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Adult Neurogenesis: Beyond Learning and Memory

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Abstract

New neurons continue to be generated in the dentate gyrus throughout life, providing this region of the hippocampus with exceptional structural plasticity, but the function of this ongoing neurogenesis is unknown. Inhibition of adult neurogenesis produces some behavioral impairments that suggest a role for new neurons in learning and memory; however, other behavioral changes appear inconsistent with this function. A review of studies investigating the function of the hippocampus going back several decades reveals many ideas that seem to converge on a critical role for the hippocampus in stress response and emotion. These potential hippocampal functions provide new avenues for investigating the behavioral functions of adult neurogenesis. And, conversely, studies in animals lacking adult neurogenesis, which are likely to have more limited and more specific impairments than are seen with lesions, may provide valuable new insights into the function of the hippocampus. A complete understanding of the function of the hippocampus must explain its role in emotion and the relationship between its emotional and memory functions.

Contents

INTRODUCTION

Most mammalian brain regions receive their full complement of neurons before birth, with each neuronal population added during a very specific time window in development. The hippocampal granule cells, which are the primary excitatory neurons of the dentate gyrus and the recipients of the majority of inputs into the hippocampus, begin to be produced late in development and, unlike most neurons, continue to be generated in large numbers throughout life. Anatomical and electrophysiological studies provide strong evidence that these adult-born neurons become synaptically linked into hippocampal circuits, suggesting that they are functional. The rate of adult neurogenesis is strongly regulated by environmental factors and experience, providing indirect evidence that these new neurons may be involved in mediating interactions with the environment. However, the role that these neurons play in cognition and behavior is still unclear. There is a great deal of interest in adult neurogenesis from both fundamental and clinical perspectives, but in order for the field to continue to move forward, it is critical to understand how ongoing neurogenesis contributes to behavior. Identifying the specific behaviors in which new neurons play a role, and the particular function of the new neurons in these behaviors, is a necessary first step toward understanding why these neurons continue to be generated, whether inhibition of neurogenesis is detrimental, and whether increasing neurogenesis through pharmacological or behavioral interventions might be beneficial.

This review begins by describing animal models in which adult neurogenesis can be specifically inhibited and the behaviors that are affected in these models. Because some of the behavioral changes in animals lacking young neurons seem at odds with presumed roles in learning and memory, evidence for nonmnemonic effects of inactivating or lesioning the hippocampus itself are then discussed, followed by a broader discussion of historical and more recent ideas about

hippocampal functions outside of learning and memory. These alternative functions suggest a potential role for new neurons in aspects of decision making and emotion in addition to, or possibly even instead of, predicted roles in learning and memory.

ELIMINATING NEW NEURONS

For many years, hints about the function of adult neurogenesis have been sought by examining parallel changes in performance in hippocampus-dependent behavior tasks and numbers of new neurons. Behavior tasks that increase the survival of young neurons seem likely to involve those new neurons in an important way. Similarly, manipulations of genes or experiences (e.g., exercise) that alter both numbers of new neurons and particular behaviors suggest a possible link between the two effects. However, assuming that parallel changes in adult neurogenesis and behavior indicate a causal relationship is problematic (Lazic 2010, 2012).

Fortunately, tools are now available to specifically inhibit or enhance adult neurogenesis. Several methods are available, each with positive and negative features. The first method used to inhibit adult neurogenesis was pharmacological treatment with a chemotherapeutic agent, methylazoxymethanol acetate (MAM) (Shors et al. 2001). Studies continue to use pharmacological cell division inhibitors, though cytarabine and temozolomide are now more commonly used than MAM. The primary advantages of pharmacological inhibition of adult neurogenesis are that (*a*) it can be used in any strain or species since it does not require a transgene, (*b*) it does not require expensive equipment, and (*c*) it can be administered via simple systemic injection, obviating the need for surgeries or anesthetics that could potentially alter neurogenesis or behavior. The primary limitation of these chemotherapeutic agents is that they inhibit cell proliferation throughout the body, potentially producing immunological, gastrointestinal, or other side effects. Cell division inhibitors can be injected into the brain directly, although this procedure then requires anesthesia and invasive surgery with the associated potential for pharmacological and immunological side effects as well as surgical damage to the targeted region. Effective use of these agents requires that the doses be minimized and potential side effects carefully controlled for to isolate the specifically affected behavior (Shors et al. 2001).

Several pharmacogenetic models have been developed to specifically inhibit or enhance adult neurogenesis. These models use stem cell–specific promoters to target the neuronal precursors, combined with drugs that confer temporal specificity, enabling inhibition of neurogenesis to be limited to adulthood, after normal hippocampal development is complete. The herpes simplex virus thymidine kinase (HSV-TK) models target stem cells using their glial fibrillary acidic protein (GFAP) or nestin expression, causing these cells to produce a herpes virus protein that leads to DNA damage and cell death if they attempt to divide in the presence of an antiviral drug (Saxe et al. 2006, Snyder et al. 2011b). Several other models drive drug-inducible Cre protein specifically in stem cells, e.g., via nestin promoters, allowing injections of tamoxifen to permanently insert or remove useful genes in these cells during adulthood. As an example of this type of targeting, one mouse strain expresses the diphtheria toxin receptor in stem cells, which then causes newly generated cells to die following injection of diphtheria toxin. This method has the advantage of being able to mark adult-born cells as they are dividing and then kill them at later stages after they are functionally mature, allowing behavioral training to occur when neurogenesis is intact (Arruda-Carvalho et al. 2011). Another model uses the same inducible Cre gene to specifically knock out a subtype of glutamate receptors, NR2B-containing receptors, in the young neurons, inhibiting their normal functioning (Kheirbek et al. 2012b). A third inducible Cre model, and the only method to specifically increase numbers of new neurons, uses this strategy to eliminate expression of the proapoptotic gene, *Bax*, preventing the cell death that normally occurs in a

large fraction of new neurons during maturation (Sahay et al. 2011a, Snyder 2009a). Cre models provide a great deal of flexibility, but because they affect cells independent of mitosis, nonspecific expression of Cre in other brain regions is a potential concern (Sun et al. 2014).

Perhaps the most commonly used method for eliminating adult neurogenesis in the rodent is irradiation. Although whole-body irradiation has major effects on the immune and other systems, irradiation targeted to the brain has surprisingly few detectable effects aside from inhibiting neurogenesis (Tan et al. 2011, Wojtowicz 2006). Following targeted brain irradiation, rats show no changes in numbers of red or white blood cells, axonal conduction velocity, and synaptic release probability in the dentate gyrus and hippocampal CA1 region (Snyder et al. 2005). Small (5–10%) decreases in weight gain have been reported in irradiated rats relative to their sham-irradiated counterparts (Snyder et al. 2005), but it is not clear whether this a nonspecific effect or a result of losing neurogenesis, perhaps part of an affective syndrome (Dzirasa & Covington 2012). The primary disadvantage of irradiation is that it uses large, expensive equipment requiring specialized knowledge to run and maintain. However, it has the unique advantage of being able to noninvasively target the hippocampus specifically, using collimation and/or shielding to direct irradiation to the caudal portion of the rodent brain, thus sparing the subventricular zone precursor cells that generate olfactory bulb neurons (Santarelli et al. 2003, Snyder et al. 2011b). All of the pharmacogenetic models to date target adult neurogenesis in the olfactory bulb as well as the hippocampus, as do chemotherapeutic agents, unless the drugs are injected into the hippocampus itself. Advanced shielding and image-guided irradiation promise to allow even more specific spatial targeting, concentrating the highest dose of irradiation in the hippocampus or even a portion of the hippocampus (Tan et al. 2011, Wu & Hen 2014). Irradiation has been used to demonstrate that social interaction deficits are specific to olfactory neurogenesis and that anxiety/depressive-like behavior changes are produced specifically by loss of hippocampal adult neurogenesis (Feierstein 2012, Santarelli et al. 2003, Snyder et al. 2011b). However, because of the lack of spatial specificity of most methods, including irradiation in many studies, it is frequently not clear whether observed behavioral deficits reflect the loss of new neurons from the hippocampus, the olfactory bulb, or potentially even other neurogenic regions including the hypothalamus, striatum, and neocortex (Dayer et al. 2005, Ernst et al. 2014, Robins et al. 2013).

