final level of conditioned fear produced, as multiple-trial CFC was insensitive to neurogenesis ablation even when the shock intensity was adjusted to equate fear between single- and multiple-shock procedures. Furthermore, the effects of neurogenesis

ablation on CFC could be abolished by providing mice with additional context exposure prior to the context-shock pairing. Neurogenesis ablation had no effect on tone fear, consistent with lesion studies indicating that tone fear does not require the hippocampus [59, 89]. These findings have 2 important implications. First, the absence of ablation-induced effects on multiple-shock and tone fear suggests that adult neurogenesis contributes to context memory but not to conditioned fear itself. This is consistent with an idea developed by Fanselow and Rudy [87, 90], namely, that the role of the hippocampus in CFC is to build a mnemonic representation of the context, whereas the emotional valence assigned to the context arises not within the hippocampus itself but through hippocampal interactions with the amygdala. The second key implication is that adult-born neurons may be particularly important for rapid context learning. In the Drew et al. [75] study, providing an extra 197 s of context exposure prior to the context-shock pairing abolished the effect of neurogenesis ablation. Providing additional context exposure (without additional shocks) does not, however, abolish the effects of a nonspecific hippocampus lesion [88]. These data suggest that rapid-context learning within the hippocampus depends critically on adult-born neurons [91].

Why are adult-born neurons required for CFC? To answer this question, one must consider that AHN does not merely add cells to the existing population of granule neurons; rather, it maintains a transient and distinct population of excitable, highly plastic young cells. A postmitotic neuroblast requires approximately 2 months to develop into a fully mature granule neuron. During this period of development, the young neuron progresses through a series of stages in which it exhibits unique properties relative to mature granule cells. In the first weeks after mitosis, neurons in the DG are excited by γ-aminobutyric acid (GABA) rather than inhibited, owing to their high intracellular chloride concentration [92]. Perhaps as a result, these cells appear able to undergo long-term potentiation (LTP) under conditions of strong GABA-ergic activity, conditions that block LTP in mature neurons [73, 93, 94]. By ~4 weeks after their birth, adult-born neurons have developed inputs and outputs [95, 96], and their dendrites undergo a period of over-branching [97]. In weeks 4 to 6 after their birth, adult-born granule cells exhibit a reduced threshold for LTP induction and a larger LTP magnitude relative to mature neurons [92, 98]. These properties are related to the activation of T-type Ca^{2+} channels [98] and the presence of elevated levels of NR2B-containing *N*-methyl-D-aspartate (NMDA) receptors [92]. The increased excitability of young granule cells appears to be balanced by low excitatory innervation, which maintains sparseness of activity even in this highly excitable population [99–101]. By 6 weeks after their birth, their dendrites have undergone extensive pruning, consistent with having become fully integrated [97]. These findings illustrate that adult neurogenesis is a process in which discrete time windows are associated with unique functional properties.

These unique properties might be key to the contribution of adult-born neurons to CFC. Blocking neurogenesis may impact behavior not because it eliminates the addition of new mature granule cells, but rather because it deprives the hippocampus of young neurons with special properties. Because low-dose cranial irradiation kills neural progenitor cells but not terminally differentiated neurons [102–104], we were able to estimate the age at which adult-born neurons begin to contribute to CFC [91]. We did so by conducting CFC in different groups of mice at 4, 6, or 8 weeks after irradiation. The impairment in CFC arose between 4 and 6 weeks after irradiation, suggesting that the impairment is caused specifically by the absence of 4- to 6-week-old neurons. In another study [80], a retrovirus was used to selectively transduce dividing progenitors with the inhibitory opsin archaerhodopsin-3 (Arch). Importantly, the retrovirus transduces only those cells dividing at the time of the virus injection, which has the effect of producing a single age-matched cohort of adult-born neurons expressing Arch. When mice were trained in CFC or Morris water maze 4 weeks after retroviral transduction, Arch-mediated silencing of the transduced neurons impaired expression of the learning. However, when training occurred 8 weeks after transduction, there was no effect of silencing. The data suggest that 4-week-old adult-born neurons preferentially contribute to memory formation compared with their younger or more mature counterparts.

One attractive possibility is that young adult-born neurons are preferentially recruited into memory networks by virtue of their increased excitability and plasticity [105]. According to one hypothesis, young granule cells are recruited into memory networks while in an immature highly plastic stage, and as these cells mature, the corresponding decline in plasticity favors memory maintenance and protection from interference by new experiences [106, 107]. Studies of developmentally-generated neurons in the hippocampus and amygdala suggest that elevating intrinsic excitability can, in fact, increase the likelihood that a neuron is recruited into a memory network [108–111].

