

# Adult Hippocampal Neurogenesis, Fear Generalization, and Stress

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The generalization of fear is an adaptive, behavioral, and physiological response to the likelihood of threat in the environment. In contrast, the overgeneralization of fear, a cardinal feature of posttraumatic stress disorder (PTSD), manifests as inappropriate, uncontrollable expression of fear in neutral and safe environments. Overgeneralization of fear stems from impaired discrimination of safe from aversive environments or discernment of unlikely threats from those that are highly probable. In addition, the time-dependent erosion of episodic details of traumatic memories might contribute to their generalization. Understanding the neural mechanisms underlying the overgeneralization of fear will guide development of novel therapeutic strategies to combat PTSD. Here, we conceptualize generalization of fear in terms of resolution of interference between similar memories. We propose a role for a fundamental encoding mechanism, pattern separation, in the dentate gyrus (DG)–CA3 circuit in resolving interference between ambiguous or uncertain threats and in preserving episodic content of remote aversive memories in hippocampal–cortical networks. We invoke cellular-, circuit-, and systems-based mechanisms by which adult-born dentate granule cells (DGCs) modulate pattern separation to influence resolution of interference and maintain precision of remote aversive memories. We discuss evidence for how these mechanisms are affected by stress, a risk factor for PTSD, to increase memory interference and decrease precision. Using this scaffold we ideate strategies to curb overgeneralization of fear in PTSD.

*Neuropsychopharmacology Reviews* (2016) **41**, 24–44; doi:10.1038/npp.2015.167; published online 8 July 2015

## INTRODUCTION

### A Circuit-Based Approach to Understanding the Neurobiology of PTSD

The efficient processing of threatening and fearful stimuli is central to generation of adaptive behavioral and physiological responses. Inability to disambiguate safe from threatening stimuli or to calibrate physiological responses to uncertainty of threats can produce uncontrollable expression of fear, dysregulation of stress hormones, and sustained anxiety states. Exposure to traumatic events or stressful life experiences is known to tax our fear and threat processing systems. It is therefore not surprising that although the lifetime prevalence of generalized anxiety disorder (GAD) and posttraumatic stress disorder (PTSD) is between 5 and 10% in the general population (Newman *et al*, 2013; Parsons

and Ressler, 2013), the prevalence of PTSD is of greater magnitude in individuals repeatedly exposed to trauma (20–30%) (Catani *et al*, 2008; Parsons and Ressler, 2013). The relatively low prevalence of PTSD in the general population suggests that exposure to a severe traumatic event is not sufficient for its pathogenesis (Yehuda and LeDoux, 2007; Holmes and Singewald, 2013), but that genetic predisposition may be important. Seminal studies on monozygotic twins discordant for trauma exposure demonstrated that vulnerability to PTSD is explained in part (30–70%) by genetic risk (Afifi *et al*, 2010; Pitman *et al*, 2012). More recently, single-nucleotide polymorphisms in genes encoding BDNF, the serotonin transporter SERT, and the glucocorticoid chaperone protein FKBP5 (Mahan and Ressler, 2012) have been associated with increased susceptibility to PTSD. These findings have been followed up with genome-wide analysis studies that have identified a plethora of putative culpable genes for PTSD (Cornelis *et al*, 2010; Koenen *et al*, 2013). Furthermore, alterations in epigenetic mechanisms may impair the adaptive regulation of gene expression that moderates vulnerability or resilience to stressful life events (Zovkic and Sweatt, 2013; Kwapis and Wood, 2014). Indeed,

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Received 16 March 2015; revised 29 May 2015; accepted 5 June 2015; accepted article preview online 12 June 2015

epigenetic modifications observed in PTSD patients are persistent (Malan-Muller *et al*, 2014) and, intriguingly, may be transmissible through the germline across generations (Yehuda *et al*, 2014; Dias *et al*, 2015). Thus, it is now recognized that PTSD arises from an interaction of environmental factors such as stressful, traumatic life events, and genetic risk factors.

Emerging neurobiology of PTSD suggests a role for both associative and nonassociative learning mechanisms (Lissek and van Meurs, 2014). Associative learning mechanisms are thought to underlie processes such as fear inhibition (Jovanovic and Ressler, 2010), extinction (Milad and Quirk, 2012), overgeneralization (Kheirbek *et al*, 2012b; Lissek, 2012), and memory consolidation and reconsolidation (Besnard *et al*, 2012; Nader *et al*, 2013; Parsons and Ressler, 2013). In addition, associative learning may also underlie time-dependent incubation and reorganization (Pitman *et al*, 2012) of memories to produce recurrent experiencing of traumatic events through flashbacks, nightmares, intrusive thoughts, and overgeneralization of fear (Pickens *et al*, 2009; Sauerhofer *et al*, 2012). On the other hand, nonassociative learning mechanisms are thought to contribute to sensitization, resulting in exaggerated startle responses to trauma-unrelated stimuli, hypervigilance, and increased avoidance behaviors (Pitman *et al*, 2012).

The contribution of environmental factors and potentially hundreds of genetic risk factors to development of PTSD underscores the challenges of developing new treatments. One approach to this problem is to instantiate the neural circuit-based mechanisms underlying associative and non-associative learning-dependent processes theorized to occur in PTSD (Lissek and van Meurs, 2014). There are several reasons why this approach is likely to be therapeutically meaningful. First, neural circuits are the point of convergence for multitudinous genetic risk and environmental factors. Thus, measuring and targeting circuit performance is more tractable than targeting each of the putative genetic and environmental risk factors individually. Second, neural circuits of the hippocampus important for fear processing and anxiety are homologous between rodents (Gross and Canteras, 2012; Herry and Johansen, 2014; Luthi and Luscher, 2014; Tovote *et al*, 2015) and humans (Shin and Liberzon, 2010). The rich dialogue between studies probing causal roles of neural circuits underlying fear processing in preclinical models and human functional brain imaging is testament to the conservation of structure and function of neural circuits in posttraumatic psychopathology (Ressler and Mayberg, 2007; Holtzheimer and Mayberg, 2011; Milad and Quirk, 2012). Finally, characterization of circuit-based mechanisms permits generation of circuit based-endophenotypes that may be measured with high resolution and thus confer quantitative assessment and stratification of risk and treatment responses (Leboyer *et al*, 1998; Gottesman and Gould, 2003).

Here, we conceptualize fear generalization in terms of resolving interference between threats that are ambiguous or uncertain and previously encoded traumatic memories. We

begin by familiarizing the reader with studies showing hippocampal involvement in resolution of interference and maintenance of precision of remote memories. (1) We hypothesize that pattern separation in the dentate gyrus (DG) plays a pivotal role in decreasing interference between ambiguous or uncertain threats and previously stored memories and in maintaining the precision of remote traumatic memories. (2) We discuss evidence supporting a role for the DG in pattern separation in rodents and humans before evaluating the contribution of adult-born dentate granule cells (DGCs) as neural substrates of pattern separation and orchestrators of temporal decay of precision of remote memories. (3) We invoke local circuit mechanisms by which adult-born DGCs influence pattern separation and the neural pathways that link encoding functions of adult-born DGCs with adaptive fear responses. (4) These sections set the stage for understanding how stress through its effects on adult hippocampal neurogenesis affects pattern separation to produce overgeneralization of fear. (5) We conclude by leveraging our framework about how adult-born DGCs contribute to pattern separation and maintain remote memory precision to ideate novel approaches to constrain overgeneralization of fear in PTSD.

### Hippocampal Interference, Ambiguous or Uncertain Threats, and Fear Overgeneralization

In order to express fear only when it is appropriate, we have to constantly perform comparisons between previously encoded associations and what actually happens. Such a mechanism is adaptive in that it allows an individual to anticipate a potential threat by detecting relevant cues present in the environment. Efficient appraisal of threat requires disambiguation of contextual information associated with safety and threat as well as the discernment of the probability (certainty) with which a cue predicts the threat (Maren *et al*, 2013). Essential to this process is the need to decrease interference between new information and previously stored similar traumatic memories. Increased interference between new and stored memories will promote reactivation of traumatic memories and elicit inappropriate expression of fear resulting in fear overgeneralization.

Considerable evidence supports a role for the hippocampus in discrimination of similar contextual representations to constrain the overgeneralization of fear. Rats with anterograde dorsal hippocampal lesions exhibit normal levels of freezing in the conditioning context but are impaired in discriminating between similar contexts that are not associated with a foot-shock (Maren *et al*, 1997; Frankland *et al*, 1998; Antoniadis and McDonald, 2000). Genetically abolishing synaptic plasticity at perforant path-DG synapses impairs discrimination between a context in which mice were conditioned to a foot-shock and a similar, but not, distinct neutral context (McHugh *et al*, 2007). These behavioral studies allude to hippocampal-dependent mechanisms in minimizing interference between ambiguous

threats (similar, neutral context) and stored memories (training context).

The hippocampus is also implicated in resolving interference between competing goals to gate approach–avoidance behaviors (Gray and McNaughton, 2000). This ‘comparator’ function permits resolution of uncertainty and unpredictability through risk assessment (signal of punishment, signal of nonreward, novelty, innate fear stimuli) by increasing vigilance and inhibition of motor functions (behavioral inhibition, arousal, attention) (Gray and McNaughton, 2000; Bannerman *et al*, 2014). Consistent with this proposal, unpredictable shocks in a given context retard subsequent acquisition of discrete cue–fear association in the same environment (Hinson, 1982; Foa *et al*, 1992). Imaging studies in humans have suggested a role for the hippocampus in processing uncertainty of threats. The anterior hippocampus (ventral hippocampus in rodents) was found to exhibit increased BOLD (blood oxygen level dependent) responses with uncertainty of probabilistic sequential events or unpredictable shock (Strange *et al*, 2005; Alvarez *et al*, 2011). Direct evidence for hippocampal engagement in encoding probabilistic cue–outcome associations comes from a study that performed *in vivo* recordings in the hippocampus of epileptic patients while they learned to associate cues with monetary rewards. The authors found that uncertainty of reward produced the largest event-related potentials in the anterior hippocampus (Vanni-Mercier *et al*, 2009). Together, these observations suggest that levels of interference in the hippocampus may contribute to resolution of uncertain or ambiguous threats to constrain fear overgeneralization.