Each method of inhibiting adult neurogenesis has strengths and weaknesses, and each is likely to have some level of nonspecificity, even if none has been detected. Nevertheless, the irradiation, chemotherapeutic, and pharmacogenetic methods described above can all inhibit adult neurogenesis without obvious nonspecific effects. And, importantly, these methods produce behavioral changes that are frequently replicated using another, suggesting that the particular methods used to inhibit neurogenesis not likely to explain apparent differences between findings. Therefore, the behavioral findings in animals lacking adult neurogenesis are discussed below, in many cases without reference to which of these specific methods was used to inhibit adult neurogenesis.

FUNCTION OF NEW NEURONS IN THE HIPPOCAMPUS

Eliminating newborn granule neurons should logically produce impairments that are related to, but likely more limited than, those seen after lesion or inactivation of the entire hippocampus. Most studies of adult neurogenesis function, therefore, have focused on well-known hippocampus-dependent tasks involving learning and memory.

Trace Fear Conditioning

The first published study directly assessing the function of adult neurogenesis showed impaired eyeblink fear conditioning in rats lacking adult neurogenesis (Shors et al. 2001). This study showed

decreased cue responding in MAM-treated rats trained in a trace cue condition, in which there is a 500-ms interval between the end of the cue and the unconditioned stimulus, but not in a delay condition in which the shock occurred during the last 100 ms of the noise cue. A similar impairment was also found in freezing in a cued fear conditioning task with a trace interval but not in spatial maze learning, contextual fear conditioning, novel context exploration, or anxiety-like behavior in the elevated plus maze (Shors et al. 2002). Because trace fear conditioning is the most slowly learned of these tasks, these authors suggested that task difficulty might be an important determinant of the requirement for new neurons.

Recognition

In addition to the negatively motivated learning tasks described above, behavioral changes in animals lacking adult neurogenesis have also been found in spontaneous investigation tasks. Several studies have found deficits in social investigation tasks in mice lacking adult neurogenesis (Lagace et al. 2010, Mak & Weiss 2010). However, because of the importance of olfaction in rodent social recognition (Sanchez-Andrade & Kendrick 2009), these impairments are generally thought to reflect depletion of olfactory neurogenesis rather than hippocampal neurogenesis- -a possibility that has been demonstrated in at least some social recognition tasks (Feierstein et al. 2010). Investigation of novel objects is also altered in mice lacking adult neurogenesis, and this behavior is unlikely to rely on newborn olfactory neurons, because olfaction is controlled for in these tests by using objects with identical odors (e.g., objects built from Lego blocks) or by switching the objects during training and testing days with identical objects. Interestingly, the first study reporting a role for new neurons in novel object exploration found that mice lacking adult neurogenesis showed increased exploration of a novel object, whereas control mice of this strain showed no preference (Denny et al. 2012). This finding suggests enhanced recognition or memory over the three-minute intertrial interval in the mice lacking new neurons rather than the impairment that might be expected. A study of mice lacking NR2B-type glutamate receptors in new neurons found decreased focus on the novel object relative to the familiar one (Kheirbek et al. 2012b). These authors, however, also reported that mice with NR2B-deficient young neurons spent less time exploring the objects in the sample session, which suggests that behavior in this test may not reflect altered initial investigation rather than impaired recognition memory.

Spatial Memory

Spatial mapping is believed to be an important function of the hippocampus and, consistent with this idea, neurogenesis-related deficits have been observed in several spatial paradigms. Behavioral changes have been found in contextual fear conditioning, i.e., learned fear of a place where an animal has received shock, in some but not all studies. Decreased contextual fear conditioning has been demonstrated in several studies of irradiated rats (Snyder et al. 2009a, Winocur et al. 2006, Wojtowicz et al. 2008), but not in two other rat studies (Groves et al. 2013, Shors et al. 2002). Snyder et al. (2009a) found decreased contextual freezing that developed between three and four weeks after inhibition of adult neurogenesis in rats but found no effect on freezing even after eight weeks in mice. Drew et al. (2010) showed that mice do require adult neurogenesis for contextual fear conditioning, but only when the animals are given very limited training. Taken together, the evidence suggests that new neurons do play a role in contextual fear conditioning under some conditions, but the specific features of testing situations sensitive to the loss of new neurons have not been completely elucidated. One possibility is that new neurons are required when the association is made more difficult, consistent with the hypothesis of Shors et al. (2002) described above.

Perhaps the most widely used hippocampus-dependent spatial task is the Morris water maze. In contrast to the impairments seen after hippocampal lesions, performance on standard spatial water maze training and probe trials is consistently spared in mice and rats lacking adult neurogenesis (Arruda-Carvalho et al. 2011, Ben Abdallah et al. 2013, Snyder et al. 2005, Wojtowicz et al. 2008). However, more difficult tests, for example using long delays, or more subtle behavioral analyses of strategies used to locate a previously learned spatial location, identify impairments in animals lacking new neurons in some, though not all, experiments (Ben Abdallah et al. 2013, Garthe & Kempermann 2013, Snyder et al. 2005). The Barnes maze is in many ways similar to the Morris water maze, and is often thought of as a dry version of the spatial water maze. In the Barnes maze, mice lacking adult neurogenesis are slower than normal mice to use a spatial strategy (Raber et al. 2004), consistent with findings in spatial water maze tasks (Garthe & Kempermann 2013). A decreased bias toward the correct quadrant during a probe trial has been observed in the Barnes maze (Raber et al. 2004, Wong-Goodrich et al. 2010), suggesting that this test may be more sensitive than the water maze to effects of neurogenesis. However, eliminating adult neurogenesis using pharmacogenetic methods does not appear to produce similar impairments in the Barnes maze (S.J.E. Wong-Goodrich & H.A. Cameron, unpublished results).

Pattern Separation

One idea that has recently gained dominance, based in part on computational models (Aimone et al. 2009, Becker et al. 2009, Noguès et al. 2012), is that new neurons are important for pattern separation (Agis-Balboa & Fischer 2014, Aimone & Gage 2011, Aimone et al. 2010, Deng et al. 2010, Groves et al. 2013, Sahay et al. 2011b). Kesner (2013, p. 2) has described pattern separation as "a process to remove redundancy from similar inputs so that events can be separated from each other and interference can be reduced, and in addition can produce a more orthogonal, sparse, and categorized set of outputs." Although pattern separation was initially conceived as a network process, it is widely interpreted as predicting an impairment in behavioral tasks requiring discrimination of similar events or places, in which correct and incorrect targets are nearby or similar in appearance, resulting in a high level of interference. For example, although mice and rats lacking adult neurogenesis are not consistently impaired in contextual fear conditioning, they could be impaired at discriminating between the context in which they were shocked and a similar no-shock context sharing many features of the shock context.

Impairments consistent with this definition of pattern separation have been found in several contextual discrimination studies: mice with impaired neurogenesis are slower to show differential freezing to highly similar contexts but are unimpaired when contexts are very different (Kheirbek et al. 2012a, Nakashiba et al. 2012). Conversely, mice with increased neurogenesis are quicker to demonstrate discrimination of highly similar contexts (Sahay et al. 2011a). In an immediate-shock paradigm, in which mice were first familiarized with two contexts then later shocked in only one, freezing behavior in the two contexts was less different in mice lacking adult neurogenesis than it was in controls (Niibori et al. 2012). Spatial separation effects have also been tested in a radial arm maze task, where mice lacking neurogenesis made more errors than control mice when arms were closely spaced but not when they were distant, although this difference arises in part from a change in the normal mice, which counterintuitively showed better performance on the closely spaced arms than on greater separations (Clelland et al. 2009). Using very similar radial arm maze tasks in rats lacking adult neurogenesis, two other groups have found no impairment in distinguishing between adjacent or distant maze arms (Groves et al. 2013, Piatti et al. 2014).

Several additional findings in tasks focused on memory interference can be interpreted as supporting a role in pattern separation. Although rats and mice without neurogenesis show clear

evidence of learning a second platform location in the spatial water maze in some experiments (Groves et al. 2013, Saxe et al. 2006), two studies have identified somewhat more subtle problems in this reversal task. One of these categorized the specific strategies used on reversal trials in the Morris water maze and determined that mice lacking adult neurogenesis show diminished use of precise spatial strategies, relative to normal mice, during reversal learning but not during initial learning (Garthe et al. 2009). A second study found that in a probe trial without the platform, mice lacking adult neurogenesis search in both the original location and the new location, whereas normal mice focus much more on the newer location (Arruda-Carvalho et al. 2011). In an active place-avoidance spatial reversal task, mice lacking adult neurogenesis also showed impairment when a shock zone on a rotating platform was switched to a new location (Burghardt et al. 2012). In all of these reversal tasks, the novel memory for the initial platform location may interfere with the memory for the additional location. Distinguishing these two similar memories may be a form of behavioral pattern separation.