However, *in vivo* studies of adult-born neuron recruitment into memory networks have yielded conflicting evidence. Several studies used thymidine analogs to birthdate and tag developmentally- or adult-born neurons at different time points prior to training in the Morris water maze, a hippocampus-dependent memory task. Immediate-early gene (IEG) assays were then used to characterize activation of the tagged cells during maze acquisition or subsequent recall. Such learning tasks appear to suppress IEG expression in adult-born neurons less than 4 weeks of age, suggesting that cells at this age are unlikely to be recruited into memory networks [112, 113]. Consistent with the previously discussed time-course of new neuron

differentiation and circuit integration, task-related activation of adult-born neurons reached a maximum by about 1 month after cell birth [114]. However, studies have reached different conclusions on whether the activity of more mature adult-born neurons differs from that of developmentally-born neurons. In one study in rats, water maze-evoked IEG expression in 4-month-old adult-born neurons greatly exceeded that of 2- or 4-month-old developmentally-generated neurons [115]. In contrast, another study in mice found that water maze-evoked activity of 2-month-old adult-born neurons did not differ from that of developmentally-generated neurons of the same age [114]. It seems unlikely that the discrepancy between these 2 studies reflects differences in activity between 2- and 4-month-old adult-born neurons. Snyder et al. [116] explicitly compared water maze-evoked activity in adult-born neurons ranging in age from 1 to 10 weeks in both mice and rats. Maze-evoked IEG expression was significantly higher in rats than in mice. In both species, activity peaked at 3 weeks of age and declined or stayed the same thereafter. This peak in maze-evoked IEG expression was significantly higher in rats than in mice, suggesting that behavioral recruitment of adult-born neurons, at least in the Morris water maze, is more significant in rats than in mice, and potentially accounting for differences between the Stone and Tronel results. In summary, *in vivo* IEG studies provide some support for the idea that young adult-born neurons are more responsive to behavioral stimulation than are developmentally-generated neurons. This observation could mean that adult-born neurons are more readily recruited into memory networks than their developmentally-generated counterparts, or it may simply reflect the fact that the former population is more excitable.

An alternative hypothesis about the contribution of adult-born neurons to memory is that these cells regulate local neural activity but do not directly code remembered information [117–119]. The place fields of young adult-born neurons are slightly but significantly less spatially selective than those of their developmentally-generated counterparts [120, 121], suggesting that adult-born neurons may be less suited for coding spatial information. In addition, ablation of adult neurogenesis alters excitability within the DG [118, 122], susceptibility to seizures [122], and coordinated network activity [119], suggesting that adult-born neurons play a role in regulating the strong inhibitory tone necessary for sparse coding within DG. Consistent with this idea, optogenetic activation of young adult-born neurons drives activity in interneurons in both the DG and CA3 [95, 123]. One weakness of these studies is that the effect of AHN ablation was not compared with the effect of ablating a population of developmentally-generated neurons of equivalent size. Thus, it has not been established that the apparent role of adult-born in regulating DG activity is a unique one. Nevertheless, the hypothesis that AHN modulates memory performance by regulating DG activity is worthy of consideration and further study.

In summary, an extensive literature has emerged documenting a role for AHN in modulating hippocampus-dependent versions of fear conditioning. The role of AHN, however, is limited. Fear conditioning tasks requiring rapid context learning may be more sensitive to manipulations of AHN than tasks permitting more gradual context learning. The role of AHN in fear conditioning also appears to relate more to context memory than to fear processing *per se*. That is, AHN appears to support memory for the place in which an aversive event occurs but not necessarily the assignment of emotional valence to the memory. Studies of the role of AHN in fear learning highlight two important considerations for the design of clinical interventions targeting AHN. First, such manipulations are likely to have mnemonic effects outside of the emotional domain, a conclusion that is supported by numerous studies on the role of AHN in non-fear-based mnemonic tasks [91, 124–127]. A related point is that at least some of the emotional effects of manipulating AHN are likely to be indirect, in that they are mediated through more general changes in memory function. That is to say, the effect on fear learning of perturbing AHN may be akin to the effects of hippocampal lesions, which abolish CFC by impairing memory for the feared context rather than by impairing fear itself. Finally, evidence that AHN is required for efficient acquisition of hippocampal fear memories may mean that manipulations that enhance AHN will have the unintended consequence of enhancing the formation of fear memories rather than weakening them.

