The role of adult-born dentate granule neurons in the regulation of mood

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Introduction

There is growing recognition that the dentate gyrus (DG) sub region of the hippocampus contributes to both cognition as well as regulation of mood. Since adult hippocampal neurogenesis provides a source of new neurons throughout life in mammals, it represents a unique form of neural plasticity that may be targeted to restore or rejuvenate DG functions when compromised, such as in different disease states and during normal ageing. In this review we address whether the role of adult-born neurons in modulation of anxiety and depression-like behaviors is dependent on their proposed function in pattern separation. Towards this goal, we discuss evidence for adult-born neurons in pattern separation and mood regulation. We suggest that the functions of adult-born neurons in pattern separation may be particularly relevant for anxiety disorders such as post-traumatic stress disorder (PTSD), and that antidepressants may engage both pattern separation dependent and independent functions of adult-born neurons to produce therapeutic effects

Adult-born dentate granule neurons and pattern separation

Recent studies in rodents have implicated adult-born neurons in a range of hippocampal dependent tasks including processing of contextual information and spatial learning. Within the domain of contextual processing, there is growing evidence supporting a role for hippocampal neurogenesis in pattern separation, a mnemonic process by which similar perceptual patterns are separated or transformed into orthogonal neural representations. The proposed role for adult-born neurons in pattern separation was antedated by a foundation of computational and experimental studies implicating the DG in pattern separation (Rolls and Kesner, 2006; Treves et al., 2008). Experimental evidence for the DG in pattern separation first came from lesion studies in rodents showing that colchicine-induced ablation of the DG impaired discrimination of two spatial locations based on distal contextual cues, especially when the overlap of the distal cues was large i.e. spacing of the two locations was small (Gilbert et al., 2001). These findings were corroborated by studies using genetic approaches to specifically manipulate DG functions. For example, genetic disruption of synaptic transmission and plasticity at perforant path-dentate granule synapses was found to impair an animal's ability to differentiate between two similar contexts (McHugh et al., 2007). However, the capacity to distinguish between two distinct contexts was unaffected in these mice, suggesting that entorhinal inputs to CA3 were sufficient for this function. In concordance with previous computational modeling work, these studies suggested that the DG is required to minimize interference between overlapping spatial or contextual information. However, since these studies employed manipulations that affected the whole DG, they were unable to distinguish the contribution of adult-born neurons from those generated during development of the DG.

Electrophysiological analyses of adult-born neurons during their maturation have identified critical periods of heightened synaptic and structural plasticity relative to developmentally generated neurons, suggesting that young adult-born neurons contribute preferentially to DG functions in encoding (Ge et al., 2007; Saxe et al., 2006; Snyder et al., 2001; Zhao et al., 2006). Furthermore, young adult-born neurons may account for up to 10% of the DG (Imayoshi et al., 2008; Snyder and Cameron, 2012). Recent studies using loss-of-function and gain-of-function approaches have

demonstrated that adult-born neurons are indispensable for pattern separation. For instance, mice in which adult hippocampal neurogenesis is ablated using targeted irradiation are less efficient than controls in detecting small, but not large, separations of maze arms or objects on a touch screen (Clelland et al., 2009). More recently, Sahay et al. showed that mice in which adult hippocampal neurogenesis is genetically increased are better at discriminating between two similar contexts than controls (Sahay et al., 2011a). In this task, during initial training both groups of mice generalized their conditioned responses (freezing) to both the aversive, training (CS+) and safe, unconditioned (CS−) contexts. As mice were tested in CS+ and CS− contexts over several days with reinforcement of the CS+ context, but not the CS− context, the mice with more adult-born neurons were better in discriminating between the two contexts than controls. Conversely, the authors found that blockade of adult hippocampal neurogenesis by targeted x-irradiation produced impairments in contextual fear discrimination learning. Similar results were obtained using a genetic approach to block adult hippocampal neurogenesis (Tronel et al., 2010). Paralleling these findings, Kheirbek and colleagues showed that genetic blockade of synaptic plasticity of just the young adult-born neurons, a manipulation that did not affect their survival, was sufficient to impair discrimination learning. Importantly, in these studies genetic augmentation or abrogation of adult neurogenesis (or synaptic plasticity of young adult-born neurons) did not impact discrimination of distinct contexts, suggesting (as in the spatial radial arm maze task, (Clelland et al., 2009) that adult-born neurons were more likely to be required for reducing interference between two similar representations and that general mechanisms underlying behavioral inhibition were not altered. Together, these studies suggest that in the absence of adult-generated neurons, the vast majority of dentate granule neurons fail to compensate in pattern separation,and beg the question as to what functions the older neurons have in encoding. A recent study by Nakashiba and colleagues provides intriguing insight into this question (Nakashiba et al., 2012). These authors showed that transgenic mice in which synaptic output of mature dentate granule cells, but not that of younger immature neurons, is inhibited, were better at pattern separation than controls. Furthermore, these mice were impaired in pattern completion, a process by which a full pattern is retrieved based on a partial or degraded cue. These observations suggest that young-adult born neurons and developmentally generated neurons may have opposing roles in mediating pattern separation and pattern completion, respectively, and that simply varying the number of new neurons may shift the balance between these two mnemonic processes. Given the pivotal role of CA3 in pattern completion (Marr, 1971; Nakazawa et al., 2002; O'Reilly and McClelland, 1994; Rudy and O'Reilly, 1999), it may be that mature DG neurons exhibit distinct patterns of connectivity relative to young-adult generated neurons.