Additional types of interference also cause problems for rodents performing spatial and nonspatial tasks. Rats lacking neurogenesis made more errors than did controls in a cued delayed nonmatch-to-sample task after delays of several minutes but not at very short delays (Winocur et al. 2006). This time delay could increase interference from competing thoughts or memories of previous trials. Irradiated rats also made more errors in a cued water maze when a high-interference task (using similar cues), but not an uncued low-interference task, was performed for several days between training and memory testing (Winocur et al. 2012). The role of interference in impairment associated with loss of neurogenesis is also seen in a nonspatial interference task, in which rats without neurogenesis learn a list of odor pairs normally but then make more errors when learning a second list that repeats some of the same odors (Luu et al. 2012). Taken together, these studies suggest that new neurons are more likely to play a role in behavioral tasks involving greater interference, yet even tasks with apparently high levels of potential interference can often be performed without adult neurogenesis. Since it is difficult to compare interference levels across tasks, it is possible that high-interference conditions in some tasks are simply not high enough to require new neurons. Alternatively, another feature that is associated with high interference, such as difficulty, may be more important for determining the need for new neurons.

Nonmnemonic Tasks

In addition to the behavioral changes observed in many learning and memory tasks, the loss of adult neurogenesis alters behavior in several tasks that have no apparent memory component. One of these, described above, is the decreased exploration of objects the first time they are encountered, in mice with NR2B-deficient new neurons (Kheirbek et al. 2012b). Several possible behavioral changes could produce this effect, including decreased exploratory motivation or increased anxiety. Interestingly, spatial exploration is frequently used to assess anxiety-like behavior in tests such as the open field and elevated plus maze. However, animals without neurogenesis consistently show normal behavior in these tests, as seen in a meta-analysis of data from 25 studies (Groves et al. 2013), a finding that argues against a direct role for neurogenesis in these behaviors—despite the deficits produced in these tasks by impairing hippocampal function with drugs or lesions. Loss of adult neurogenesis does, however, affect behavior in a slightly different exploratory task, the novelty-suppressed feeding (NSF) test, if animals are stressed (Snyder et al. 2011b). This task measures the conflict between hunger, which motivates animals to eat food in the center of an open field, and the feeling of safety, which drives rodents to stay close to the walls and venture out into open spaces only briefly. Mice lacking new neurons showed normal latency to feed under baseline conditions but increased latency to feed relative to normal mice if they were acutely restrained

just before testing (Snyder et al. 2011b). The NSF test is thought to model depressive behavior as well as anxiety because it is affected by both anxiolytics and antidepressants. Antidepressants generally only alter NSF behavior when adult neurogenesis is intact (Airan et al. 2007, David et al. 2009, Santarelli et al. 2003, Wang et al. 2008), although this requirement is not seen in a highly anxious mouse strain (Holick et al. 2008). Two additional depression-related behaviors are affected by loss of adult neurogenesis. Mice lacking new neurons become immobile more quickly in a one-trial forced swim test and also drink less sucrose in a two-bottle sucrose preference task, a model of anhedonia (Snyder et al. 2011b). Taken together, these changes suggest a possible role for adult neurogenesis in limiting depressive-like behavior. The increased immobility in the stressful forced swim test and increased latency in the NSF test following restraint further suggest a role for new neurons in response to stress—a role that is supported by the prolonged stress hormone (corticosterone) response to restraint (Snyder et al. 2011b). Importantly for the current discussion, none of the changes seen in NSF test latency to feed, forced swim test immobility, novel object exploration, or glucocorticoid release following acute stress seem to rely on prior knowledge or experience. As such, effects on pattern separation or other aspects of learning and memory, as they are normally conceived, cannot readily explain these roles for new neurons. So although the loss of adult neurogenesis alters behavior in several learning and memory tasks, particularly in more difficult tasks, it also has effects in novel stressful and nonstressful situations that must be accounted for by theories of new neuron function.

HIPPOCAMPUS-DEPENDENT BEHAVIORS WITHOUT CLEAR MEMORY COMPONENTS

If inhibiting adult neurogenesis in the dentate gyrus has behavioral effects that are independent of learning and memory, as described above, this implies that inactivation of larger populations of hippocampal neurons can also have nonmnemonic effects. Most current studies of hippocampal function employ tasks specifically designed to test various aspects of spatial or other forms of memory, so any effects can be interpreted in this light. In this section, we describe findings from experiments looking at hippocampal function using nonmnemonic tasks, primarily one-trial assessments that rely on innate behaviors and require no specific prior learning. These behavioral findings do not argue against previously described functions of the hippocampus in learning and memory, but they suggest that ideas about hippocampal function need to be broadened to include critical roles for the hippocampus in aspects of emotion, threat assessment, and attention.

Anxiety

Prominent behavioral effects in early studies of rats with hippocampal lesions were increased activity in a novel open field containing food, increased time eating food if food deprived, and increased consumption of water with novel flavoring (Jarrard 1968, Miller et al. 1986)—all of which are consistent with decreased anxiety. Early lesions removed the entire structure, including fibers of passage, so it is possible that these effects did not truly reflect hippocampal loss. However, later studies using more selective, fiber-sparing lesions of the ventral hippocampus also found decreased anxiety-like behavior in unconditioned exploratory tasks; these selectively lesioned animals spend more time exploring open arms of the elevated plus maze, more time exploring the center of an open field, and less time to begin feeding in a neophagia task (Bannerman et al. 2002, 2003; Deacon et al. 2002; Kjelstrup et al. 2002). Similar decreases in anxiety-like behavior in the elevated plus maze and open field have been observed in mice lacking functional *N*-methyl-D-aspartate (NMDA) receptors in dentate gyrus granule cells (Barkus et al. 2010) and in rats with ventral dentate gyrus

lesions (Weeden 2012), suggesting that loss of functional granule neurons mimics loss of the entire hippocampus. In addition, ventral hippocampus-lesioned animals show decreased freezing behavior in response to an innate/unlearned stimulus (cat odor) as well as to a conditioned stimulus, either a cue or context previously associated with shock (Pentkowski et al. 2006, Richmond et al. 1999). These effects do not appear to involve a deficit in freezing per se, because the lesioned rats freeze normally in response to an actual cat and show other behavioral changes consistent with decreased anxiety, i.e., decreased crouching, increased sniffing, and increased rearing, in response to cat odor (Pentkowski et al. 2006). These changes in innate anxiety-like responses do not rely on memories for specific past experiences and instead point to emotional functions of the hippocampus.

Recent studies using targeted activation or inactivation of specific hippocampal inputs or neuronal populations also support a role for the hippocampus in anxiety. Optogenetic inhibition of inputs from the basolateral nucleus of the amygdala to the ventral hippocampal CA3 pyramidal cells decreases anxiety-like behavior, increasing open arm exploration in the elevated plus maze and increasing center exploration in the open field, consistent with lesion studies (Felix-Ortiz & Tye 2013). Conversely, optogenetic activation of basolateral amygdalar inputs has an anxiogenic effect, decreasing open arm and center exploration time and increasing latency to begin feeding in a novelty-suppressed feeding task. Somewhat surprisingly, a recent study found that optogenetic stimulation of granule cells in the ventral dentate gyrus has an anxiolytic-like effect on open field and elevated plus maze exploration (Kheirbek et al. 2013). This finding that massive stimulation of granule cells mimics hippocampal lesions might be explained by the strong input from granule cells to inhibitory interneurons, which can result in net inhibition of CA3 (Acsády et al. 1998).

Endocrine Response to Stress

It has been known for more than 50 years that lesioning the rodent hippocampus increases circulating glucocorticoid levels, whereas electrical stimulation has the opposite effect (Fendler et al. 1961, Knigge 1961, Slusher & Hyde 1961). Similar effects of stimulating the hippocampus have been observed in humans as well (Mandell et al. 1963, Rubin et al. 1966). Subsequent studies suggested that hippocampal lesions primarily affect the termination of the glucocorticoid response following acute stress, prolonging the recovery to baseline glucocorticoid levels (Herman et al. 1998, Jacobson & Sapolsky 1991). The hippocampus seems to play a bigger role in modulating glucocorticoid response in situations involving psychogenic or anticipatory stress, where there is only a potential threat of danger, than in responses to systemic stressors, which involve actual physical threat (Jankord & Herman 2008). This suggests that the hippocampal role in stress response may be in assessing potentially stressful situations, consistent with a role in anxiety as discussed above and below. Several studies have investigated the relationship between glucocorticoids, anxiogenic behavior, and the hippocampus. Rats bred for high-anxiety-like behaviors show decreased open arm exploration but similar glucocorticoid levels, relative to low-anxiety rats, when freely exploring an elevated plus maze. However, the glucocorticoid levels of high-anxiety rats are higher than those of low-anxiety rats when forced to sit on the open arm (Landgraf et al. 1999, Liebsch et al. 1998), suggesting that voluntary behavior may be modulated to maintain certain glucocorticoid limits, which do not differ between high-anxiety and low-anxiety rats. Damage to the hippocampus (ventral subiculum) in normal rats increases time in open arms on an elevated plus maze and also increases glucocorticoid response (Mueller et al. 2004), suggesting that the hippocampus may play a role in setting the stress/glucocorticoid tolerance level, which in turn affects willingness to engage in anxiogenic behaviors. Although this potential relationship among the hippocampus, glucocorticoids, and anxiety-like behavior is highly speculative, it is evident that

the effects of hippocampal lesions on stress response are not secondary to learning and memory effects because they are observed on initial exposure to an environment or experience.