AHN Modulates Memory Maintenance

A key remaining question about the role of AHN in fear learning regards fear expression. The research reviewed above indicates that AHN supports acquisition of new memories, but are adult-born neurons also required for maintenance or expression of memories? And, if so, is the role of adult-born neurons in retrieval limited to memories acquired during their (the neuron's) lifetime? Of two recent studies to specifically address the role of adult-born neurons in expression of context-evoked fear, both found that adult-born neurons contribute to CFC retrieval. Post-training ablation of adult-born neurons 6 weeks old and younger impaired the specificity of context fear expression [128], and optogenetic silencing of 4-week-old adult-born neurons impaired the expression of context-evoked fear [80]. Our own laboratory has replicated the latter effect using Arch to silence young adult-born neurons specifically during CFC expression (unpublished data).

What is the nature of this contribution? Context memory is believed to be mediated by the activity of discrete context-specific neuronal ensembles within hippocampus [129–133]. Adult-born neurons may be required for CFC retrieval because they constitute a significant component of the memory-encoding ensemble (the "engram"). Alternatively, as

previously discussed, adult-born neurons might modulate the behavior of other cells that participate in the memory ensemble [117]. These different mechanisms have potentially important behavioral implications. If adult-born neurons participate in the memory ensemble, then their role in retrieval should be limited, in that adult-born neurons should modulate retrieval only of those memories acquired during their lifetime or during some fraction of their lifetime. On the other hand, if the primary function of adult-born neurons is to modulate behavior of other neuronal populations, the role of adult-born neurons in retrieval could be very broad. If the former, therapeutic manipulations targeting AHN may alter only those memories acquired during treatment, but if the latter, these manipulations may also modulate memories formed prior to treatment.

Recent evidence suggests that AHN manipulations could have very interesting, and potentially very broad, effects on memory retention in the hippocampus and may contribute to the hippocampus' status as a temporary memory store. The idea that the hippocampus is a temporary memory store derives originally from seminal studies of patient H.M., whose temporal lobes (including hippocampi) were resected bilaterally in treatment of severe epilepsy [134, 135]. One of H.M.'s subsequent symptoms was temporally graded retrograde amnesia. He could not remember events from the years immediately preceding his temporal lobe resection, but he could remember information about childhood events that occurred many years prior to the surgery. This apparent shift in the hippocampus-dependence of memories ("systems consolidation") has since been modeled in rodents using CFC [59, 62]. Lesions to the hippocampus impair retrieval of recent context fear memories acquired 7 days prior to the lesion but not "remote" context fear memories acquired 30 days prior to the lesion. The shift from hippocampus-dependence to hippocampus-independence is accompanied by a shift in memory quality [136]. Remote context fear memories are less precise than recent ones, in that remote context fear more readily generalizes to contexts other than the training context. A lack of precision was also observed in remote memories of patient H.M. [137]. Findings like these have led to the idea that the hippocampus is necessary for acquisition of declarative (and contextual) memory, but over time, neocortical memory traces become strengthened and can eventually support memory retrieval in the absence of a functioning hippocampus (see also [138]).

Several theoretical models posit that the addition of neurons to the hippocampus destabilizes existing memories, while simultaneously providing a substrate for encoding of new memories [139, 140]. Consistent with this theoretical work, recent studies suggest that AHN modulates maintenance of hippocampal memories. One very elegant series of studies examined the effects of increases and decreases in AHN on maintenance of contextual fear memory [141]. AHN was suppressed via x-irradiation or increased via running-wheel exercise. Mice were then trained in CFC and the hippocampus-dependence of CFC was evaluated by silencing the hippocampus during a CFC retrieval test. Manipulation of AHN bidirectionally modulated the speed with which CFC memories became hippocampus-independent. In control mice with normal AHN, CFC memory became hippocampus-independent within 28 days of training. Meanwhile, in irradiated mice, CFC memories continued being hippocampus-dependent beyond 28 days, while in running mice CFC memories were hippocampus-independent by 7 days after training. These findings suggest that the addition of neurons to the hippocampus modulates the systems consolidation process in which the control of memory retrieval and/or storage gradually migrates from the hippocampus to the neocortex.