### Hippocampal Interference, Time-Dependent Erosion of Memory Precision, and Fear Overgeneralization

It is widely recognized that memories lose precision and details with passage of time. As such, traumatic memories when no longer bound by the conjunctive representation of the trauma will generalize to produce inappropriate expression of fear in contexts that are similar to that in which the trauma occurred. Consistently, fear generalization in contexts not associated with the shock is observed in rodents when the fear response is measured at remote time points (see, eg, Biedenkapp and Rudy, 2007; Wiltgen and Silva, 2007; Winocur *et al*, 2007; Ruediger *et al*, 2011). This unwanted cue-dependent recall of fear memory is thought to be due to changes in associative rather than nonassociative learning mechanisms (Acheson *et al*, 2012; Sauerhofer *et al*, 2012) and involves consolidation of memories in hippocampal–cortical networks.

Studies over the past two decades on the time-dependent reorganization and consolidation of episodic memories have generated tremendous insights into how loss of precision of remote aversive memories contribute to overgeneralization of fear in PTSD (Zola-Morgan and Squire, 1990; Squire and Zola-Morgan, 1991; Kim and Fanselow,

1992; Frankland and Bontempi, 2005; Wang and Morris, 2010; Wiltgen *et al*, 2010; Sutherland and Lehmann, 2011; Dudai, 2012; Goshen, 2014). The proposed roles of the hippocampus in time-dependent reorganization of memories have been influenced by the hippocampal memory index theory that posits a role for the hippocampus as an archive of indexes of neocortical engrams (Teyler and DiScenna, 1986; Teyler and Rudy, 2007). Specifically, episodes are encoded by strengthened connections between activated cortical ensembles and hippocampal indexes. Subsequent retrieval of memory within a subset of cortical neurons in the original trace and its corresponding hippocampal index reinstates the entire cortical trace. Thus, the hippocampal index is critical for reinstating and strengthening the cortical trace and decreasing interference with other cortical traces. As a consequence, interference between indexes (hippocampal ensembles) determines whether overlapping memory traces in the cortex are activated and the extent to which cortical traces are consolidated. The continued involvement of the hippocampus in maintenance of precision of remote contextual memories (Sutherland *et al*, 2008; Wang *et al*, 2009; Wiltgen *et al*, 2010; Goshen *et al*, 2011; Sparks *et al*, 2011) suggests that hippocampal–cortical system consolidation of remote memories may require the maintenance of hippocampal indexes.

Building on different theories of systems consolidation, the hippocampal index theory, and the general property of episodic memories to become more semantic with time (McClelland *et al*, 1995; Nadel and Moscovitch, 1997; Frankland and Bontempi, 2005; McKenzie and Eichenbaum, 2011), Hardt *et al* (2013) proposed that levels of interference in the hippocampus dictates the episodic-to-semantic shift in consolidated memories to influence time-dependent generalization. Specifically, a time-dependent decay of the hippocampal index would increase interference between overlapping cortical traces and render the memory less conjunctive and more semantic-like. This loss of episodic details in remote memories could induce overgeneralization of fear as fear is no longer constrained by conjunctive representation of the trauma and it is evoked by individual or elemental features of the traumatic context (Acheson *et al*, 2012). Conversely, this model predicts that decreasing interference in the hippocampus will slow down the decay of the hippocampal index over time and, consequently, ensure strengthening of the cortical trace and maintenance of the conjunctive representation and episodic details. In addition, we propose that increasing interference among cortical engrams would allow updating of the aversive memory trace by recruitment of trauma-unrelated cues whenever this trace is reactivated by its corresponding hippocampal index. This would result in unwanted expression of fear in response to trauma-unrelated cues, a key feature of PTSD. Thus, we propose that understanding the mechanisms that resolve interference in the hippocampus will edify (1) how uncertain or ambiguous threats are distinguished from past aversive memories and (2) how

hippocampal indexes are maintained to influence time-dependent generalization of fear. In the next two sections, we discuss evidence for neural mechanisms in the DG that contribute to resolution of interference in the hippocampus.

### Pattern Separation in DG Promotes Efficient Appraisal of Ambiguous and Uncertain Threats by Decreasing Interference

One mechanism by which interference between new information (ambiguous and uncertain threats) and previously stored similar memories is minimized in the hippocampus is pattern separation in the DG–CA3 circuit (Treves and Rolls, 1992; McClelland and Goddard, 1996; Colgin *et al*, 2008). Computational models, guided by the connectivity of the hippocampus, have proposed a role for two complimentary operations, pattern separation and pattern completion, by which the hippocampus forms new episodic memories without interfering with those previously stored (Marr, 1971; McNaughton and Morris, 1987; O'Reilly and McClelland, 1994). Pattern separation is the process by which similar cortical inputs are made more distinct, thereby minimizing interference during storage, and is thought to require the DG (Treves and Rolls, 1992; McClelland and Goddard, 1996; Colgin *et al*, 2008). Pattern completion refers to the process by which a complete sequence of activity pattern is reinstated based on partial features of that pattern and is thought to require CA3 (O'Reilly and McClelland, 1994). Several distinct neuroanatomical features and physiological properties of the DG such as sparseness of activity and strong feed-back and feed-forward inhibition support its role in pattern separation (Jung and McNaughton, 1993; Freund and Buzsaki, 1996; Acsady *et al*, 1998; Gonzales *et al*, 2001; Chawla *et al*, 2005; Ramirez-Amaya *et al*, 2005; Tashiro *et al*, 2007). In contrast, the highly recurrent collaterals in CA3 serve the purpose of an associative network in which memories are stored within the network and can be retrieved even with partial inputs, facilitating pattern completion (Marr, 1971; McNaughton and Morris, 1987; Rolls, 1996; Nakazawa *et al*, 2002; Neunuebel and Knierim, 2014).

*Studies examining the role of DG in resolving interference and pattern separation in rodents.* Pioneering experimental studies in rodents probing the involvement of different hippocampal subregions in modulating interference have suggested a role for the DG in pattern separation (Kesner, 2013). Rodents with colchicine-induced ablation of the DG showed impaired discrimination of two spatial locations based on distal environmental cues, especially when there was large overlap of the distal cues, namely, spacing between the two locations was small (Gilbert *et al*, 2001). Consistent with these observations, genetic disruption of synaptic plasticity at perforant path-DG synapses in adult mice renders them inefficient discriminators of similar, but not distinct, contexts (McHugh *et al*, 2007). More recently,

studies using optogenetic approaches have found that the DG also modulates interference of competing goals or contingencies. Optogenetic silencing of the dorsal DG in an active place avoidance task does not affect acquisition or retrieval of a stationary spatial location associated with a foot-shock in a rotating arena (Kheirbek *et al*, 2013). In this active avoidance task, the rotating platform continuously forces the animal to confront the original fear memory with the new rule by which the area no longer predicts a foot-shock. Interestingly, when the location of the shock zone is switched to the opposite side of the rotating arena, thereby necessitating resolution of two conflicting contingencies of a memory of a shock zone, optogenetic silencing of the dorsal DG impairs identification of the new shock zone (Kheirbek *et al*, 2013).

Electrophysiological recordings of place cells, internal representations of the external world, have instantiated a critical role for the DG and CA3 in pattern separation and pattern completion. By examining conditions under which place cells undergo remapping, either by changing their rate (rate remapping) or their rate and location (global remapping), various groups have found that subtle changes or parametric morphing of a rodent's environment elicits remapping of place cells in the DG (Leutgeb *et al*, 2007; Neunuebel *et al*, 2013; Neunuebel and Knierim, 2014). CA3 exhibits global remapping when the environment undergoes large changes, but place field is maintained even in the presence of degraded cues, reflective of pattern completion (Lee *et al*, 2004). Thus, tradeoff between pattern separation and pattern completion in CA3 relies on the extent of parametrical changes in the environment (Leutgeb *et al*, 2005; Neunuebel *et al*, 2013; Neunuebel and Knierim, 2014).

Cellular imaging approaches such as cellular compartment analysis of temporal activity by fluorescence *in situ* hybridization (catFISH) have permitted network-level examination of how the DG–CA3 circuit contributes to pattern separation and pattern completion. By tagging neurons using probes or genetic reporters that capture the timing of immediate early gene expression (IEG), it is possible to ascertain patterns of reactivation of neuronal ensembles over minutes or even weeks, and in response to specific contexts to probe global remapping. Such approaches have demonstrated that global remapping occurs in CA3 in situations of mismatch between two separate experiences, interpreted as pattern separation (Guzowski *et al*, 2004; Vazdarjanova and Guzowski, 2004; Schmidt *et al*, 2012a; Skinner *et al*, 2014). On the other hand, changing local cues in the environment leads to a modest remapping suggestive of a pattern completion mechanism in CA3 (Guzowski *et al*, 2004; Vazdarjanova and Guzowski, 2004). Consistent with electrophysiological studies, discrimination of similar contexts has been shown to elicit global remapping in the DG as well as in CA3 (Deng *et al*, 2013; Czerniawski and Guzowski, 2014). However, global remapping in the DG is not just observed during discrimination of contextual representations, instead resolving conflicting goals also engenders

global remapping in the DG (Satvat *et al*, 2011; Schmidt *et al*, 2012b). Thus, pattern separation in the DG–CA3 circuit may constrain the overgeneralization of fear in ambiguous threatening contexts or when threat is uncertain. Consistent with this idea, two different studies using rodents have found that impaired discrimination between a similar, but not distinct, safe context and a fearful context is accompanied by impaired remapping of place cells in CA3 (McHugh *et al*, 2007; Czerniawski and Guzowski, 2014).