Behavioral Inhibition

Rats display a flexible repertoire of normal defensive behaviors that are used to collect information about, to hide from, or to escape a potential threat. The specific range of behaviors varies depending on the magnitude of the danger and the possibility for escape (Gray & McNaughton 2000, McNaughton & Corr 2004). The initial response is behavioral inhibition, that is, halting whatever behaviors were ongoing before the threat was detected. Freezing behavior, or complete immobilization, can be part of behavioral inhibition, but other risk assessment behaviors such as scanning of the environment also play a role (Blanchard et al. 1989, Gray & McNaughton 2000). After this assessment, behaviors can be adjusted to reflect the specific situation. In a confined area with no escape options, adult rats confronted by a threat such as a cat show complete cessation of movement, i.e., freezing, which is unaffected by hippocampal lesions, but when an escape path is available, lesioned animals display enhanced avoidance compared to controls (Blanchard & Blanchard 1972, Pentkowski et al. 2006). When exposed to cat odor, instead of a cat, hippocampal-lesioned rats freeze less than controls. Together these findings suggest that loss of the hippocampus leads to more active responses to potentially threatening situations unless there is a clear, unavoidable threat. This effect may be related to the increased exploration seen in the less threatening environment of a novel open field in hippocampus-lesioned rats and in mice during optogenetic stimulation of the granule cells (Kheirbek et al. 2013).

During development, preweanling rat pups freeze when placed in a cage with a potential predator, an unfamiliar adult male rat (Takahashi 1992). Injection of glucocorticoids into the dorsal dentate gyrus accelerates the maturation of the granule neurons and facilitates this behavioral inhibition response (Gould et al. 1991, Takahashi 1995). Conversely, dorsal dentate gyrus lesions and drugs that disrupt normal maturation of the dentate gyrus inhibit this freezing response (Gould & Cameron 1997, Takahashi 1995). These studies indicate that the hippocampus is critical for behavioral inhibition in response to innate predators in both young and adult rats and, interestingly, demonstrate an effect of stress hormones on development of this behavior.

In addition to its role in defensive situations, a form of behavioral inhibition is also seen in learning situations, in which incorrect responses must be suppressed while correct responses are allowed. This positively motivated form of behavioral inhibition is also hippocampus dependent. Lesions of the ventral hippocampus or disconnection from the ventral prefrontal cortex increase impulsive responses, in which rats press touchscreen icons prematurely, as well as perseverative responses, in which rats press multiple times when only the first press is needed to trigger a reward (Abela & Chudasama 2013, Chudasama et al. 2012). The animals' correct responses demonstrate that they have learned the associations, but they appear less able to withhold responses at times when responses are ineffective.

The hippocampus, then, appears to increase inhibition of prepotent, i.e., ongoing or habitual, behavior in both aversive and rewarded situations. It is important to note that this inhibition results in freezing, or complete cessation of behavior, in some situations, but in other situations stops only specific ongoing behaviors, enabling alternative and potentially more adaptive behaviors to emerge.

Orienting and Attention Shifting

Although the hippocampus is rarely included in models of attention circuits, several rodent studies demonstrate that hippocampal damage affects attention to simple stimuli. Rats with hippocampal

lesions fail to orient toward a novel clicking noise, as do normal controls, when they are focused on drinking water. However, hippocampal-lesioned rats orient normally if they are exploring an empty arena, a finding that suggests that the change in behavior reflects a failure to shift attention to a novel stimulus rather than a sensory impairment (Hendrickson et al. 1969). Likewise, hippocampus-lesioned rats trained to seek a reward at the end of a linear runway fail to slow their running speed to attend to novel visual cues on the walls, whereas controls significantly reduce their speeds in response to the visual distractors (Raphelson et al. 1965). This altered investigation of novel cues may play a role in the decreased novel object exploration found in the NR2B-knockout mice (Kheirbek et al. 2012b) and the decreased investigation associated with pattern separation errors in humans (Molitor et al. 2014), both described above. In another study of attention shifting, rats were presented with light-tone cue pairs. When presented with both light options following a tone cue, normal rats looked at the light that was inconsistent with the presented tone. However, rats with hippocampal lesions oriented toward the expected light cue. This does not appear to reflect a learning deficit, because rats that failed to learn the associations should show no preference between the cues. Instead, these results suggest that the hippocampal damage altered the animals' attention preference (Honey & Good 2000). This finding is consistent with Simonov's idea, described below, that the hippocampus focuses attention on low-probability events (Simonov 1974).

A recent study of visual search strategy in humans found that participants with hippocampal damage explored novel scenes to look for hidden targets in a disorganized manner, whereas normal control subjects showed highly systematic exploration. Interestingly, these hippocampal-damaged subjects were able to successfully retain and retrieve information about object location; despite the impaired search strategy, there was no group difference in the ability to head directly back to the starting point (Yee et al. 2014). Together, these studies suggest that the hippocampus organizes visual search strategy and enhances attention to novel or unexpected stimuli. In some cases, these unexpected stimuli may act as potential threat cues (e.g., the noise in the Hendrickson et al. experiments). However, in other examples described here, there does not appear to be any potential threat, which suggests that these attention changes may be independent of negative emotion.

Innate Fear Response in Nonhuman Primates

The role of the hippocampus in contextual fear conditioning is widely known, but the hippocampus also alters response to innate fear. This is shown clearly in an approach/avoidance conflict test in macaque monkeys with excitotoxic lesions (Chudasama et al. 2008, 2009). In this task, monkeys were required to reach over a clear plastic box containing a rubber snake, a rubber spider, or a neutral object in order to retrieve a food reward. In unoperated control monkeys, food retrieval was six times slower on snake/spider trials than on neutral trials. Control monkeys also spent less time approaching the snake/spider than the neutral objects and displayed many more defensive behaviors, such as avoiding visual contact, in the presence of the snake/spider. Upon first presentation of the snake/spider stimulus, monkeys with hippocampal lesions behaved much like controls (Chudasama et al. 2009, Machado et al. 2009). However, on subsequent presentations of the fearful stimulus, monkeys with hippocampal lesions showed latencies similar to those in the neutral condition and displayed very few innate fear responses, whereas the behavior of control monkeys changed very little from the initial presentation. Interestingly, although food retrieval latency was similar in monkeys with hippocampal and amygdala lesions, monkeys with amygdala lesions spent a significant amount of time looking directly at the snake/spider, whereas animals with hippocampal lesions showed no clear interest in the snake/spider, which suggests that the hippocampal lesions

diminished emotional reactivity, diminished interest or arousal, and/or decreased attention toward the innately fearful stimuli. The behavioral changes shown by these monkeys point to connections between the other hippocampus-dependent behaviors described above in rodents; the monkeys' responses are consistent with decreased anxiety, decreased behavioral inhibition, and decreased attention to arousing stimuli.

Orienting toward an unknown stimulus is a first step in identifying and assessing a potential threat, and behavioral inhibition also allows for further assessment of danger. With hippocampal damage, anxiety and behavioral inhibition are decreased, and behaviors ongoing before the potential threat (prepotent behaviors) are maintained. Although hippocampal regulation of glucocorticoid release is not a behavioral function, it is also related to threat assessment because it occurs in response to psychogenic stress, or the perception of potential danger. All of these hippocampal functions could be characterized as regulating emotion in response to a potential threat and occur without reference to specific memories for prior experience. That is, these findings indicate that the hippocampus has emotional roles that do not rely on memory, in addition to any roles in learning and memory.