Recent studies relying on functional magnetic resonance imaging (fMRI) and immediate early gene (IEG) based circuit mapping have begun to examine the neural correlates of pattern separation in humans and in rodents. In rodents, Leutgeb et al. showed that dentate granule neurons, but not CA3 neurons, showed a remapping response to subtle morphing of contexts (Leutgeb et al., 2007). Interestingly, rather than exhibiting global remapping as is seen in CA3, where nonoverlapping/ independent

ensembles of neurons are activated in response to different environments, the authors found the same population of DG neurons to be reactivated, albeit with different firing rates (also known as rate remapping). More recently, it has been suggested that adult-born neurons exhibit rate remapping during behavioral foraging and that the mature dentate granule neurons are relatively silent and fire only in a single location (global remapping) (Neunuebel and Knierim, 2012). Although visualization of neuronal ensembles of activated neurons using IEG expression has consistently found sparse activation of the DG with 2-4% of dentate granule neurons active in a given context, current IEG based studies support a role for global, rather than rate, remapping in the DG (Schmidt et al., 2012) as a substrate for pattern separation.

Human studies using high-resolution functional magnetic resonance imaging (fMRI) have also supported a role of the DG in pattern separation. Bakker et al. had participants view a series of pictures of objects, which could be either new, a repetition of a previously shown object, or a slightly different version of a previously shown object (lure). Whereas different regions of the temporal lobe were activated by a novel object, only the DG-CA3 circuit, but not other sub regions, showed elevated levels of activity similar to that seen upon first presentation of an object, in response to lures (Bakker et al., 2008). This response to the lure was interpreted as pattern separation since it suggested recognition of a subtle difference in the object relative to previously observed opbjects. In contrast, an activation pattern similar to that of a repetition would indicate pattern completion. To explicitly address pattern separation in the DG-CA3 circuit, the same authors used a similar encoding task except that object similarity was varied parametrically (Lacy et al., 2011) akin to the context morphing used in *in vivo* place cell recording studies in rodents (Leutgeb et al., 2007). The authors found greater activation of DG-CA3 relative to CA1 for lures that had high similarity suggestive of a pattern separation like mechanism that transforms input similarity to generate divergent output. More recently, the authors found using this task that aged adults are less efficient than younger adults in pattern separation and that degradation of the perforant path as well as putative changes in CA3 dendritic architecture may underlie these differences in pattern separation efficiency (Yassa et al., 2011).

The preponderance of evidence favoring a role for adult-born neurons in pattern separation underscores the need to identify how a small number of adult born neurons influences encoding functions in the DG. Although several models addressing this question have been developed (Aimone et al., 2011; Appleby et al., 2011; Becker et al., 2009; Myers and Scharfman, 2008; Wiskott et al., 2006), we recently proposed a non-cell autonomous role for adult-born neurons as modulators of excitability of the DG (Lacefield et al., 2010; Sahay and Hen, 2007; Sahay et al., 2011b) via their connections with hilar interneurons and mossy cells (Toni et al., 2008). In such a model, the introduction of new adult-born neurons into the DG circuit would increase the threshold for activation of the whole DG by recruiting feedback inhibition mediated by hilar mossy cells and interneurons, thereby generating a sparser pattern of firing, a feature thought to be conducive for orthogonalization of information and consequently, pattern separation (Kesner, 2007; Leutgeb et al., 2007; Treves et al., 2008). It may also constrain pattern completion functions of mature neurons when a similar environment is encountered since mature neurons preferentially respond to previously experienced environments (Aimone et al., 2011; Tashiro et al., 2007). Conversely, a familiar