*Studies examining the role of DG in resolving interference and pattern separation in humans.* Functional magnetic resonance imaging (fMRI) studies in humans have suggested a conserved role for the DG in pattern separation (Yassa and Stark, 2011; Deuker *et al*, 2014). In a landmark study, Bakker *et al* (2008) used fMRI in combination with an incidental encoding task in which subjects are presented a series of objects of varying similarity (Yassa and Stark, 2011). This task is predicated on the concept of repetition–suppression effect, that is, the response of a circuit adapts to repeated presentation of an object. Exploiting this concept of repetition–suppression, the authors found that the DG–CA3 circuit, rather than other regions of the medial temporal lobe, is most likely to be activated when object similarity is high. Furthermore, experiments in which BOLD fMRI was performed as mnemonic similarity was parametrically varied found that the DG–CA3 circuit showed greater activity than CA1 in response to subtle, but not large, changes in input (highly similar objects) (Lacy *et al*, 2011). Together, these data suggest that the DG in humans may perform input–output transformations similar to that seen in rodents (Leutgeb *et al*, 2007).

A crucial unanswered question is whether pattern separation in the DG is impaired in individuals with PTSD. Although a high-resolution structural MRI study found a selective reduction in volumes of DG and CA3 subfields in individuals with PTSD (Wang *et al.*, 2010), how these structural changes affect pattern separation–completion balance in the DG–CA3 circuit is yet to be determined. One study measured physiological parameters (risk assessment and electromyography) in healthy subjects and individuals with PTSD as they were shown a series of images that morphed from a conditioned danger stimulus (large circle) associated with a finger shock into a smaller circle that was not associated with the shock (conditioned safety stimulus). In this task, healthy controls exhibited a steep decline in physiological responses as the conditioned danger stimulus was morphed into the safe stimulus indicative of efficient discrimination of ambiguous threats. Although the PTSD group exhibited increased sensitization to the conditioned stimulus, they also exhibited increased threat perception to the intermediate cues closest in similarity to the conditioned danger cue reflective of increased interference (Lissek and Grillon, 2012). Whether these generalization gradients engage pattern separation in

the DG necessitates further studies that combine fMRI and incidental encoding.

### Pattern Separation in DG May Maintain Precision of Remote Fear Memories by Decreasing Cortical Interference

As discussed in the section ‘Hippocampal interference, time-dependent erosion of memory precision, and fear overgeneralization,’ modulation of interference in the hippocampus may dictate the stability of the hippocampal index of neocortical memory representations, thereby promoting their consolidation and protecting them from the interference-dependent loss of episodic detail. Based on this idea, one would predict that decreased pattern separation in the DG would result in loss of memory precision at remote time points to increase time-dependent overgeneralization of fear (Hardt *et al*, 2013). In support of this hypothesis, recent cellular activity tagging studies showed that at remote time points, when mice generalize fear in novel, safe contexts, there is a decrease in global remapping in the DG and CA3 (Denny *et al*, 2014). Conversely, reinstating the cortical trace and potentially maintaining the hippocampal index by exposing mice to the training context before testing remote memory has been shown to maintain remote memory precision (Wiltgen and Silva, 2007; Wiltgen *et al*, 2010). Further studies are needed to determine whether there is a causal link between pattern separation in the DG and precision of remote memories.

### Adult Hippocampal Neurogenesis Modulates Pattern Separation to Resolve Conflict, Disambiguate Threats, and Maintain Precision of Remote Memories

New DGCs are continuously generated from neural stem cells in the DG of hippocampus in humans and rodents throughout life (Altman and Das, 1965; Kaplan and Hinds, 1977; Cameron *et al*, 1993; Kuhn *et al*, 1996; Eriksson *et al*, 1998; Seri *et al*, 2001; Spalding *et al*, 2013). Anatomical and electrophysiological studies have demonstrated that adult-born DGCs functionally integrate into the neuronal network and that they exhibit heightened synaptic and structural plasticity during early stages of maturation (Zhao *et al*, 2008; Ming and Song, 2011; Aimone *et al*, 2014; Christian *et al*, 2014). Numerous studies have found that levels of adult hippocampal neurogenesis are highly sensitive to both aversive and enriching experiences and interventions (Ming and Song, 2011; Aimone *et al*, 2014; Ernst and Frisen, 2015; Opendak and Gould, 2015). Together, these observations suggest that the adult-born DGCs may act as substrates for experience-dependent neural circuit plasticity and may configure the DG in response to the animal’s experiences and environments over its lifetime. Indeed, recent findings from studies in rodents suggest that rates of neurogenesis may contribute to emergence of individuality (Freund *et al*, 2013).

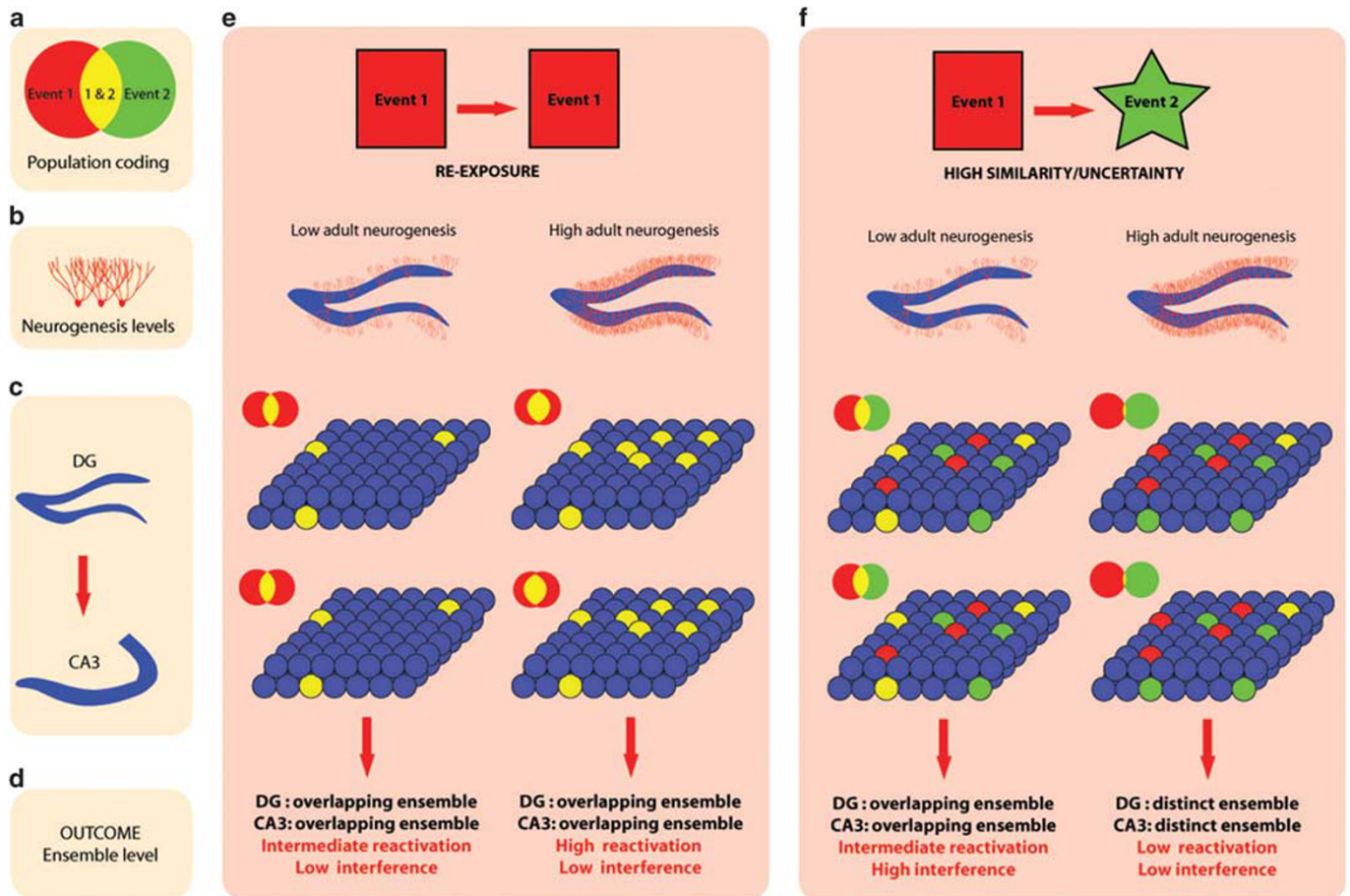
The past two decades have witnessed tremendous experimental and theoretical investigation of the functions of adult hippocampal neurogenesis in cognition and multiple theories have been proposed (Aimone *et al*, 2014; Cameron and Glover, 2015) including pattern separation to modulate interference (Wiskott *et al*, 2006; Becker and Wojtowicz, 2007; Deng *et al*, 2010; Sahay *et al*, 2011a; McAvoy *et al*, 2014), cognitive flexibility (Kempermann, 2008; Burghardt *et al*, 2012), pattern integration (Aimone *et al*, 2010), encoding of temporal contexts (Aimone *et al*, 2006; Rangel *et al*, 2013), memory resolution (Aimone *et al*, 2011), decay of remote memories (Arruda-Carvalho *et al*, 2011; McAvoy *et al*, 2014; Wang *et al*, 2014), and forgetting (Frankland *et al*, 2013; Akers *et al*, 2014). Here, we discuss the evidence from studies in rodents implicating adult-born DGCs in modulation of interference in DG-CA3 circuit and articulate how adult hippocampal neurogenesis may constrain the overgeneralization of fear through pattern separation in the DG.

*Modulation of spatial interference.* Recapitulating the logic of pioneering studies implicating the DG in modulation of spatial interference (Gilbert *et al*, 2001), the impact of blocking adult hippocampal neurogenesis was assessed in a two-choice touch screen spatial discrimination task and a delayed nonmatching to place radial arm maze task to probe a mouse's ability to correctly distinguish closely or far spaced arms or objects (Clelland *et al*, 2009). In both tests, the correct choice that mice were required to make (selecting a new maze arm from one previously visited based on spaced distal room cues or choosing one of two boxes spaced apart on a touch screen with a nose poke) relied on discrimination of small or large spatial separations. Consistent with previous lesion studies of the DG, the authors found that blockade of adult hippocampal neurogenesis by X-irradiation impaired the animal's ability to make fine, but not large, spatial discriminations. That is, hippocampal X-irradiated mice were not as efficient in discriminating between the choice and sample maze arms or boxes on the touch screen when they were close together, but not when spaced far apart. Studies using genetic approaches to ablate adult hippocampal neurogenesis in mice and rats have produced ambiguous results in the radial arm maze (Pan *et al*, 2012b; Groves *et al*, 2013; Zhang *et al*, 2014) and in the touch screen task (Swan *et al*, 2014). The basis for this incongruence across studies and between species is not clear, and may be because of differences in the experimental approaches used to ablate adult hippocampal neurogenesis (X-irradiation vs genetic approaches) and testing protocols.