ALTERNATIVE IDEAS ABOUT HIPPOCAMPAL FUNCTION

It is widely accepted that the function of the hippocampus is to support memory and/or spatial maps (Eichenbaum & Cohen 2014). There are lively discussions and differences of opinion regarding its importance in spatial versus nonspatial memory; long-term, short-term, and/or working memory; memory acquisition, consolidation, or retrieval, etc., but few disagree with the general principle that the hippocampus is primarily a mnemonic machine. This has not always been the case (Altman et al. 1973, Amsel 1993, Woodruff et al. 1975). Early thinking about hippocampal function centered on various roles in emotion. The idea that the hippocampus plays a critical role in emotion continues to appear only sporadically in current thinking (Bannerman et al. 2014), but it may be critical for understanding behavioral changes found in animals lacking adult neurogenesis. In this section, we discuss the hippocampus-dependent behaviors described in the broader context of nonmnemonic theories of hippocampal function that have been proposed over the past 80 years.

Emotion

In one of the oldest systematic theories of hippocampal function, Papez (1937) proposed that it is the key structure in a circuit responsible for the control and expression of emotion. He argued, based primarily on the symptoms and neuropathology of rabies in humans, that emotions are generated within the hippocampus and then relayed through a circuit containing the mammillary bodies, anterior thalamic nuclei, anterior cingulate gyrus, parahippocampal gyrus, and then back to the hippocampus. Although the anatomical connections of the Papez circuit are not in dispute, the amygdala, rather than the hippocampus, is now widely considered the central hub for emotionality (Dalgleish 2004). Nevertheless, the view of the hippocampus as a critical structure for emotion fits with the well-characterized effects of hippocampal lesions on anxiety described briefly above and in more detail in a recent review (Bannerman et al. 2014).

Although both fear and anxiety elicit emotional responses, there is a conceptual difference between the two states that relates to differences in the circuitry controlling them (McHugh et al. 2004). Fear can be thought of as the emotion generated when an adverse event is imminent, whereas anxiety is generated when the *potential* for threat is present (Bannerman et al. 2004, McNaughton & Corr 2004). According to this distinction, fear is processed in the amygdala, and anxiety is processed in the hippocampus (Bannerman et al. 2004, McHugh et al. 2004, McNaughton & Corr

2004). When fear is elicited, animals will rapidly try to leave the threatening situations or, if this is not possible, attempt to protect themselves in some other way, e.g., attacking or freezing. In the case of anxiety, however, rodents normally display risk-assessment behaviors, often characterized as anxiety-like behaviors, to gather more information about the potential threat (Blanchard et al. 2011, Lever et al. 2006, McHugh et al. 2004).

Interestingly, animals lacking adult neurogenesis, unlike their hippocampal-lesioned counterparts, do not generally show decreased anxiety-like behavior. The classic tests of unconditioned anxiety, the open field test and elevated plus maze, have been examined in multiple studies of both rats and mice lacking adult neurogenesis. A meta-analysis of these data convincingly shows that loss of new neurons has no consistent effect on either task (Groves et al. 2013). No stress-induced changes in these tests were observed in mice lacking new neurons either, despite the effects on novelty-suppressed feeding (Snyder et al. 2011b). It should, perhaps, not be surprising that eliminating a subset of neurons in one region of the hippocampus would have fewer behavioral effects than removing the entire structure. Mature granule cells, for example, may be sufficient for generating anxiety, or these behaviors may require only the hippocampus proper and not the dentate gyrus. Comparing hippocampal functions with roles of new neurons specifically should provide valuable clues to how different hippocampal subregions work together to produce specific behavioral outcomes.

Consistent with the role in emotion suggested by Papez, the hippocampus has important interactions with the stress response system. Stress is produced by conditions that put a high demand on an individual, particularly in unpredictable or uncontrollable situations (Koolhaas et al. 2011). Stress produces a neuroendocrine cascade via the hypothalamic-pituitary-adrenal (HPA) axis. Corticotrophin-releasing hormone produced by the paraventricular nucleus of the hypothalamus stimulates the release of adrenocorticotropic hormone (ACTH) by the anterior pituitary gland. ACTH then triggers the adrenal glands to synthesize and release glucocorticoid stress hormones, including cortisol, the primary glucocorticoid in humans, and corticosterone, the primary glucocorticoid in rodents (Jankord & Herman 2008, Ulrich-Lai & Herman 2009). Regulation at all of these levels acts to tightly control the output of glucocorticoids, which affect not only the brain but also systems throughout the body, including the immune and cardiovascular systems (McEwen 1998). Recognizing and preparing for adverse situations is clearly advantageous, but dysregulation of the stress-response system is associated with mood disorders and other psychiatric illnesses. As described above, lesions or inactivation of the hippocampus increase corticosterone and ACTH levels, whereas electrophysiological stimulation of the hippocampus decreases corticosterone levels (Jankord & Herman 2008). These effects suggest that the hippocampus adds another layer of regulation to the HPA axis (Jacobson & Sapolsky 1991, McEwen et al. 1968, Sapolsky et al. 1984). The hippocampus has a very high density of receptors for stress hormones, enabling it to directly detect systemic glucocorticoid levels (Gerlach & McEwen 1972, McEwen et al. 1968).

Stress and glucocorticoids have effects on hippocampus-dependent behaviors and hippocampal structure that are clear but complex and not fully understood. In rodent models, chronic stress, acting through glucocorticoids, also alters the structure of the hippocampus by inhibiting adult neurogenesis, decreasing the length of the CA3 pyramidal cell dendrites, and decreasing the volume of the hippocampus. Decreased hippocampal volume has been reported in humans following high-dose glucocorticoid therapy, chronic stress, or posttraumatic stress disorder (Bremner et al. 2008, Gianaros et al. 2007, Sapolsky 2000). Chronic stress affects hippocampus-dependent spatial behavior in rodents, decreasing spontaneous alternation in the Y-maze and facilitating contextual fear conditioning in ways that appear consistent with the negative impact of chronic stress on hippocampal structure. The stressor-induced changes in dendritic shrinkage follow the same

time course as the behavioral changes, and tianeptine treatment, which prevents the dendritic retraction, also prevents the spatial memory changes associated with stress (Conrad 2006).

However, as discussed by Conrad (2006), stress-induced changes in spatial memory and hippocampal structure do not always go hand in hand. For example, although tianeptine blocks both stress-induced CA3 dendritic atrophy and spatial memory impairment, it does not prevent facilitation of contextual fear conditioning. Furthermore, chronic injection of corticosterone mimics the effects of chronic stress on CA3 dendritic atrophy but does not consistently impair spatial memory. This latter finding provides an important clue to the relationship between hippocampal structural changes and spatial memory (Conrad 2006). Following chronic stress, Conrad and colleagues gave rats metyrapone, which prevents stress-induced release of glucocorticoids, just before testing the animals in the Y-maze. Stressed animals that were not given metyrapone showed the expected impairment in Y-maze alternation, but when corticosterone release was blocked, rats showed normal alternation, identical to unstressed controls. This finding suggests that chronic stress, acting via structural changes in the hippocampus, affects spatial behavior by altering HPA axis response during behavioral testing. And in fact, chronically stressed rats do show higher corticosterone release than unstressed rats show during novel testing situations. Rats treated chronically with corticosterone do not show this stronger corticosterone response. This seems paradoxical at first, because stress causes corticosterone release. However, although both endogenous and exogenous corticosterone lead to dendritic atrophy, chronic activation of the HPA axis results in enlargement of the adrenals and enhanced glucocorticoid response to future stress, whereas exogenous corticosterone activates only the negative feedback portion of the HPA axis, resulting in adrenal atrophy and diminished response to future stress (Conrad 2006). Hippocampal changes cannot increase corticosterone release if the downstream portion of the HPA axis is atrophied.

The effects described above develop only after chronic stress, but acute stress alters behavior and neurogenesis as well. Glucocorticoids are released rapidly in response to novel or arousing situations, with increased serum levels detectable within five minutes. However, the high-affinity corticosteroid receptors have relatively slow effects requiring gene transcription, and the rapid nongenomic effects are mediated by low-affinity receptors that require near-peak levels of corticosteroids, which are slower to appear (de Kloet et al. 2008). Therefore, most corticosterone effects on brain function will occur several minutes to hours after the stressful triggering event rather than in the critical first few minutes after a threat is detected. These slow effects, as well as the morphological and anatomical effects of corticosterone that occur with an even more prolonged time course, suggest that the most important role of glucocorticoids in the brain may be to affect future behavior. It follows, then, that effects of stress on the hippocampus may function to facilitate adaptation to adverse, or at least challenging, conditions over the course of days to weeks. Failure to adjust behavior to newly adverse conditions, and failure to reassess and readapt behavior if conditions improve, could both have negative consequences for an organism.