environment will preferentially reactivate a specific cohort of old neurons, and this may inhibit the new neurons and favor pattern completion. In addition to feedback inhibition of the DG, young-adult-born neurons may recruit feed forward inhibition through interneurons in the stratum lucidum to modulate pattern completion functions in CA3. As stated earlier, unraveling the precise patterns of functional connectivity of adult-born and mature neurons with mossy cells, interneurons and CA3 neurons will shed light on their functions in pattern separation and pattern completion, respectively. It is also important to address how adult-born neurons contribute to place cell remapping. Specifically, are adult-born neurons the primary substrates for rate remapping in a context morphing task? Do adult-born neurons contribute to global remapping under certain conditions such as when task demands are integrated into behavioral paradigms in which the context is morphed. Integration of *in vivo* recordings with visualization of the underlying cell-types in mice in which levels of neurogenesis are selectively modulated will undoubtedly address some of these questions.

Adult-born dentate granule neurons and mood regulation

In addition to a role for adult generated DG neurons in pattern separation, increasing evidence suggests a relationship between new neurons, stress, and mood regulation. Early studies using growth factors and viral expression systems from the Duman lab and other simplicated the DG in mood regulation (Adachi et al., 2008; Chen et al., 2001; Hunsberger et al., 2007; Lee et al., 2009; Son et al., 2012). For example, BDNF infusions into the DG, but not CA1, were sufficient to produce antidepressant - like behavioral effects in the learned helplessness paradigm and the forced swim test (Shirayama et al., 2002). Since the first observations that selective serotonin reuptake inhibitors increased neurogenesis in the DG of adult rodents (Malberg et al., 2000), it is now evident that this is true for all FDA approved antidepressants. The first demonstration of a role for adult-born hippocampal neurons in mood regulation came from studies in which mice received low-dose hippocampal irradiation while concomitantly receiving antidepressant treatment (Santarelli et al., 2003). The authors found that blocking adult hippocampal neurogenesis abrogated the response to antidepressants in the novelty suppressed feeding (NSF) task and chronic unpredictable stress paradigm. Recent studies in mice have obtained similar results using a chronic corticosterone mouse model of depression (David et al., 2009). Studies using genetic manipulations to modulate levels of neurogenesis have corroborated some of these findings. Li et al. showed that inhibition of adult DG neurogenesis through conditional deletion of the gene encoding the neurotrophin receptor, TrkB, in neural progenitor cells in the adult DG rendered mice insensitive to effects of chronic antidepressant treatment in behavioral tasks of anxiety or depression (Li et al., 2008). Antidepressants are not the only mood promoting interventions that appear to require adult hippocampal neurogenesis; the adaptive behavioral responses conferred by environmental enrichment during recovery from stress was also shown to be dependent on this form of neural plasticity (Schloesser et al., 2010).

Although the precise mechanism(s) by which new neurons mediate these

antidepressant-behavioral responses remains largely unknown, stress and the main stress hormone system, the hypothalamo-pituitary-adrenal (HPA) axis—has emerged as a potential functional link between adult-born neurons, mood regulation, and antidepressant treatment responses. Stress plays a key role in mood and anxiety disorders, with abnormalities in HPA axis activity, including loss of inhibitory feedback, often associated with these disorders (Holsboer et al., 1987; Nemeroff et al., 1984). The hippocampus serves as a regulator of the HPA axis, modulating the activity of the paraventricular nucleus (PVN) of the hypothalamus through a polysynaptic pathway providing negative feedback (Herman et al., 1995; Sapolsky et al., 1984) (Herman et al., 1998; Herman and Mueller, 2006; McEwen, 2001). To test the hypothesis that adult-born DG neurons play a critical role in the hippocampal regulation of the HPA axis and mood regulation, several groups have inhibited adult neurogenesis in rodents by different means while measuring the downstream effects on HPA axis activity and behavior at baseline and under conditions of stress. Surget and colleagues found that ablating hippocampal neurogenesis by targeted x-irradiation did not lead to deficits in HPA axis regulation in the context of uncontrollable chronic mild stress, but, rather, impaired the ability of fluoxetine to reverse these deficits. The authors also showed using dexamethasone injections into the ventral DG in combination with IEG based circuit activation mapping that fluoxetine treatment reverses the stress-induced dis-inhibition (over activation) of the PVN. However, whether this effect of fluoxetine required intact adult hippocampal neurogenesis was not assessed. Thus, chronic stress impaired hippocampal regulation of several components of the stress response and intact neurogenesis was critical for restoration of behavioral responses by antidepressant treatment.