The contextual fear discrimination learning task also enables assessment of the role of adult hippocampal neurogenesis in modulating spatial interference. As stated earlier, cellular imaging studies have found using this task that discrimination between similar contexts is accompanied by network-level mechanisms of pattern separation in the DG and CA3 such as global remapping (Niibori *et al*, 2012; Deng *et al*, 2013; Czerniawski and Guzowski, 2014). Blockade of adult hippocampal neurogenesis by genetic

means or hippocampal-targeted X-irradiation or disruption of synaptic plasticity in adult-born DGCs impairs discrimination of a safe, similar context from the context associated with a foot-shock (Sahay *et al*, 2011b; Kheirbek *et al*, 2012a; Nakashiba *et al*, 2012; Niibori *et al*, 2012; Tronel *et al*, 2012; Wu and Hen, 2014). Consistent with these findings, X-irradiation-dependent blockade of adult neurogenesis produced impairments in a visual discrimination water maze task only under conditions of high interference (Winocur *et al*, 2012). Conversely, we found that genetic enhancement of adult hippocampal neurogenesis by blockade of cell death of adult-born DGCs, or more recently by enhancing integration of adult-born DGCs, was sufficient to enhance discrimination between a shock-associated context and a similar, but not distinct, neutral context (Sahay *et al*, 2011b; McAvoy *et al*, 2014). Importantly, using catFISH we have found that enhancing the integration of adult-born DGCs increased global remapping in the DG only under conditions of high interference, namely, similar context but not low interference, that is, distinct context (McAvoy *et al*, 2014). Together, these studies suggest that adult-born DGCs may facilitate spatial discrimination and constrain fear overgeneralization by minimizing interference between overlapping contextual representations (Figure 1).

*Resolution of conflicting contingencies and goals.* As discussed in the section 'Pattern separation in DG promotes efficient appraisal of ambiguous and uncertain threats by decreasing interference,' impairments in pattern separation mechanisms that minimize interference between conflicting goals and contingencies may contribute to fear overgeneralization. Several studies have suggested that adult hippocampal neurogenesis mediates cognitive flexibility by minimizing proactive interference (Wiskott *et al*, 2006; Becker and Wojtowicz, 2007; Kempermann, 2008). Reversal learning using the Morris water maze in which an animal must learn the new location of a hidden platform or using a touch screen task or an active place avoidance task is one way of probing proactive interference and cognitive flexibility. Studies using X-irradiation (Wojtowicz *et al*, 2008), chemical (Garthe *et al*, 2009), genetic (Pan *et al*, 2012b), or pharmacogenetic (Zhang *et al*, 2008, 2014) approaches to block adult hippocampal neurogenesis have consistently found perseveration in the original platform location at the expense of spending time in the new location, reflective of proactive interference (Garthe and Kempermann, 2013). Similar impairments in cognitive flexibility were observed following genetic ablation of adult hippocampal using an active place avoidance task (Burghardt *et al*, 2012) or a touch screen task (Swan *et al*, 2014). Conversely, we found using a novel strategy that enhancing the integration of adult-born DGCs decreased proactive interference in reversal learning using the Morris water maze (McAvoy *et al*, 2014). Whether these behavioral effects of titrating levels of adult hippocampal neurogenesis on cognitive flexibility and proactive interference engage pattern separation mechanisms in the DG remains to be determined.



**Figure 1.** Adult hippocampal neurogenesis dictates population-based coding to gate memory reactivation and interference in DG–CA3. (a) Schematic representation of population-based coding of two separate events in DG and CA3. Neurons encoding event 1 are shown in red and event 2 in green. Neurons reactivated in response to repeated exposure of event 1 or event 2 are shown in yellow. Event 2 has high similarity with event 1 or may convey uncertainty of threat. (b) For each condition (reexposure of event 1 or event 1 followed by event 2), population coding is shown for high and low levels of adult hippocampal neurogenesis. (c) Schematic of engram in DG and CA3 under conditions of low and high adult hippocampal neurogenesis. (d) Outcome at network/population level. (e) When an event is re-encountered, greater reactivation of DGCs and CA3 neurons is seen with high levels of adult hippocampal neurogenesis (more yellow cells) and the converse is seen with low levels of adult hippocampal neurogenesis (fewer yellow cells). This may explain why enhancing adult hippocampal neurogenesis promotes memory persistence. (f) When there is interference because of similarity between two experiences or because of uncertainty of contingencies, high level of adult hippocampal neurogenesis promote population-based coding (global remapping) in the DG and CA3 (fewer yellow cells) to resolve interference. This orthogonalization of ensembles in DG and CA3 may prevent proactive interference and time-dependent decay in memory precision.

Although experimental evidence supporting a role for encoding uncertainty or unpredictability of threats is currently lacking, a recent study found using *in vivo* recordings of place cells in the DG that levels of adult hippocampal neurogenesis influence encoding of temporally separated exposures to a context in nonoverlapping ensembles of DGCs (Rangel *et al*, 2014). It is plausible that such a mechanism may minimize interference between cues associated with predictable and unpredictable contingencies to govern adaptive fear responses to uncertain threats. Together, these studies suggest a role for adult hippocampal neurogenesis in modulating proactive interference to promote conflict resolution when threats are ambiguous or uncertain (Figure 1).

*Adult hippocampal neurogenesis and maintenance of memory precision.* As discussed in the preceding sections,

theoretical proposals and preliminary experimental evidence suggests that maintaining hippocampal indexes and modulating interference in the DG moderates the time-dependent erosion of memory precision. One mechanism by which hippocampal indexes may be maintained is by preventing their decay. Several lines of evidence from genetic loss-of-function and gain-of-function studies compellingly implicate adult hippocampal neurogenesis in the maintenance of remote memories and prevention of their decay. Genetic ablation of adult-born DGCs that were present during training in the contextual fear conditioning or spatial learning tasks resulted in degradation of the memory when the mice were tested shortly after training, suggesting that adult-born DGCs are substrates of the memory trace (Arruda-Carvalho *et al*, 2011). Furthermore, blocking adult hippocampal neurogenesis by genetic ablation of extracellular signal-regulated kinase 5 (ERK5) in neural stem cells

and progenitors in the adult DG before, or immediately after, contextual fear conditioning increased the decay of remote memory, arguing for a role for adult-born DGCs in modulating memory persistence (Pan *et al*, 2012a). These studies corroborate an early report that used whole-brain irradiation to ablate adult hippocampal neurogenesis in rats before training and observed decreased remote spatial memory (Snyder *et al*, 2005). Conversely, genetic activation of ERK5 signaling in adult-born DGCs enhanced memory strength at remote time points in the novel object location, novel object recognition, and Morris water maze spatial learning tasks (Wang *et al*, 2014). Consistent with these observations, we have found that genetically enhancing integration of adult-born DGCs is sufficient to enhance remote contextual fear memory (McAvoy *et al*, 2014). One prediction from these studies is that time-dependent generalization of fear is decreased when decay of memory trace is slowed down by enhancing neurogenesis. Although blockade of adult hippocampal neurogenesis by elimination of ERK5 in neural stem cells and progenitors did not increase time-dependent generalization of fear in a novel context, the controls also failed to show an increase in freezing behavior to a novel context at remote time points in this study (Pan *et al*, 2012a). In contrast, posttraining ablation of adult-born DGCs present during encoding of a visual discrimination task impaired discrimination at remote time points (Arruda-Carvalho *et al*, 2011). Detailed analysis of the animal's swim patterns in this study suggested that elemental associations such as cue–platform location were maintained. This study supports the idea that neurogenesis-dependent modulation of interference may govern memory precision at remote time points by potentially preserving the conjunctive representation in the cortex. Such a mechanism would also constrain the erroneous updating of memories.

### Model for How Adult Hippocampal Neurogenesis Influences Pattern Separation In Dg to Govern Overgeneralization of Fear