A role for the hippocampus in stress response fits well with recent findings on the function of adult neurogenesis. Acute stress has no effect on NSF behavior in normal mice, but it increases latency to feed, an anxiety/depressive-like behavior, in mice without adult neurogenesis. New neurons, therefore, appear to buffer mice against the behavioral effects of the stressful experience (Snyder et al. 2011b). New neurons also mediate antidepressant-induced reversal of reward seeking following chronic stress (Surget et al. 2011). Without prior stress, mice lacking new neurons show increased depressive-like behavior in a forced-swim test (Snyder et al. 2011b). Because this test is itself stressful, that is, it poses an apparent unavoidable threat to the animals, it may be that testing stress acts in place of restraint stress in this experiment. These findings suggest that new neurons play a role in regulating behavioral responses to stress, consistent with a role for the hippocampus as a whole in stress adaptation. More work is needed, however, to determine

specifically how new neurons alter behavioral responses and whether dysregulation of neurogenesis produces maladaptive effects in more realistic situations.

Orienting and Behavioral Inhibition

A recent study in humans suggests that errors in pattern separation may be related to attention (Molitor et al. 2014). Earlier functional imaging studies linked responses to lures (visual items that are novel but similar to previously seen items) to the hippocampus, specifically the CA3/dentate gyrus region (Bakker et al. 2008). Molitor and colleagues (2014) focused on behavior associated with pattern separation errors, defined as responding to lures as if they were previously seen (presumably mistaking them for the similar items). They found that this type of error was associated with less time looking at the initial studied item, which suggests that the pattern separation error resulted from changes in attention and initial encoding rather than differential degradation of memory. A role for the hippocampus in driving attention was recognized many years ago. Pribram & McGuinness (1975) suggested that the hippocampus acts as a comparator, detecting uncertainty or conflict relative to expectations and regulating arousal and attention in response. In the presence of a novel stimulus, an animal initially displays an orienting response, which aids in collecting information to assess this unexpected event. In the absence of any reward, repeated encounters with the stimulus update expectations such that the stimulus will no longer drive an orienting response. Monkeys with hippocampal lesions fail to show this type of habituation; they continue to be distracted by irrelevant cues long after the distractors have ceased to slow responses in control monkeys (Douglas & Pribram 1969).

Pribram and colleagues' findings seem inconsistent with data from orienting studies indicating that hippocampal damage decreases, rather than increases, distractibility. As described above, rats with hippocampal lesions fail to show normal orienting responses toward novel visual or auditory stimuli in several different tasks (Hendrickson et al. 1969, Honey & Good 2000, Raphelson et al. 1965, Wickelgren & Isaacson 1963). This apparent contradiction could reflect the different aspects of mismatch detection targeted by the different experiments. Douglas & Pribram (1969) focused on habituation of responses to meaningless stimuli presented during learning of rewarded stimuli, whereas the orienting studies focused on the initial responses to the unexpected stimulus after other associations or behaviors had been well learned. All of the studies, then, seem consistent with increased focus on prepotent behaviors and decreased updating of attention processes in animals with hippocampal damage. Another possibility is that the difference is due to the valence of the stimuli. In the Douglas & Pribram (1969) study, the distracting stimuli were similar to cues that predicted rewards, so the monkeys might expect these cues to predict reward and certainly had no reason to find the cues aversive. In the orienting tests, however, the unexpected noises or flashing lights might suggest a potential threat. Perhaps the hippocampus drives attention toward stimuli that could predict a threat and away from stimuli that are neither threatening nor rewarding. Studies directly investigating the role of the hippocampus in response to innately fearful stimuli seem consistent with this idea (Chudasama et al. 2008, 2009; Machado & Bachevalier 2008). Normal monkeys presented with rubber snakes or spiders in front of a food reward showed several fear behaviors while focusing their attention on the snake/spider. Monkeys with amygdala lesions showed little fear but maintained a great deal of interest in the snake/spider. Hippocampal lesions, however, eliminated both the fear behavior and the visual attention toward the snake/spider. Interestingly, hippocampus-lesioned monkeys showed normal levels of attention and defensive behaviors during their first trial with the spider or snake but then showed little interest or fear on subsequent trials, suggesting that they habituated to the fearful stimulus very quickly relative to normal monkeys. This rapid habituation and low level of attention paid to the fearful stimulus,

which was essentially a distractor from the food-grasping task, parallels the effects of hippocampal lesion in the orienting studies (Hendrickson et al. 1969, Honey & Good 2000, Raphelson et al. 1965, Wickelgren & Isaacson 1963) and differs from those in the neutral stimulus learning experiments (Douglas & Pribram 1969). The possibility that the hippocampus helps to drive and maintain attention toward threatening cues and away from neutral cues adds an emotional element to the role in attention, consistent with the emotional functions described above.

Wickelgren & Isaacson (1963) pointed out that the failure of hippocampus-lesioned rats to stop and investigate a novel cue could reflect a failure to notice the stimulus or a failure to stop running toward the goal despite registering the novel stimulus. This latter interpretation fits with another once-common idea that a primary function of the hippocampus is "braking" or inhibiting ongoing behaviors (Altman et al. 1973, Douglas 1967, Gray & McNaughton 2000, Silveira & Kimble 1968). This inhibition is often observed in response to threatening cues. When this system is engaged, it increases attention/vigilance and risk-assessment behaviors while inhibiting behaviors that were occurring prior to the threat (Gray & McNaughton 2000). The dentate gyrus–dependent freezing behavior observed in pups placed near an anesthetized adult male rat is a classic example of this threat-induced behavioral inhibition (Takahashi 1995, 1996). The decreased behavioral inhibition in response to novel and potentially threatening situations can cause hippocampus-lesioned animals to appear reckless or hyperactive in some situations. These behaviors led Altman and colleagues (1973) to suggest that the late development of the hippocampus may be responsible for the maturation of behavior from erratic and reckless in juveniles to more observant and cautious in adults, although clearly even preweanling pups show behavioral inhibition under the right circumstances. The cautious behavior produced by behavioral inhibition is clearly adaptive, as it should tend to prevent animals from running headlong into potentially dangerous situations and enable animals to gather information to assess the situation.

Hippocampal lesions produce impairments in what could also be called behavioral inhibition in nonthreatening, reward-mediated learning tasks as well. In these situations, braking serves to slow or inhibit responses that have been previously conditioned when reward decreases or is ambiguous. Inhibition of prepotent behavior in these situations does not serve to protect the animal from harm but rather allows the animal to change its current course of action and seek out alternatives to try to maximize reward. Animals with hippocampal lesions tend to maintain the responses they are initially biased toward, through innate preference or prior conditioning, longer than control animals and therefore fail to maximize rewards. This was shown by Isaacson & Kimble (1972), who found that in a Y-maze, naïve rats generally begin the task with an innate tendency to approach the dark, rather than the light, arm and also with an inclination to form a position hypothesis—that is, to seek rewards in the same place rather than in the arm of the same color. Depending on the rules of the task set by the experimenter, these biases will either lead to correct responses or must be overcome to produce maximal rewards. Rats with hippocampal lesions held onto "hypotheses," such as a position hypothesis leading the animal to consistently choose the left arm of the maze, longer than did control animals. In some cases, their initial hypotheses happened to be correct, and performance was as good as, or better than, that of controls. A related effect has been seen in several other studies, in which prior experience on tasks that are different but share the same general rules can benefit rats with lesion or inactivation of the hippocampus (Bannerman et al. 1995, Beylin et al. 2001, Saucier & Cain 1995). However, when a rat's initial hypothesis was incorrect, choosing the left arm when the white arm is always rewarded regardless of position, for example, animals with hippocampal lesions persisted longer in their original choices and did poorly on the task, failing to update their hypothesis. These findings suggest that activation of the hippocampus may increase behavioral flexibility in order to maximize reward, whereas inhibition of the hippocampus might be expected to maximize persistence in the face of partial reward.

Hypothesis updating in response to low probability of reward, as observed by Isaacson & Kimble (1972), is consistent with Simonov's idea that the hippocampus shifts attentional demands to events that have a low probability of occurrence (Pigareva & Preobrazhenskaya 1991, Simonov 1974). Similarly, stimulus pairs that are inconsistent based on prior learning, which by definition have a lower probability of occurrence than repeatedly paired stimuli, are attended to (preferred) by normal rats, whereas hippocampus-lesioned rats attend to the expected stimulus, i.e., the one with the higher probability of occurrence (Honey & Good 2000). Interestingly, rats with hippocampal lesions show normal behavior, maximizing reward when choosing between a large reward with low probability of occurrence and a small reward with a high probability of occurrence (Abela & Chudasama 2013). This seems somewhat counter to the idea that hippocampal damage impairs attention to low-probability events, but since the probabilities were well established by extensive training, it may be that the hippocampus plays a role in low-probability unpredictable events but is not necessary for predictable low probabilities.