Another recent series of experiments indicates that weakening of memory maintenance by AHN contributes to the phenomenon of infantile amnesia. A wide range of species, including humans, display amnesia for episodic memories acquired during infancy. The period of infantile amnesia coincides with a developmental stage during which hippocampal neurogenesis is very high [140, 142]. Akers et al. [143] demonstrated that infantile amnesia is not present in 2 mammalian species (degus and guinea pigs) that exhibit low AHN during infancy. Furthermore, infantile amnesia for context fear could be attenuated in mice by suppressing neurogenesis, whereas amnesia for context fear could be induced in adult mice by stimulating neurogenesis. The data are consistent with earlier computational models and experimental data suggesting that ongoing neurogenesis destabilizes hippocampal memories, thereby supporting the notion that therapeutic manipulations targeting AHN might have the capacity to modulate retention of aversive memories.

While treatments designed to stimulate AHN could have the clinical benefit of accelerating the forgetting of aversive memories, the available research suggests two important caveats. First, the effects on forgetting are not likely to be limited to aversive memories. Positive memories will presumably be lost, potentially negating some of the benefit of losing aversive memories. Second, because systems consolidation of contextual fear memory is accompanied by an increase in fear generalization [136], there is the possibility that treatments enhancing neurogenesis will increase fear generalization, which is problematic as increased fear generalization is associated with anxiety disorders (below and [49]).

AHN and Fear Generalization

The DG has long been hypothesized to perform pattern separation, which is the decorrelation of neural inputs into the hippocampus [144–146]. The DG's ability to pattern separate arises from the sparse activity of granule cells [147] and possibly also from the ability of granule cells to modulate their firing rate in response to subtle changes in the external environment [148]. These features are thought to facilitate the

ability of the DG to assign unique population codes to different memories [149] and thereby reduce memory interference during pattern completion in CA3.

Tasks that require animals to distinguish among very similar stimuli appear to be highly sensitive to disruptions of the DG and its presumed pattern separation function. A now-classic series of experiments by Gilbert et al. used a location-discrimination task in which rats could find food in either of 2 locations [146]. Task difficulty was manipulated by varying the distance between the correct and incorrect locations. Lesions to the DG impaired performance when the locations were very close together but not when they were far apart, suggesting that DG pattern separation was necessary for discriminating between very similar spatial locations but not when spatial locations were quite different.

Suppression of AHN appears to compromise DG pattern separation. Frankland and colleagues showed that suppression of AHN reduced the extent to which 2 similar contexts activated unique neuronal ensembles in CA3 [150]. That is, in mice with suppressed AHN, the probability of an individual CA3 neuron being active in both contexts was increased. This apparent impairment of neural context coding was associated with increased fear generalization between the two similar contexts. Overgeneralization has also been shown in context fear generalization tasks, in which rodents receive alternating exposures to two similar conditioning chambers with footshocks administered in one but not the other. Rodents typically acquire a discrimination, such that fear responses are stronger in the shock context than the non-shock context. Suppression of adult neurogenesis [85, 151–153], optogenetic silencing of young adult-born neurons [120], or disrupting the plasticity of adult-born neurons [154] increase generalization between the fear and neutral contexts. Adult-born neurons appear to be necessary for the acquisition of discriminated fear but not for its expression, as optogenetic silencing of adult-born neurons only after the discrimination has been acquired does not impair the discrimination [120].

If suppressing AHN impairs context discrimination, it may follow that enhancing AHN improves it. Using a novel strategy to block apoptosis of newborn granule cells, Sahay and colleagues [151] investigated the clinically important question of whether increasing AHN enhances the specificity of fear memory. The pro-apoptotic gene *Bax* was selectively deleted in neural progenitor cells using an inducible Nestin–CreERT2 line. After induction of the deletion, the apoptosis rate among newly generated neurons was greatly diminished, leading to more than a doubling of the number of newborn neurons surviving for at least one month. Although CFC acquisition was normal in the mice with enhanced AHN, the mice displayed enhanced context fear discrimination, suggesting that increasing AHN enhances specificity of fear memory.

The apparent support of pattern separation by AHN seems paradoxical. If pattern separation in DG depends on the sparse activity of granule cells, why would the presence of young neurons with increased excitability support pattern separation? Recent findings provide two potential answers. First, as noted above, the increased intrinsic excitability of young granule cells is balanced by low excitatory innervation [101]. As a result, activation of entorhinal inputs actually produces less spiking in young than mature granule cells. In addition, during their period of elevated intrinsic excitability, immature adult-born granule cells preferentially activate inhibitory interneurons in CA3 [95]. Within the DG, activation of young adult-born cells may similarly recruit inhibitory interneurons, as increasing AHN via *Bax* deletion reduces DG population activity evoked by entorhinal stimulation [118]. Furthermore, as previously mentioned, optogenetic stimulation of young adult-born neurons drives activity in DG and CA3 interneurons [95, 123]. Thus, young adult-born neurons may enforce sparse activity in hippocampus rather than undermine it [155].