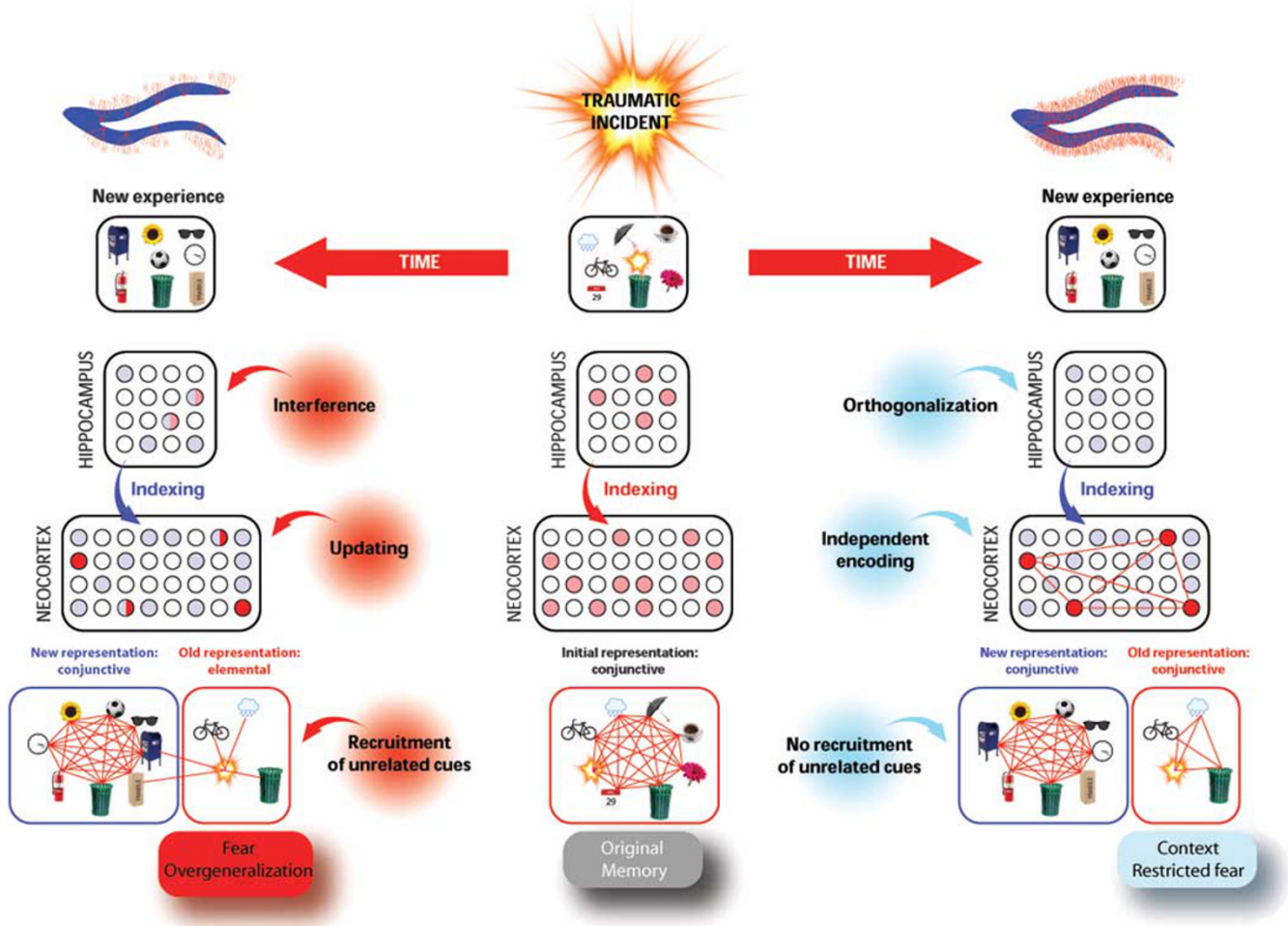
Building on the framework established in the preceding sections, we outline how levels of adult hippocampal neurogenesis dictate pattern separation in the DG to govern the overgeneralization of fear using the example of a traumatic memory of a bomb blast (Figure 2). An individual experiences a bomb blast in a café on a rainy day. The memory trace of this traumatic event is encoded in an ensemble of DGCs (pink circles in DG). This traumatic memory is consolidated as a conjunctive representation comprising a green trashcan, cup of coffee, umbrella, a red flower, and a bicycle within a cortical engram. The consolidated memory trace is made up of pink cortical neurons and corresponding pink DGCs serve as its hippocampal index (middle column, Figure 2). With normal levels of neurogenesis, the encoding of a new experience at a later time recruits a distinct ensemble of DGCs as a new hippocampal index (light blue circles in DG) through efficient pattern separation. Under these conditions, because

of high global remapping in the DG, there is low interference, that is, overlap between the light blue DGCs and the pink DGCs that were recruited to encode the original traumatic memory (right column, Figure 2). This new (light blue DGCs) hippocampal index promotes the consolidation of this new representation within a cortical engram that is only partially overlapping with the cortical engram of the original traumatic memory. Although there is a natural time-dependent decay of irrelevant features of the traumatic memory, many details are strengthened (red cells in cortex) within a conjunctive representation (red box). The second conjunctive representation of the new experience (blue box) develops without recruitment of trauma-related cues in the original memory (there is no updating). In contrast, decreased levels of adult hippocampal neurogenesis (left column, Figure 2) results in decreased global remapping and increased reactivation of some of the DGCs recruited to encode the original traumatic memory (overlap between light blue DGCs and pink DGCs), thereby increasing interference between the new similar experience and the original traumatic memory. Consequently, the hippocampal index for the new experience is made up of pink and light blue DGCs. Impaired pattern separation in the hippocampus will therefore result in collocation of the new memory representation with the original representation in the neocortex (updating). The repetition of such a process over time accelerates the conjunctive to elemental shift in the original traumatic memory whose features are no longer bound within the cortical engram as a conjunctive representation (red box) (left column, Figure 2). As reactivation of a traumatic memory in similar, safe environments may arise because of excessive pattern completion, the combination of excessive pattern completion and impaired pattern separation in DG–CA3 circuit may create a closed loop permissive to persistent reactivations of traumatic memory and increased incorporation of trauma-unrelated cues into the cortical trace. Thus, the accelerated decay of conjunctive trace and incorporation of trauma-unrelated cues produces overgeneralization of fear. Consistent with these ideas, a recent study found a positive correlation between re-experiencing the traumatic event and the degree of fear overgeneralization in individuals with PTSD (Kostek *et al*, 2014).

### Circuit Mechanisms by Which Adult-Born DGCs Resolve Interference to Moderate Temporal Decay of Memory Precision

Instantiating the circuit-based mechanisms by which adult-born DGCs modulate interference in the DG is critical to understanding how environmental risk factors for PTSD such as stress and genetic risk interact to affect pattern separation and fear generalization. In addition, a circuit-based framework will also guide strategies to improve hippocampal circuit performance in individuals at risk for developing PTSD and those who already suffer from trauma-related psychopathology (Figure 3). Here, we critique



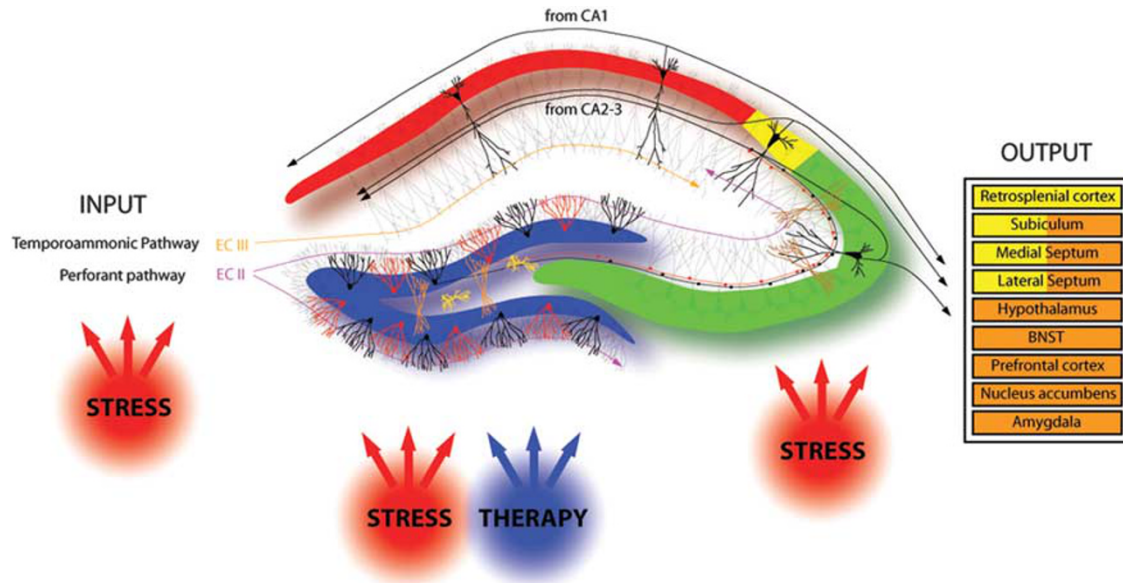


**Figure 2.** Adult hippocampal neurogenesis modulates time-dependent overgeneralization of fear through pattern separation. Experiencing a traumatic event results in incorporation of episodic features into the memory trace (eg, rain, umbrella, coffee, bike, date of event, trashcan, flower). The memory trace of this traumatic event is allocated to an ensemble of neurons in the neocortex (pink cells) and a corresponding hippocampal ensemble that serves as an index (pink DGs; middle column). Consolidation promotes the stabilization of this original memory into a conjunctive representation (middle column, red box) consisting of a collection of features bound together (middle column, red lines). New experiences that share similarity with original experience lead to new learning within the same hippocampal–cortical network. Normal levels of adult hippocampal neurogenesis (right column) facilitate efficient orthogonalization within the hippocampus through pattern separation (low overlap between light blue DGs and pink DGs) and results in allocation of the new memory trace to a distinct neuronal ensemble in the neocortex (light blue cells, independent encoding). Although there is time-dependent decay of irrelevant features of the traumatic memory, many details are strengthened (emergence of interconnected red cells and loss of pink cells) within a conjunctive representation (red box). Importantly, the conjunctive representation of the new experience (blue box) develops without recruitment of trauma-related cues in the original memory. In contrast, decreased levels of adult hippocampal neurogenesis (left column) impedes efficient orthogonalization in the hippocampus, thereby increasing interference between the new similar experience and the original memory trace (overlap between pink and light blue DGs or indexes). Impaired pattern separation in the DG will therefore result in collocation of cells of the new memory representation within the original representation in the neocortex (updating). The repetition of such a process over time accelerates the conjunctive to elemental shift in the original traumatic memory whose features are no longer bound by context (red box, note that items of the new memory are linked to the traumatic memory but not to each other). This unbound memory trace may recruit trauma-unrelated stimuli upon new learning/experiences. Together, the accelerated decay of conjunctive trace and incorporation of trauma-unrelated cues produces overgeneralization of fear.

evidence for putative circuit-based mechanisms by which adult-born DGs may modulate pattern separation in the DG–CA3 circuit.