A related body of work suggests that the hippocampus is important in driving response to a decrease or delay of an expected reward. Recent work has shown that rats with hippocampal lesions choose rapidly received small rewards over larger delayed rewards (reviewed in Abela & Chudasama 2013). These animals do choose the high reward options when delays are similar, however, which suggests that learning and memory for the reward association and the preference for large rewards are not affected. Several older studies deal with behavioral responses during the extinction phase of reward learning, when rewards are not just delayed but are absent. It has long been known that behavioral extinction occurs more slowly after training with partial reinforcement than with continual reinforcement, the so-called partial reinforcement extinction effect (PREE) (Amsel 1990). Studies of this effect compare different reward schedules during learning, generally in a runway task, in which the speed of running toward a potential reward is measured, or in an operant conditioning task, in which lever pressing for rewards is assessed. The PREE is somewhat paradoxical from a learning standpoint because partial reinforcement leads to stronger resistance to extinction even though it should produce a weaker association between the action and the reward given that it uses fewer response-reward pairings than does continuous reinforcement (Amsel 1992). Instead of reflecting stronger learning, then, this increased resistance to extinction is thought to reflect an emotional component that is activated when the expected reward is absent. This emotional response to the lack of an expected reward has been called frustration or disappointment (Amsel 1958, Levine et al. 1972). That the PREE effect critically involves emotion is supported by findings that glucocorticoid levels rapidly increase following smaller-than-expected rewards and, conversely, rapidly decrease following greater-than-expected rewards (Levine et al. 1972). Extinction also leads to other apparent emotional responses including aggressive behavior toward other rats or toward the lever (Levine et al. 1972).

Both lesions of the hippocampus and depletion of the granule cell population (via early postnatal brain irradiation) eliminate the PREE (Coover et al. 1971, Rawlins et al. 1980). Interestingly, animals with hippocampal damage show slower extinction than do controls following continuous reinforcement training but more rapid extinction than controls following partial reinforcement. Although the tasks used to study the PREE are learning tasks, the role of the hippocampus does not appear to be on learning per se; hippocampal lesions have no effect in the training/learning phase of the experiments, and, importantly, behavior is unaffected by lesions on a similar learning task when reward and nonreward days alternate (Amsel 1990). Hippocampal lesions do, however, prevent the increased glucocorticoid release normally seen in response to unexpected nonreward (Levine et al. 1972). These findings suggest that the hippocampal role in this task is related to emotion, specifically, in generating frustration when expected rewards are not received (Coover et al. 1971). Taken together, these studies suggest that the hippocampus may play a role in emotional response

to outcomes relative to expectations and in this way may help set the balance between persisting in a particular behavior or strategy and switching to alternate behaviors in the face of changing stimuli.

Prediction

One recently proposed idea is that the central role of the hippocampus is not in remembering the past but instead in predicting the outcome of future events (Buckner 2010, Mullally & Maguire 2013). Buckner points out that memory, the commonly accepted function of the hippocampus, exists primarily to improve future behavior or decision making, and, as such, memory and prediction may be strongly connected and difficult to separate in many studies. This is a particular problem in animal studies, because animals cannot be asked to imagine the future. Most behaviors that rely on predictions also rely on previous learning and memory, just as most real-world predictions utilize memories and previously learned associations. The hippocampus, in this view, uses memory of past experience but is primarily concerned with flexibly recombining these memories to imagine or predict possible outcomes and optimize future behavior.

Support for this idea comes from rodent studies of hippocampal place cells as well as from human imaging studies. Hippocampal place cells are neurons—generally pyramidal neurons but also granule neurons—that fire when the rat is in a particular location of a testing arena. The existence of these cells, which show stable place fields over time, has long been viewed as an indication that the function of the hippocampus is to maintain spatial maps to guide navigation (O'Keefe & Nadel 1978). As animals move along a runway, place cells fire in sequences that can be observed at later time points, during rest or sleep, leading to the interpretation that these replay events reflect consolidation of the memory for the experience in the runway (Carr et al. 2011, Dragoi & Tonegawa 2011). However, recent studies have found that place cell firing sequences recorded during rest can be observed several minutes later when animals are traversing a novel track (Dragoi & Tonegawa 2011, 2013). This "preplay" cannot reflect memory for the spaces that the animals have not yet encountered, but it seems to predict later activity in a way that is reminiscent of imagination in human studies (Mullally & Maguire 2013).

This possibility is addressed more directly by studies of hippocampal network activity during decision making. To investigate this process, animals are run in more complex mazes including choice points at which the animal must make a decision of which direction to head in order to reach a reward. When rats are tested in a multiple-choice-point T-maze, place cell ensemble activity "flows" down each arm, often ahead of the animal's current position (Johnson & Redish 2007), suggesting that the animals may be imagining the outcome of each arm choice. This possibility is strengthened by recent findings that place cell firing sequences are predominant during the early stages of learning and predict immediate future behavior in an open field with multiple start and goal locations (Pfeiffer & Foster 2013, Singer et al. 2013). These findings provide evidence at the level of neuronal activity that fits with behavior seen in rodents at choice points, namely vicarious trial and error (VTE). VTE behavior is defined as looking back and forth at different potential routes before making a choice. More of this behavior is seen during a difficult discrimination, in the early stages of learning, and when there is a price to be paid for making the incorrect choice, such as on apparatus with a gap that must be jumped to return to the choice point (Tolman 1938). Increased VTE behavior is correlated with faster learning, and, conversely, damage to the hippocampus decreases VTE behavior and impairs learning on tasks in which VTE behavior is normally displayed (Bett et al. 2012, Hu & Amsel 1995, Tolman 1938). VTE appears to reflect hippocampus-dependent prediction and evaluation of future outcomes that occurs when animals are uncertain about a decision (Schmidt et al. 2013).

In humans, functional magnetic resonance imaging studies suggest that the hippocampus is strongly activated by episodic memory retrieval but is activated to an even greater degree when imagining the future than remembering the past (Addis & Schacter 2011, Buckner 2010). Because memories are used for constructing imaginary events, and because imagined events (and the experience of imagining them) likely are then stored in memory for future use, imagining and remembering are almost intractably intertwined and at the very least difficult to separate in an experimental paradigm. However, a recent study has attempted to disentangle these processes by comparing imagination of novel future events with "reimagination" of events imagined the previous day (Gaesser et al. 2013). Investigators found that when future events were constructed for the first time, the posterior hippocampus, which is homologous to the rodent dorsal hippocampus, of the left hemisphere was activated relative to the reimagination condition. This finding, along with an earlier study from this group (Martin et al. 2011), suggests that the posterior hippocampus in humans is important for constructing imagined future events, whereas the anterior region may be important for encoding these imagined events. Taken together, both human and rodent studies, using very different methodology, support the possibility that a key function of the hippocampus is in predicting the outcomes of potential actions, based on flexible recombination of prior experience, in order to improve on trial-and-error learning through mental testing of various options.

The view of the hippocampus as a key structure in a system that makes predictions about upcoming events brings together aspects of several other views of hippocampal function, including learning and memory and hypothesis testing. However, imagination and prediction as described above, and by Buckner (2010), do not have any obvious emotional component and so do not appear at first glance to fit with this aspect of hippocampal function. However, studies of emotion in rats many years ago suggested a direct link between prediction and emotion—and proposed a specific role for the hippocampus as well. Simonov's (1991) "need-informational theory of emotions" posits that emotions are determined by a need and by the prediction of the likelihood of its satisfaction: A low probability of goal achievement produces negative emotions, and a high or increased probability of satisfaction leads to positive emotions. The role of the hippocampus in predicting satisfaction of a need, according to Simonov, is in directing attention toward low-probability events. He says of rats with hippocampal damage that it "is not possible to speak of a general memory defect" but instead that their behavior "is no longer complicated by predictions of events unlikely to happen in a given situation" (Simonov 1974, p. 35) so that they behave like "living automata without hesitation and doubt" (Simonov 1991, p. 106).