Studies of the role of AHN in context fear generalization have several important implications for therapeutic use of AHN. The ability to limit expression of fear memories to appropriate contexts is obviously adaptive. Overgeneralization of fear is present in anxiety disorders such as PTSD and social anxiety (reviewed in [33]). As such, treatments that limit generalization may be valuable. However, the preclinical work reviewed above identifies two potential limitations associated with use of AHN to modulate fear generalization. As shown by Danielson et al. [120], adult-born neurons appear to modulate the acquisition of a discriminated fear memory but not the expression of an established fear memory. Thus, treatments targeting AHN may fail to ameliorate anxiety disorders stemming from aversive experiences occurring before the treatment. Second, there is evidence that suppression of AHN affects the specificity of memories involving reward, such as memory for the location of a food pellet or a rewarded spatial discrimination [124, 125]. Thus, therapeutic enhancement of AHN may decrease generalization of both negative and positive memories. The under-generalization of positive memories may counterbalance any improvement in symptoms resulting from the increased specificity of aversive memories.

Modulation of Nonassociative Fear Learning by AHN

As the research detailed above illustrates, the long-lasting effects of aversive experience are commonly studied using Pavlovian fear conditioning, which focuses on the acquisition of aversive valence by specific CSs. In addition to producing Pavlovian conditioning, traumatic experiences can cause generalized changes in fear and anxiety that are not tied to a particular CS. “Nonassociative” learning of this nature was famously documented in Kandel’s seminal studies in the mollusk *Aplysia californica* [156, 157]. Kandel and colleagues showed that exposure to electrical shock alone, without

pairings with a CS, causes long-lasting enhancement of various defensive responses. For instance, in a naïve *Aplysia*, a gentle touch to the tail elicited little or no activation of the gill withdrawal defensive response. However, if the animal was given several electrical shocks, for several days afterward the gentle touch would elicit a strong gill withdrawal response. This learning was said to be nonassociative because 1) it did not require pairings between the gentle touch and the shock; and 2) the effect was a general increase in responsiveness that was manifest across multiple different defensive responses and multiple different eliciting stimuli.

In mammals, too, some of the long-term effects of traumatic experience appear to be nonassociative. Exaggerated startle responses and hypervigilence are considered hallmarks of PTSD [158]. In rodents, strong aversive experiences, such as exposure to intense footshock or to a predator, cause long-lasting increases in anxiety-like behavior and can potentiate future fear conditioning. For instance, Fanselow and colleagues [159, 160] have demonstrated that exposure to a single session of intense footshock causes a long-lasting enhancement of subsequent Pavlovian fear conditioning. These and other behavioral effects are believed to be nonassociative because 1) they can be detected in environments very different from the context of the original trauma [159, 161, 162]; 2) extinction of conditioning related to the original trauma does not abolish the sensitized responses [160, 163–165]; and 3) some neural interventions that block fear conditioning do not abolish the sensitization [166]. Thus, nonassociative sensitization is thought to be a distinct mechanism through which traumatic experiences cause long-lasting changes in fear learning and anxiety-like behavior.

AHN appears to modulate nonassociative sensitization of fear and anxiety. Seo et al. [78] used inducible expression of the suicide gene *herpes–simplex thymidine kinase (HSV-TK)* to ablate neural progenitors in adult mice. Consistent with earlier work by Wotjak and colleagues [167], Seo found that exposure to fear conditioning increased anxiety-like behavior in the open field and elevated plus maze. Interestingly, the fear conditioning-induced increase in anxiety-like behavior was larger in the neurogenesis-arrested mice than in controls. Neurogenesis-arrested and control mice did not differ in preconditioning anxiety tests, consistent with other work ([12], [36], [73], and [86], but see also [168]), nor did they differ in the level of associative fear conditioning to tone or context. The data suggest that suppression of AHN sensitized mice to nonassociative effects of fear conditioning (see also [169]).