*Sparseness of activity and feed-back inhibition.* *In vivo* recordings and imaging using IEGs have shown that the DG exhibits a sparse pattern of activity (Jung and McNaughton, 1993; Chawla *et al*, 2005; Neunuebel and Knierim, 2012,2014). Computational models have long recognized an

importance for sparse coding as conducive to decorrelation of similar inputs (McClelland and Goddard, 1996). Analysis of network-level pattern separation mechanisms in the DG and CA3 using catFISH and genetic tagging approaches suggest that the vast majority of DGs that contribute to global remapping are the mature DGs (Deng *et al*, 2013; Denny *et al*, 2014). *In vivo* recordings and calcium imaging in slices suggest that mature DGs exhibit high input specificity (Marin-Burgin *et al*, 2012; Neunuebel and



**Figure 3.** Stress affects adult-born DGC-dependent circuit-based mechanisms important for resolving interference. The principal layers of the hippocampus are DG (blue), CA3 (green), CA2 (yellow), and CA1 (red). The perforant path arises in the entorhinal cortex (EC) layer II and projects to the DG and CA3. The temporoammonic pathway arises in EC layer III and targets CA1. Within the DG, immature (red) and mature (black) DGCs extend mossy fibers through the hilus where they contact GABAergic interneurons (orange) and mossy cells (yellow). The activity of these interneurons and mossy cells modulates sparse activity in the DG through feed-back inhibition. Mossy fibers project to CA3 and CA2 where they form synaptic contacts with pyramidal cells (black) to mediate feed-forward excitation (FFE) and GABAergic interneurons (brown) to mediate feed-forward inhibition (FFI). CA3 pyramidal cells (black) send projections out of the hippocampus (Fimbria) to the dorsolateral septum. The same pyramidal neurons in CA3 also project to stratum radiatum of CA1 (Schaeffer collaterals). CA1 pyramidal cells (black) project to the subiculum as well as neocortical areas. Subiculum redirects the information to cortical areas and limbic regions indicated in the output box (yellow and orange indicate dorsal and ventral hippocampal outputs, respectively). These projections control emotional and cognitive processing. Stress (red arrows) decreases levels of neurogenesis in the DG and potentially affects afferent and efferent connectivity of DG–CA3 circuit. Collectively, these effects would lead to increased interference in the DG. Stimulating adult hippocampal neurogenesis or reverting stress-induced changes (blue arrows) in afferent and efferent connectivity of dentate granule neurons may maintain pattern separation functions to resolve interference and ensure context-appropriate gating of fear responses.

Knierim, 2012; Dieni *et al*, 2013). These observations beg the question of how adult-born DGCs influence global remapping in the DG and CA3 (Piatti *et al*, 2013).

We recently proposed a role for adult-born DGCs in recruiting feed-back inhibition to modulate sparseness of coding to support pattern separation in the DG (Sahay *et al*, 2011a; Drew *et al*, 2013). According to this model, increasing the number of adult-born DGCs would enhance sparseness of activity in the DG and consequently promote global remapping. To begin testing this hypothesis, we used voltage-sensitive dye imaging (VSDI) in combination with laser photostimulation and electrical stimulation of the granule cell layer (GCL) to visualize depolarization-induced spread of the VSD signal in slices from mice in which either adult hippocampal neurogenesis was blocked or increased (Ikrar *et al*, 2013). Interestingly, we found that genetically enhancing adult hippocampal neurogenesis resulted in a reduction in spread of activity and strength of neuronal activation in the DG, whereas blocking adult hippocampal neurogenesis produced a trend toward increased excitability of the DG *ex vivo*. These observations are consistent with a study showing that ablation of adult hippocampal neurogenesis diminished sparseness of activation in the DG in mice only under conditions of high interference

(Burghardt *et al*, 2012). Furthermore, although indirect, support for a link between adult hippocampal neurogenesis and GABAergic inhibition comes from studies showing that blockade of adult hippocampal neurogenesis decreases seizure threshold, vesicular GABA transporter VGAT, and baseline inhibitory synaptic transmission in the DG while increasing gamma burst activity (Singer *et al*, 2011; Lacefield *et al*, 2012; Schoenfeld *et al*, 2013; Iyengar *et al*, 2015). A recent study used optogenetics in slices from mice in which adult-born DGCs were labeled at different stages of maturation with channelrhodopsin to examine the extent of feed-back inhibition recruited by adult-born DGCs. The authors found adult-born DGCs recruit greater feed-back inhibition as they mature (Temprana *et al*, 2015). Further studies are needed to determine how feed-back inhibition recruited by adult-born DGCs influences sparseness of activity in DG and global remapping *in vivo*.

*Experience-specific reactivation and memory persistence.* Extensive studies in rodents have suggested that during the course of their maturation, adult-born DGCs acquire greater input specificity, become sensitive to GABAergic inhibition, and exhibit higher threshold for synaptic plasticity (Snyder *et al*, 2001; Schmidt-Hieber *et al*, 2004; Esposito *et al*, 2005;

Laplagne *et al*, 2006; Saxe *et al*, 2006; Ge *et al*, 2007, 2008; Laplagne *et al*, 2007; Gu *et al*, 2012). In other words, it has been suggested that adult-born DGCs exhibit a critical period for heightened plasticity during which they may be particularly sensitive to experience-dependent modifications. In this way, neurogenesis populates the DG with units that essentially reflect the organism's experiences. Furthermore, it has been suggested that once mature, adult-born DGCs preferentially respond to inputs to which they had been previously exposed (Tashiro *et al*, 2007; Trouche *et al*, 2009; Aimone *et al*, 2011). Although there is no evidence directly demonstrating that young adult-born DGCs used during encoding are reactivated at remote time points when they are mature, the idea that maturation of adult-born DGCs dictates their availability for encoding (when young) and retrieval (once mature) is appealing (Figure 1). Such a mechanism may explain the growing number of loss-of-function and gain-of-function studies implicating adult hippocampal neurogenesis in maintenance of remote memories (Figure 1). Thus, the high input specificity of mature adult-born DGCs coupled with strong feed-back inhibition would maintain the hippocampal index by decreasing interference in the DG and consequently preserve the conjunctive nature of the cortical engram of the remote aversive memory (Figure 2).

Given the role of the hippocampus in replay-dependent consolidation of episodic memories (Carr *et al*, 2011) and evidence implicating CA3 in consolidation of contextual fear memories and ripples (Nakashiba *et al*, 2008, 2009), adult-born DGCs may also influence the precision of remote memories through replay. Consistent with this proposal, it has been suggested that recently tagged synapses of young excitable adult-born DGCs are more sensitive to strengthening during replay in sleep (Xia and Storm, 2012). Addressing circuit-based mechanisms by which adult-born DGCs contribute to reorganization and consolidation of cortical traces will undoubtedly impact our understanding of the role of adult hippocampal neurogenesis in maintenance of memory precision and moderation of time-dependent fear generalization.

*Feed-forward inhibition in mossy fiber–CA3 circuit and contextual gating.* The storage of new memories without interference with those that have been previously encoded necessitates understanding of how the DG communicates with CA3 (Figure 1). The axons of DGCs, mossy fibers, synapse onto both CA3 pyramidal neurons and GABAergic interneurons via large presynaptic terminals called mossy fiber boutons (MFBs) (Acsady *et al*, 1998) and numerous filopodia emanating from the MFBs, respectively. The MFB contacts with thorny excrescence-like spines of CA3 pyramidal cells mediate feed-forward excitation (FFE), whereas the disproportionately more numerous filopodial contacts with inhibitory interneurons mediate feed-forward inhibition (FFI) onto CA3 pyramidal neurons (Nicoll and Schmitz, 2005). It is thought that a balance between FFE and FFI onto CA3 neurons is required for dictating the temporal

window of activation of CA3 neurons, facilitating sparse coding, and modulating excitation of the recurrent collateral circuitry of CA3; features long recognized as conducive to pattern separation–completion balance (Treves and Rolls, 1992; O'Reilly and McClelland, 1994; Bragin *et al*, 1995; McClelland and Goddard, 1996; Acsady and Kali, 2007; McBain, 2008; Cerasti and Treves, 2010; Torborg *et al*, 2010; Ikrar *et al*, 2013; Piatti *et al*, 2013). Furthermore and importantly, decreased FFI connectivity has been associated with increased time-dependent loss of memory precision and generalization of fear (Ruediger *et al*, 2012).

The *in vivo* analysis of FFI connectivity of adult-born DGCs suggests that young adult-born DGCs have significantly more filopodial contacts with GABAergic interneurons than mature DGCs (Restivo *et al*, 2014) (N Guo and A Sahay, unpublished observations). Although it is not known how FFI recruited by adult-born DGCs influences CA3 activity, a recent study found that loss of adult-born DGCs impaired global remapping in CA3, that is, increased overlap in CA3 neurons activated in two similar contexts (Niibori *et al*, 2012). Further evidence in support of a role for young adult-born DGCs in modulating remapping in CA3 comes from a study showing that silencing the output of only the mature DGCs does not affect rate remapping in CA3 (Nakashiba *et al*, 2012). Based on these observations, it is plausible that levels of adult hippocampal neurogenesis dictate FFI in the DG–CA3 circuit to influence pattern separation and time-dependent fear generalization.

### Stress Confers Vulnerability to Overgeneralization of Fear Through Changes in Adult Hippocampal Neurogenesis

One of the most consistent brain structural abnormalities in PTSD is decreased hippocampal volume (Pitman *et al*, 2012). A landmark study that examined hippocampal volumes of identical twins discordant for combat exposure and PTSD found that the twins in whom one co-twin developed PTSD had smaller hippocampal volumes than the twins who did not develop PTSD. This study suggested that a smaller hippocampus confers a predisposition to stress-related psychopathology (Gilbertson *et al*, 2002). Within the hippocampal formation, DG–CA3 volume is decreased in individuals with early-life stress history (Teicher *et al*, 2012) and in PTSD (Neylan *et al*, 2010; Wang *et al*, 2010). A recent study found impaired pattern separation in the DG of individuals with elevated depression scores (Fujii *et al*, 2014). Although it is not clear whether stress contributes to the higher depression scores (or depressed mood) in these individuals, these observations suggest, although indirectly, that stress alters pattern separation in the DG–CA3 circuit. How changes in hippocampal volume and DG–CA3 volumes in PTSD manifest at the level of encoding is not clear. Preclinical studies have begun to bridge this gap in our understanding by examining how stress affects adult hippocampal neurogenesis.

Stressful experiences, as studied in rodents and primates, is known to decrease the proliferation of neural stem cells and progenitors and survival of maturation of young DGCs (Schoenfeld and Gould, 2013; Miller and Hen, 2015; Opendak and Gould, 2015; Schoenfeld and Cameron, 2015). These effects of stress on adult hippocampal neurogenesis are thought to be mediated by glucocorticoid and mineralocorticoid receptors that are expressed during distinct stages of maturation of adult-born DGCs (Garcia *et al*, 2004) as well as changes in glutamatergic transmission (Joels and Baram, 2009; Lupien *et al*, 2009; Popoli *et al*, 2012). Examination of how different stressors affect adult hippocampal neurogenesis along the septotemporal axis suggests increased sensitivity of the ventral DG to stress (Tanti and Belzung, 2013).