Emotions may not only be generated by predictions, they may also feed into predictions in the form of cognitive bias. Predictions and decisions are not made solely on the basis of memories and factual observations but rather are influenced, or biased, by emotional states. Stress, anxiety, and depression elicit a negative bias that affects how people interpret perceptions, especially ambiguous threatening cues, and tends to augment the remembrance of negative as opposed to positive events or details (Clark & Beck 2010). The same appears to be true in animal models of these states. When rats are trained to associate one tone with a lever that signals reward and a second tone with a lever that must be pressed to avoid shock, intermediate tones produce mixed responses. Rats genetically bred to show learned helplessness, a depression-like phenotype, show normal behavior in response to the trained tones but respond to the intermediate tones with more presses of the lever signaling shock compared with controls (Enkel et al. 2010). The same is true in standard lab rats acutely treated with corticosterone and the noradrenaline reuptake inhibitor reboxetine. In this experiment, neuronal activation was also greater in the dentate gyrus and amygdala of treated rats than of controls, a finding that suggests roles for these brain regions in this behavior. In another test, mice lacking the serotonin 1A receptor show normal behavior toward a cue that

predicts a shock but show increased anxiety-like behavior toward a cue that ambiguously predicts the shock (Tsetsenis et al. 2007). When the dentate gyrus granule cells are silenced, this effect is eliminated, which suggests that this part of the hippocampus is critical for the increased responding to the ambiguous cue. Together, these findings suggest a possible role for the hippocampus in emotionally biasing predictions and behavioral decisions. An overactive hippocampus may increase negative bias inappropriately, altering decision making in the face of novelty or even the mildest potential threats, resulting in anxiety (Gray & McNaughton 2000).

Another bias that is introduced into this loop of decisions and predictions is attentional bias. It is well documented that people with anxiety disorders show enhanced threat detection, persistently pay more attention to these stimuli, and show a bias in threat appraisal (Britton et al. 2011). Although the role of the hippocampus in this attention bias is not clear, such a role does seem consistent with hippocampal function in orienting, attention, and persistence, as discussed above.

The evidence that the hippocampus plays a role in prediction is strong, but as the discussion above alludes to, there are several different steps in prediction, and it is not clear which are most likely to involve the hippocampus. The hippocampus could participate in selecting relevant knowledge from which to form predictions, flexibly recombining selected knowledge to imagine potential outcomes, estimating the probability of various outcomes, and/or weighing the outcomes to choose the optimal course of action. Selecting relevant memories from which to form predictions appears closely related to the accepted role of the hippocampus in memory retrieval. The idea of a hippocampal requirement for flexible use of memory also seems to fit with this prediction step, because memories could be selected using a wider or more flexible net, leading to increased imagination or creativity, or with a narrower rule regarding what applies to the current situation. Weighing the various outcomes seems closely related to Gray & McNaughton's (2000) view that the hippocampus functions to choose between competing goals.

The hippocampus could also function to inject emotional bias at one or more of these steps, instead of, or in addition to, the formation of predictions per se. Different portions of the hippocampus could potentially be involved in the cognitive and emotional aspects of prediction, with, for example, the dorsal hippocampus mediating cognitive aspects of prediction and the ventral hippocampus providing emotional bias. Emotional biases may affect the prediction process at many levels, by biasing the choice of memories selected for making predictions, judgments about the probability of each outcome of a given action, and the choice of action based on predicted outcomes. If indeed emotions bias predictions and, as Simonov suggested, predictions generate emotions, then emotions and predictions appear to form a feed-forward loop whereby predictions of failure could lead to negative emotions, which then negatively bias future predictions, and so on. If the hippocampus is important for either of these pieces of the loop, this could provide a possible link between the hippocampus, and/or adult neurogenesis, and depressive illness.

CONCLUSIONS

The hippocampus is almost universally viewed as functioning primarily in learning and memory. Because of this function, recent research on the behavioral role of adult neurogenesis in the dentate gyrus has focused on mnemonic tasks and has suggested a role for the new neurons in accurate recall when stimuli are highly similar or when the delay between training and testing is prolonged. However, animals lacking adult neurogenesis also show altered behavior in tests that do not require specific prior knowledge and therefore seem inconsistent with an interpretation relying on pattern separation or other aspects of memory. These nonmnemonic behavioral changes argue for one or more of the alternative functions of the hippocampus that have been proposed over the past 75 years in emotion, attention, and prediction. Traditional roles in learning/memory and these alternative

roles for the dentate gyrus and hippocampus might be reconciled in at least two ways. First, all of the observed behavioral effects in animals lacking adult neurogenesis or a functional hippocampus might be produced by an underlying, fundamental cognitive, emotional, or behavioral change that is critical to all impaired tasks. Although some behavioral changes cannot be explained in terms of learning and memory deficits, impairments in many learning and memory tasks could potentially result from emotional or other behavioral changes. Many behavioral tasks that are thought of as testing cognitive function also have hidden or not-so-hidden stressful and/or emotional aspects. And all learning and memory tasks require many processes in addition to learning and memory, including, for example, attention to cues, motivation, decision making, and motor responses. Some of these, such as motor responses, can be readily controlled for and unlikely to involve the hippocampus, but other cognitive and behavioral changes may be very difficult to control for in learning tasks. It is at least possible, then, that a hippocampal role in a fundamental process such as attention or cognitive bias could alter behavior in a wide variety of learning and memory tasks—a possibility that is hinted at by at least one recent study (Molitor et al. 2014).

Alternatively, the hippocampus might have multiple functions that utilize the processing made possible by hippocampal networks but are otherwise independent and/or unrelated. These different functions do not have to be performed by the same cells within the hippocampus. Although the hippocampus appears to be a single structure, there is considerable evidence that the dorsal and ventral portions (or primate anterior and posterior portions) of the hippocampus are functionally distinct (Barkus et al. 2010, Fanselow & Dong 2010). There is growing support for the division of behavioral functions into spatial memory and navigation in the dorsal hippocampus and anxiety-related function in the ventral hippocampus (Barkus et al. 2010). A similar scheme separates the hippocampus into cognitive and stress/emotion/affect domains (Fanselow & Dong 2010). Support for heterogeneous functions comes from differences in gene expression patterns as well as anatomical projections to and from the two regions (Fanselow & Dong 2010). Many of the behaviors discussed in this review are closely aligned with stress, emotion, and/or affect, suggesting that they may arise from changes in the ventral hippocampus specifically. However, although double dissociations provide strong behavioral evidence for a complete functional separation in some tasks (Bannerman et al. 2004), other findings suggest that the split between dorsal memory and ventral emotion functions may not be clear-cut. For example, several spatial and context learning tasks, nominally the domain of the dorsal hippocampus, are sensitive to lesions or inactivation specific to the ventral hippocampus (Ferbinteanu et al. 2003, Long & Kesner 1996, Poucet et al. 1991, Rudy & Matus-Amat 2005). Conversely, high densities of adrenal stress hormone–responsive receptors, which might be expected primarily in the ventral hippocampus, are found throughout its dorsoventral axis (Robertson et al. 2005), and both dorsal and ventral hippocampal subregions influence HPA axis activity, suggesting that the stress response functions of the hippocampus are not limited to the ventral hippocampus. Little is known about functional separation of adult-born neurons in dorsal and ventral subregions. Two studies using immediate-early genes as markers of neuronal activation found that adult-born neurons are activated by spatial water maze learning only in the ventral dentate gyrus (Snyder et al. 2009b, 2011a). This finding implies that young granule neurons in the dorsal and ventral portions of the hippocampus have differing functions, but it also points out the difficulty of disentangling learning and emotional functions: The water maze, like nearly all behavioral tasks, has strong emotional as well as learning components. Few studies have examined behavioral or other functional changes after specific ablation of adult neurogenesis in one portion of the dentate gyrus because this is methodologically quite challenging; there are currently no known dorsal/ventral-specific genetic markers of neuronal precursors, and specific targeting of dentate gyrus subregions with drugs or irradiation is also quite challenging. Having the two poles of the hippocampus perform unrelated behavioral functions does not feel

like an elegant solution to the problem, but as Ramón y Cajal pointed out, "unfortunately, nature seems unaware of our intellectual need for convenience and unity, and very often takes delight in complication and diversity" (Ramón y Cajal 1906, p. 240). It is also possible that dorsal and ventral hippocampal functions could be different but connected, performing closely related or even directly opposing roles.

Although it is uncertain how hippocampal roles in learning/memory and emotion are related, it is clear that an accurate picture of the function of new neurons in the hippocampus must account for all of their behavioral effects, including those with emotional but not mnemonic components. One potential role for the new neurons, and the rest of the hippocampus, that appears to fit with both emotional and memory-related findings is in predicting possible outcomes of novel or ambiguous events and in emotionally biasing these predictions.

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