The circuit mechanisms for AHN modulation of nonassociative fear and anxiety have not been thoroughly investigated but could involve hippocampal negative feedback modulation of corticosterone (CORT) release [170–172]. The hippocampal formation, including DG, expresses CORT receptors (glucocorticoid and mineralocorticoid) at high levels [173]. Activation of these CORT receptors supports feedback inhibition of CORT release [174, 175]. Adult-born neurons may play a role in this feedback inhibition. Although suppression of adult neurogenesis via irradiation or an inducible genetic system had no effect on baseline levels of CORT or anxiety-like behavior, these manipulations led to increases in the magnitude and duration of CORT induction after exposure to acute stressors, suggesting that hippocampal feedback inhibition was impaired [176, 177]. An exaggerated stress response was also behaviorally evident. Although acute stress had no significant effect on anxiety-like behavior in control mice, stress increased anxiety-like behavior in neurogenesis-arrested mice [176]. Arresting neurogenesis also prevents the restoration of hypothalamic–pituitary–adrenal axis function by antidepressant drugs [178].

The long-term nonassociative effects of acute stress appear to depend critically on CORT release. Blockade of CORT synthesis or of CORT receptors in the amygdala prevent stress-induced long-term sensitization of fear learning [159]. Similarly, antagonism of corticotropin-releasing factor receptors (which regulate CORT release) blocks the long-term axiogenic effects of predator exposure [179]. This work suggests that the enhancement of nonassociative stress-induced anxiety caused by the arrest of neurogenesis [78] may be mediated by increased stress-induced CORT release in neurogenesis-arrested mice.

This hyperactivity of the hypothalamic–pituitary–adrenal axis could also explain discrepancies among published reports on the effects of neurogenesis ablation on anxiety-like behavior at nominally baseline conditions. The majority of published studies report no effect of neurogenesis ablation on anxiety-like behavior in the absence of an explicit stressor [12, 28, 73, 77, 86, 151, 180]. However, a smaller number of studies report increased anxiety-like behavior in neurogenesis-arrested animals [168, 181, 182]. If neurogenesis ablation in fact increases sensitivity to stressors, this might render neurogenesis-arrested mice especially sensitive to procedures that tend to be carried out differently across labs, such as handling and transport.

The evidence reviewed in this section suggests that treatments enhancing AHN might enhance stress resilience. Preclinical studies provide some support for this notion. In mice, chronic administration of exogenous CORT increases anxiety-like and depressive-like behavior and suppresses AHN. These effects can be reversed by treatment with antidepressant drugs [17]. Similarly, exposure to chronic unpredictable stress [28, 180] increases anxiety- and depression-like behaviors and suppresses AHN, and these effects can be prevented via treatment with antidepressant drugs. Blocking AHN in mice abrogates the effects of monoaminergic antidepressant drugs in these paradigms [17, 28, 180], supporting the hypothesis that the therapeutic effects of these drugs require AHN. Still, these studies leave open the question of whether stimulation of AHN is, by itself, sufficient to enhance stress resilience. A recent study using inducible *Bax* deletion suggests that it may be sufficient. Hill et al [36] used *Bax*

deletion to prevent apoptosis of adult-born neurons during chronic CORT treatment. *Bax* deletion was successful in preventing the suppression of AHN by CORT. The effects of CORT on anxiety- and depression-like behavior were also abolished in the *Bax*-deleted mice. Because the *Bax* deletion was specific to neural progenitor cells, the results of this study suggest that AHN-enhancing drugs may be effective as treatments for stress-related psychiatric conditions.

Conclusions

Since the first studies over 15 years ago evidencing causal links between AHN and behavior [76, 183], there has been an explosion of research on the contributions of AHN to a variety of behaviors and psychological processes. The resulting literature is complex and sometimes contradictory but unambiguously favors the conclusion that AHN influences hippocampal function in significant ways. The contributions of AHN to fear and anxiety reviewed here encourage exploration of AHN as a therapeutic target. However, the literature also suggests that therapies targeting AHN are destined to have pleiotropic effects. The pleiotropy of AHN manipulations may be the biggest challenge as AHN-targeting therapies are sought.

Studies using fear conditioning have identified 4 mechanisms through which AHN modulates the impact of trauma (Table 1). These mechanisms suggest several ways in which manipulation of AHN is likely to be clinically useful. Treatments that enhance AHN have the potential to speed the forgetting of fear memories, reduce the generalization of fear memories, and reduce the nonassociative anxiety that can result from exposure to trauma. However, the preclinical work discussed here also identifies several significant hurdles that must be overcome if AHN-based therapies are to achieve therapeutic benefits without significant side effects.