How stress affects local circuit-based mechanisms recruited by adult-born DGCs for pattern separation detailed in the previous section is poorly understood. One study examined the effects of social defeat stress on reactivation of neuronal ensembles in DG–CA3 in response to repeated exposure to a context associated with a foot-shock. The authors found that stressed mice exhibited decreased adult hippocampal neurogenesis and a reduction in reactivation of CA3 neurons, consistent with the proposal that adult-born DGCs promote reactivation of memory traces in CA3 (Denny *et al*, 2014). A second study found that long-term genetic ablation of adult hippocampal neurogenesis potentiated mild stress-induced activation of DGCs and CA3 neurons and increased glutamate release in CA3 (Schloesser *et al*, 2014). Based on these observations, we hypothesize that stress exposure disrupts FFI–FFE balance in the DG–CA3 circuit, decreases sparseness of coding, and impairs pattern separation in the DG–CA3 circuit (Guo and A Sahay, unpublished observations). Behaviorally, we predict that this would manifest as impaired discrimination and increased fear generalization under conditions of high interference.

As elevation in glucocorticoids impairs conjunctive encoding and promotes overgeneralization of fear in neutral contexts (Kaouane *et al*, 2012), it is plausible that stress-dependent changes in adult hippocampal neurogenesis may also affect fear generalization through negative feedback regulation of the hypothalamic–pituitary–adrenal (HPA) axis. The ventral hippocampus is known to control HPA axis responses through distinct pathways linking the subiculum and CA1 with hypothalamic nuclei and mammillary bodies (Tannenholz *et al*, 2014) as well as the lateral septum (Anthony *et al*, 2014; Strange *et al*, 2014). However, a role for adult hippocampal neurogenesis in regulation of the HPA axis is debated. Ablation of adult hippocampal neurogenesis in mice was found to impair negative regulation of the HPA axis in response to acute stress in some, but not all, studies (Snyder *et al*, 2011; Surget *et al*, 2011). Genetic enhancement of adult hippocampal neurogenesis did not increase the negative regulation of acute stress-induced elevation in glucocorticoids (Hill *et al*, 2015).

Given the differences in intrinsic and extrinsic connectivity of the hippocampus along the longitudinal axis (Bannerman *et al*, 2014; Strange *et al*, 2014), various groups have begun to address the behavioral impact of manipulating adult hippocampal neurogenesis in the dorsal and ventral DG. Using targeted X-irradiation to ablate neurogenesis in the adult dorsal or ventral DG, it was found that adult-born neurons in the dorsal DG play a preferential role in the discrimination of a similar context from a fearful context, whereas ventral adult-born DGCs preferentially contribute to anxiety (Wu and Hen, 2014). These results are consistent with previous work showing that dorsal hippocampal lesions impair contextual fear discrimination and increase fear overgeneralization (Frankland *et al*, 1998). Together, these observations raise the question of how pattern separation-dependent computations performed by adult-born DGCs in the dorsal DG are relayed to brain regions such as the amygdala, hypothalamus, and prefrontal cortex to govern context-appropriate fear responses (Figure 3). Extensive work has emphasized the role of communication between the hippocampus and prefrontal cortex in regulating the amygdala for expression of fear (Ressler and Mayberg, 2007; Likhnik and Gordon, 2014). In addition, we propose that the connections between CA3 and the dorsolateral septum may also play a critical role in transferring pattern separation-dependent computations to limbic brain regions (Luo *et al*, 2011) (A Besnard and A Sahay, unpublished observations). The dorsolateral septum projects to the supramammillary nucleus (SUM) (Risold and Swanson, 1997), a potent modulator of defensive behavior (exploration, freezing), arousal and stress responses, the lateral hypothalamus (Anthony *et al*, 2014), and ventral tegmental area (Luo *et al*, 2011). The primary function of the SUM is thought to bridge hippocampal-dependent cognitive operations with emotional responses mediated by the mesencephalic limbic system (amygdala, central gray, locus coeruleus, and lateral hypothalamus; Campeau and Watson, 2000; Pan and McNaughton, 2004). Although much more work is needed to establish whether the DG–CA3–CA1–prefrontal cortex or CA3–lateral septum pathway is the primary conduit for linking encoding in the DG–CA3 circuit with context-appropriate fear and stress responses, both pathways critically position CA3 as a node of vulnerability (Figure 3). Interestingly, long-term ablation of adult hippocampal neurogenesis was found to induce CA3 hypertrophy (Schloesser *et al*, 2014), reminiscent of that seen following stress (Magarinos *et al*, 1997; McEwen, 1999,2000; Sapolsky, 2000; McEwen *et al*, 2012). This raises the possibility that stress-induced decrease in adult hippocampal neurogenesis may disrupt CA3 connectivity and functions in memory processing and relaying information out of the hippocampus. Collectively, these observations begin to generate a framework to formulate how stress affects circuit-based mechanisms recruited by adult-born DGCs to modulate pattern separation and the neural pathways that link the DG–CA3 circuit with stress and fear centers in the brain.

## Future Research Directions

*Stimulating and imaging adult hippocampal neurogenesis to modulate fear overgeneralization.* The recent discovery that the human DG is host to hippocampal neurogenesis throughout life (Eriksson *et al*, 1998; Boldrini *et al*, 2009; Knoth *et al*, 2010; Spalding *et al*, 2013) together with preclinical studies suggest that adult hippocampal neurogenesis is a tractable therapeutic substrate for treating fear overgeneralization in PTSD. We demonstrated in a proof-of-concept study that genetic stimulation of adult hippocampal neurogenesis is sufficient to decrease contextual fear overgeneralization and, more recently, enhance global remapping in the DG (Sahay *et al*, 2011b; McAvoy *et al*, 2014). Exercise-dependent stimulation of adult hippocampal neurogenesis has been shown to decrease spatial interference in a rodent touch screen task (Creer *et al*, 2010) and promotes behavioral discrimination in humans (Dery *et al*, 2013; Voss *et al*, 2013). In addition, exercise also results in reorganization of afferents onto adult-born DGCs (Bergami *et al*, 2015). However, the molecular effectors recruited by exercise for these effects remain to be identified. Many different laboratories have begun to identify genes encoding molecular factors that govern neural stem activation, maturation, and survival of adult-born DGCs (Zhao *et al*, 2008; Ming and Song, 2011; Kheirbek *et al*, 2012b; Jessberger and Gage, 2014). Selective serotonin reuptake inhibitors (SSRIs), the current first-line therapy for PTSD, are proneurogenic and have been shown to constrain fear overgeneralization (McAvoy *et al*, 2015). However, adult hippocampal neurogenesis does not appear to be necessary for these effects of SSRIs on constraining fear overgeneralization, at least in middle-aged rodents (McAvoy *et al*, 2015). How SSRIs affect pattern separation mechanisms such as global and rate remapping in DG and CA3 remain to be addressed. Moving forward, a fundamental challenge is identifying small molecules with proneurogenic potential that may be used to rejuvenate the DG with new DGCs following stress exposure. The rediscovery of a diabetes drug, metformin, as a proneurogenic and procognitive agent and the identification of a novel proneurogenic compound that confers protection against the adverse effects of social defeat stress on mood exemplify efforts made to address this challenge (Pieper *et al*, 2010; Petrik *et al*, 2012; Wang *et al*, 2012; Walker *et al*, 2014). Another major challenge is imaging adult hippocampal neurogenesis in humans. Although volumetric studies have suggested reductions in hippocampal volume as a function of stress-related psychopathology in rodents and humans, the contributions of adult hippocampal neurogenesis are not known. Development of positron emission tomography ligands or identification of nuclear magnetic resonance (NMR) spectral signatures (Manganas *et al*, 2007) associated with neural stem cells or adult-born DGCs will catalyze noninvasive quantitative assessment of adult hippocampal neurogenesis in individuals at risk for stress-related psychopathology and following treatment (Kheirbek *et al*, 2012b; Ho *et al*, 2013). Although

further studies are needed to refine these technologies, such approaches in combination with fMRI would also permit longitudinal assessment of how genetic risk variants interact with stress to affect adult hippocampal neurogenesis concomitantly with pattern separation in DG-CA3.

*Reengineering intrinsic and extrinsic connectivity of the DG-CA3 circuit.* Critical to harnessing adult hippocampal neurogenesis for constraining fear overgeneralization is the need to continue to instantiate the circuit-based mechanisms by which adult-born DGCs exert their effects on computations made in DG-CA3. We predict that a circuit-based synthesis for the actions of adult-born DGCs on hippocampal-based computations and how they govern fear responses will catalyze efforts to reengineer circuits to optimize performance in disease states. Such an approach would complement the rejuvenation-based strategies described above. Specifically, the goal is to reengineer the intrinsic and extrinsic connections of DG-CA3 in such a way that the circuit performs as if there were more new adult-born DGCs. Broadly speaking, there are two complementary approaches to accomplish circuit reengineering: (1) Molecular reengineering and (2) optogenetic and electrical reengineering.

*Molecular reengineering.* The logic of molecular reengineering is that identification of molecular factors that specify discrete aspects of connectivity will facilitate harnessing these factors to reengineer connectivity *in vivo*. One example comes from studies examining how changes in intrinsic properties of neurons bias their allocation into memory traces (Han *et al*, 2007; Silva *et al*, 2009; Zhou *et al*, 2009; Kim *et al*, 2014; Yiu *et al*, 2014). In pioneering studies that first instantiated the cellular basis of an engram (Han *et al*, 2007, 2009), it was found that neuronal recruitment into fear engrams could be biased by elevating levels of a transcription factor, cAMP response element-binding protein (CREB), or intrinsic excitability (Rogerson *et al*, 2014; Frankland and Josselyn, 2015). Thus, in theory, molecular control of integration of adult-born DGCs into existing memory traces may dictate interference to influence memory precision. Along these lines, unpublished work from our lab suggests that biasing integration of young adult-born DGCs before encoding slows down decay of remote contextual fear memory (McAvoy *et al*, 2014). A second example is the use of neurofascin to specifically modulate feed-back inhibition onto the DG by axo-axonic chandelier interneurons without affecting feed-forward inhibition. The authors took advantage of restricted expression of neurofascin in the axon initial segment that is primarily innervated by axo-axonic chandelier interneurons and found that downregulation of neurofascin decreased feed-back inhibition onto the DG to impair learning (Zitman *et al*, 2014). Thus, integrating molecular logic underlying DG-CA3 connectivity with an understanding of how specific features of connectivity contribute to encoding will guide chemical screens designed to identify compounds that reprogram connectivity *in vivo*.