AHN contributions to memory are not valence-specific The hippocampal contributions to episodic, spatial, and contextual memory are independent of the emotional valence of those memories. In CFC for instance, the hippocampus appears to form a conjunctive representation of the context in which the shock occurred, but a hippocampal contextual memory is formed regardless of whether a shock is delivered [184]. The hippocampus also contributes to memory for reward contexts [185]. Thus, AHN-based therapies intended to target maladaptive fear and anxiety are likely to impact neutral and positive memories as well. While enhancing forgetting may be of value with respect to aversive memories, the loss of positive or neutral hippocampal memories would be problematic. Similarly, although enhanced specificity of a fear memory might be desirable, reduced generalization of positive or even neutral memories could prove problematic.

AHN manipulations are likely to affect only a limited domain of fear and anxiety phenomena Real-world traumatic memories are likely to involve multiple CSs, some of which require hippocampal processing and some of which do not. For instance, in PTSD, traumatic memories can be evoked by unimodal stimuli such as loud noises or odors. Specific phobias frequently involve non-contextual CSs such as snakes or spiders. Given that hippocampal manipulations typically do not affect fear conditioning with simple, discrete CSs, it is doubtful that AHN manipulations would influence fears of this nature. Furthermore, evidence that CFC can be rendered insensitive to AHN depletion by context pre-exposure or extended training suggests that AHN-based treatments may be relatively ineffectual for fears arising from repeated trauma or those occurring in familiar places.

AHN manipulations may have limited impact on aversive memories acquired before the start of treatment The time-limited role of the hippocampus in retrieval and maintenance of contextual and other memories calls into question whether AHN manipulations can influence memories acquired prior to the manipulation. The contribution of AHN to the acquisition of precise, discriminated context fear memories appears to relate primarily to memory acquisition, as silencing adult-born neurons after acquisition fails to affect contextual fear discrimination. This finding suggests that stimulating AHN will enhance the specificity of memories acquired after treatment initiation, but not of those acquired before.

On the other hand, it may be possible to render previously acquired memories sensitive to AHN manipulations. Remote contextual fear memories can be returned to hippocampus dependence through a reminder trial in which rodents are re-exposed to the context without shock. Ishikawa et al. [186] took advantage of this procedure to render remote contextual fear sensitive to neurogenesis-dependent forgetting. Increasing AHN via treatment with the drug memantine promoted forgetting of a remote context fear memory when a reminder trial was given prior to drug treatment but not when the reminder trial was omitted. This study suggests that the effectiveness of pro-neurogenic therapies might be enhanced when coupled with exposure therapy.

Designing AHN-based Therapies

AHN is a complex sequence of interacting events, seemingly offering a variety of potential interventional targets. It is beyond the scope of this article to discuss interventional strategies in detail, and these have been reviewed previously [26, 35]. However, we wish to briefly highlight a few aspects of the AHN process that may be relevant as researchers seek to devise therapeutic strategies that achieve desired clinical

Table 1 Effects of adult hippocampal neurogenesis (AHN) perturbations on aversive memory

	Fear memory acquisition	Fear memory specificity	Memory retention	Nonassociative fear/anxiety
Findings	Suppression of AHN disrupts acquisition of Pavlovian contextual and trace fear.	Decreases and increases in AHN Bidirectionally modulate generalization of context fear.	Decreases and increases in AHN Bidirectionally modulate retention and/or systems consolidation of hippocampal memories	Suppression of AHN increases the CORT induction caused by acute stress and the sensitization of anxiety-like behavior caused by acute stress
Conclusions	AHN supports the acquisition of precise hippocampal memories.		Integration of new neurons destabilizes hippocampal memory representations.	AHN buffers the physiological and behavioral responses to acute stress
Clinical Implications	Stimulating AHN might enhance acquisition of hippocampusdependent fear memories.	Stimulating AHN might enhance the specificity of fear memories and reduce fear generalization.	Stimulating AHN might speed the forgetting of traumatic memories.	Stimulating AHN could reduce the nonassociative anxiety resulting from trauma.
Additional Considerations	In rodent models, AHN manipulations do not influence hippocampus-independent forms of fear memory, such as fear conditioning with simple, unimodal CSs. Thus, AHN-based therapies may influence only a limited domain of learned fear and anxiety responses. Generalization of fear typically increases with time as memories become hippocampus-independent. Stimulating AHN post-trauma might enhance systems consolidation of the traumatic memory and increase generalization of fear. AHN manipulations are not valence-specific. Modulating AHN may alter acquisition and/or generalization of positive or neutral memories.			Do these effects reflect changes in threat processing/memory, or more direct changes in neurohormone regulation?

CORT corticosterone, *CS* conditioned stimulus

outcomes while minimizing the potential side effects discussed above.

Dorsal versus Ventral AHN One distinction that deserves attention is the functional dissociation between dorsal/septal and ventral/temporal hippocampus. The dorsal hippocampus has strong projections to areas involved in visuospatial processing, navigation, and memory [187–189] and contains more precise spatial representations [190, 191]. Ventral hippocampus is more strongly associated with limbic structures such as the amygdala and hypothalamus [170, 171, 187]. Dorsal but not ventral hippocampal lesions cause robust spatial deficits [192, 193], whereas ventral but not dorsal lesions alter anxiety-like behavior [192–195]. Focal irradiation of the dorsal versus ventral hippocampus revealed that dorsal but not ventral adult-born neurons contribute to context fear discrimination, whereas ventral but not dorsal adult-born neurons are necessary for the anxiolytic effects of antidepressant treatments [153]. The evidence suggests that the dorsal hippocampus represents a more purely "cognitive" subregion of hippocampus, whereas the ventral hippocampus is more "limbic". This apparent dissociation means that targeting clinical interventions to ventral AHN might afford the ability to influence fear and anxiety-like behavior while sparing cognitive function.

Mimicking AHN versus Stimulating it AHN does not simply add granule cells to the DG; it also produces a population of young granule cells with unique intrinsic properties and connections. Manipulations that stimulate or suppress AHN thus alter hippocampal circuits through a variety of mechanisms. It might be possible to achieve more precise effects by selectively altering the properties of existing, mature neuronal populations than by stimulating AHN. The research reviewed here suggests several strategies. Sahay and colleagues [155] have proposed that immature adult-born neurons enhance inhibitory tone within the DG, thereby supporting the ability of the DG to perform pattern separation. It may be possible to mimic the effects of AHN by selectively raising the activity level of the interneuron populations that presumably mediate the inhibitory influence of newborn granule cells. Indeed, there is evidence that increasing the activity of parvalbumin interneurons of the DG is anxiolytic in mice [196]. Alternatively, one might mimic the enhanced intrinsic excitability and plasticity of immature adult-born neurons, which are mediated, in part, by elevated expression of Ca^{2+} channels and NR2B-containing NMDA receptors. Indeed, overexpressing NR2B in the entire forebrain has been shown to enhance various forms of learning [197]. Perhaps overexpression of these channels in fully mature neurons in the dentate alone would confer some of the benefits of increased neurogenesis. Finally, there is some evidence that mature dentate granule cells can be induced to "demature"—that is, regain

some of the molecular and physiological characteristics associated with immature adult-born neurons [198]. Dematuration could potentially be harnessed to increase the effective number of "immature" neurons without the need for modulating neurogenesis. A potential concern associated with all these manipulations is that they may increase DG excitability, which could impair sparse coding and damage cognitive function [199, 200].

Manipulating Adult-Born Neurons Rather Than Neurogenesis Finally, it may be advantageous to develop treatments that selectively alter the properties of adult-born neurons themselves, rather than stimulate the production of these cells. For instance, the putative role of newborn neurons in enforcing sparse coding in the DG could be enhanced by increasing the activity of adult-born neurons. If the heightened excitability and plasticity of newborn neurons are critical to their functional impact, as has been proposed, these properties might be further enhanced using drugs with specific affinity for channels enriched in newborn neurons. For example, deletion of the NR2B NMDA receptor subunit in adult-born neurons impairs context fear discrimination and attenuates the effects of antidepressant drugs [154, 201]. Perhaps pharmacologic potentiation of NR2B activity in adult-born neurons would produce opposite effects. Strategies like these may obviate the need for restoring AHN in old age or after exposure to chronic stress; instead, the loss of AHN could be counteracted by magnifying the impact of remaining adult-born neurons.

In summary, the last 15 years have yielded considerable support for a role for AHN in aversive memory. The work identifies several mechanisms through which modulation of AHN might ameliorate psychiatric symptoms related to the experience of traumatic events. However, designing therapeutics that can achieve these benefits without significant side effects will likely require continued investigation into the cellular and circuit mechanisms underlying the effect of AHN on information processing and emotional responses.

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