**Optogenetic and electrical reengineering.** A complementary effort to molecular reengineering circuits *in vivo* is the use of optogenetics to restore or optimize circuit performance in different disease states and under conditions of stress (Chaudhury *et al*, 2013; Deisseroth, 2014; Tye, 2014). A plethora of studies using optogenetics have begun to causally interrogate neural circuits in cognition and emotion (Tye and Deisseroth, 2012). Optogenetics permit controlling the activity of cell bodies such as DGCs (Kheirbek *et al*, 2013) or specific hippocampal sub-region afferents systems (Felix-Ortiz *et al*, 2013; Lovett-Barron *et al*, 2014) or specific cell populations such as hilar GABA interneurons (Andrews-Zwilling *et al*, 2012). Combining optogenetics with optical imaging technologies that enable *in vivo* imaging of cellular assemblies in awake behaving animals (Chen *et al*, 2013, 2015b; Ziv *et al*, 2013; Gunaydin *et al*, 2014; Jennings *et al*, 2015; Resendez and Stuber, 2015) will permit assessment of the interplay of different cell types in DG–CA3 microcircuits and cortical neurons in the context of encoding and reorganization of traumatic memories with passage of time. Studies showing how populations of neurons in the hippocampus and cortex can be tagged and reactivated or silenced to express and modify fear memories have brought us closer to understanding hippocampal–cortical dialogue in maintaining memory precision and valence (Liu *et al*, 2012; Ramirez *et al*, 2013; Cowansage *et al*, 2014; Denny *et al*, 2014; Redondo *et al*, 2014; Tanaka *et al*, 2014). For example, we can ask whether the reactivation of ‘engram bearing cells’ in the DG or ‘cortical engram cells’ elicit the precise recall of a remote fear memory and how the temporal decay of memory precision is changed by increasing or decreasing levels of adult hippocampal neurogenesis.

Before determining which features of connectivity need to be molecularly or optogenetically reengineered, we need to determine at high resolution how stress affects features of intrinsic and extrinsic connectivity of the DG–CA3 circuit. Viral-based tracing approaches now allow assessment of how inputs and outputs of adult-born DGCs are changed by stress (early-life or adult stressors) (Wickersham *et al*, 2007; Lo and Anderson, 2011; Sun *et al*, 2014). New imaging technologies that permit the visualization of cell type-specific connectomes (Sun *et al*, 2014) in intact transparent brains (Chung *et al*, 2013) as well as their connectivity at the ultrastructural level by expansion microscopy (Chen *et al*, 2015a) will also prove invaluable to these efforts. Finally, human brain imaging techniques now allow the detailed imaging of brain fiber pathways (Wedeen *et al*, 2012). Together, these techniques harbor potential to understand the link between structural connectivity and brain activity in relation to overgeneralization of fear.

**Decoding neural activity to modify behavior.** Whether pattern separation is impaired in the DG–CA3 circuit of individuals with PTSD or individuals at risk for stress-related psychopathology is yet to be determined. fMRI in combination with high-resolution structural imaging at 100  $\mu\text{m}$  resolution will unveil how changes in activity of the

DG–CA3 circuit correlate with structural changes in the granule cell layer and CA3 neurons (Prudent *et al*, 2010). By extensive recording of neural activity in distinct cell types in the rodent hippocampus, researchers have also begun to decode neural activity to predict behavior (Ziv *et al*, 2013). This logic has been applied in humans to develop ‘affective brain-computer interfaces’ that decode and rectify aberrant patterns of neuronal activity to disrupt pathological behavior (Widge *et al*, 2014; Grosenick *et al*, 2015). Deep brain stimulation is already in use for multiple indications including treatment-refractory depression (Holtzheimer and Mayberg, 2011) and has proven effective in combination with exposure therapy to improve fear extinction learning (Marin *et al*, 2014). It is therefore not far-fetched to envisage that closed-loop deep brain stimulation platforms will be used to predict overgeneralization of fear by detecting impaired pattern separation in the DG or aberrant activity in brain regions such as prefrontal cortex, lateral septum, or amygdala. The development of far-red shifted opsins that permit noninvasive optical inhibition of deep brain tissue (Chuong *et al*, 2014; Klapoetke *et al*, 2014) will aid in making this a reality in the future.

**Modeling PTSD phenotypes in connectivity of human DG–CA3 neurons.** Although the study of neural circuits in rodents and humans has proven tremendously catalytic in our understanding of disorders such as PTSD, the development of reprogramming technologies that enable generation of human hippocampal neurons from skin cells (Takahashi and Yamanaka, 2006; Sanchez Alvarado and Yamanaka, 2014) has opened another avenue to link neuronal properties and connectivity with disease (McCarroll and Hyman, 2013; Hyman, 2014). The generation of DGCs (Yu *et al*, 2014) and CA3 neurons from skin cells of patients with PTSD will prove invaluable in assessment of cellular ‘endophenotypes’ at the level of basic synaptic physiology or connectivity (Wen *et al*, 2014). Although epigenetic marks are lost with reprogramming, disease signatures at the level of single-induced human neurons or DG–CA3 circuits reconstructed from induced human neurons *ex vivo* will presumably reflect the interactions between stress and genetic risk factors of PTSD. The *in vitro* reconstruction of the DG–CA3 circuit with human neurons and using optical imaging and optogenetic tools to probe how properties and connectivity of DGCs and CA3 neurons from PTSD patients differ from healthy controls may enable identification of pathological changes in these neuronal populations (Garcia *et al*, 2012a, b; Yu *et al*, 2013). Gene editing tools that enable rapid engineering of disease mutations in human DGCs and CA3 neurons will facilitate causal assessment of genetic mutations and phenotypes (Hsu *et al*, 2014). The successful implementation of induced human DGCs and CA3 neuron assays is contingent upon faithful generation of DGCs and CA3 neurons and controlling for variability in patient cell lines to extract signal from noise.

Together, these different approaches represent a circuit-based approach guided by the role of adult-born DGCs in

modulating interference and maintaining memory precision for treating overgeneralization of fear in PTSD. At the same time, some of these advances will engender debate regarding their potential for misuse (Tracey and Flower, 2014). For example, strategies to modulate interference to update memories may be used to modify memories for therapeutic impact or for detrimental effects (Redondo *et al*, 2014; de Lavilleon *et al*, 2015). These challenges notwithstanding, it is hoped that the generation of new hypotheses and innovation in basic neuroscience and stem cell medicine will ultimately lead to new treatments for PTSD.

## GLOSSARY

**Adult hippocampal neurogenesis:** Biological process by which neural stem cells in the dentate gyrus differentiate into dentate granule neurons in the adult brain.

**Semantic memory:** Memory that is factual or conceptual and is devoid of spatial and temporal context (ie, decontextualized); for example, Rome is the capital of Italy.

**Updating:** Process by which rewriting of the original memory occurs during reactivation to integrate new information.

**Consolidation:** Process by which short-term memories are stabilized to generate long-term memories.

**Episodic memory:** Memories of events involving associations between places, events, and time (eg, memory of your family vacation from last year).

**Generalization of fear:** The expression of conditioned fear in response to stimuli that is similar to the conditioning stimulus. The excessive generalization of fear is referred to as fear overgeneralization and is reflected in inability to restrict fear to trauma-related cues and contexts.

**Time-dependent generalization:** Studies in animal models show that fear memories become less precise over time and are generalized to novel contexts. This transformation of memory is thought to involve changes in associative learning mechanisms and consolidation of memories in hippocampal–cortical networks.

**Proactive interference:** Refers to the process by which previously learned material hampers or interferes with learning of new related material (eg, changing your email password).

**Orthogonalization:** Operation by which two similar input patterns are transformed into two statistically uncorrelated output patterns. This computational operation exemplifies the mechanisms by which dentate gyrus performs pattern separation in the hippocampal circuit.

**Place cells:** Cells that fire when an animal moves through a specific location in space. Within the hippocampus, place cells become active in specific places within the environment. For this reason they are thought to support the internal representation of the external environment.

**Remapping:** Emergence of distinct neural representations (eg, place cells) in response to changes in inputs to the hippocampus. Whereas rate remapping is characterized by a

change in the firing rate within the same place cells, global remapping refers to the change of firing rate within different place cells.

**Pattern separation:** Neural mechanism by which overlap between similar inputs or memories are made more distinct, thereby minimizing interference during storage and retrieval. Pattern separation in the dentate gyrus is mediated by remapping of place cells.

**Pattern completion:** Neural mechanism by which a complete sequence of activity patterns is reinstated based on partial features of that pattern. Pattern completion is thought to require CA3.

**Engram:** Cellular and synaptic substrate of memory trace.

**IEG:** Immediate early genes (eg, *c-fos*, *zif268*, *arc/arg3.1*) are genes that are transcribed in response to neuronal activity without requiring new protein synthesis.

**catFISH:** Cellular compartment analysis of temporal activity by fluorescence *in situ* hybridization is a technique by which activation of neurons is determined based on localization of transcripts of an IEG in nuclear or cytoplasmic compartments. This technique permits assessment of extent of reactivation of neuronal ensembles over short time frames.

## FUNDING AND DISCLOSURE

The authors declare no conflict of interest.

## ACKNOWLEDGMENTS

The authors are supported by 2014 NARSAD Young Investigator Award, Bettencourt-Schueller Foundation and Philippe Foundation Award (to AB), the US National Institutes of Health BRAINS 1-R01MH104175, the Ellison Medical Foundation New Scholar in Aging, Whitehall Foundation, Inscopix Decode, and Harvard Stem Cell Institute Development Grants (to AS). We thank members of our laboratory for discussions and reviewers for their comments.

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