In contrast to chronic stress, the effects of acute stress on HPA reactivity appears to be modulated by levels of adult hippocampal neurogenesis. Schloesser et al., conditionally suppressed adult neurogenesis utilizing an inducible genetic approach by which dividing progenitors in the adult brain are rendered sensitive to the antiviral drug valgancilovir (Schloesser et al., 2009). Valganciclovir treated mice, in which adult neurogenesis was inhibited, had higher corticosterone levels relative to mice with intact neurogenesis following exposure to a mild stressor (introduction to a novel envrionment) but not at baseline. These results support a role for new neurons in hippocampal inhibition of the HPA axis under conditions of mild stress. In a complimentary study, Snyder et al. (Snyder et al., 2011) employed both a genetic approach as well as hippocampal specific x-ray irradiation to inhibit adult neurogenesis, and found that HPA axis activity was heightened following stress (thirty minute acute restraint stress) as measured by corticosterone levels in mice with suppressed adult neurogenesis. Consistent with neuroendocrine dysregulation, neurogenesis deficient mice displayed depressive and anxious phenotypes in several behavioral paradigms—NSF, FST and a test of anhedonia, the sucrose preference test (SPT)—immediately following an acute stress. Surprisingly, in some tasks, such as the FST and SPT, neurogenesis-deficient mice showed baseline deficits, indicating that depending on the paradigm and task, neurogenesis may play a role that extends beyond stress response regulation. Together, through both focal irradiation and genetic approaches, the above studies support a role for hippocampal regulation of the HPA axis and disruption of negative feedback onto the HPA axis under conditions of acute stress.

While antidepressants, environmental enrichment and exercise all promote adult DG neurogenesis, stress and glucocorticoids inhibit the production and survival of adult-born neurons (Dranovsky and Hen, 2006; Mirescu and Gould, 2006). Indeed, stress, by inhibiting adult hippocamal neurogenesis, renders the hippocampal-HPA axis increasingly responsive to future stress. In the short term, this may be adaptive by mediating appropriate behavioral responses to stressors. However, over time, this may become increasingly maladaptive in giving rise to increased stress responsiveness and depressive behaviors in the absence of threatening or stressful events. Antidepressant treatment may improve this dysregulation by promoting neurogenesis, and thereby restoring the imbalance that initiated the maladaptive cascade. Since antidepressants exert multiple effects on neural circuitry besides increasing adult hippocampal neurogenesis (Duman and Monteggia, 2006; Maya Vetencourt et al., 2008), it remains to be seen whether increasing adult neurogenesis is sufficient to modulate HPA functions. In this context, it is worth point out that stimulating adult hippocampal neurogenesis may not always be beneficial. Blockade of adult hippocampal neurogenesis was found to inhibit social avoidance behavior suggesting that the timing of proneurogenic interventions may be critical to the directionality of their impact (Lagace et al., 2010). Moreover, the heightened plasticity of young adult-born neurons may make them more modifiable by stress, thereby amplifying the effector (stress), rather than curbing its effects. This may be why stressors such as social isolation drive symmetric division of stem cells rather than asymmetric divisions to generate more neurons (Bonaguidi et al., 2011; Dranovsky et al., 2011; Song et al., 2012).

As with pattern separation and pattern completion, one might ask whether the adult-born and developmentally generated neurons (mature neurons) have similar or distinct functions in mood regulation. Although chronic antidepressant treatment has been shown to accelerate maturation of adult-born neurons (Wang et al., 2008), a recent study made the intriguing observation that antidepressants also induce dematuration of mature dentate granule neurons (Kobayashi et al., 2008). Kobayashi et al. found that chronic antidepressant treatment of adult mice shifted the molecular and functional properties of a large population of mature granule cells. Four to five weeks of fluoxetine treatment in mice resulted in a reduction in expression of molecular markers of granule cell maturity, decrease in activity-dependent gene expression and a shift of electrophysiological propertiesto resemble a more immature state. They further went on to show that the dematuration effect of antidepressants may be mediated in part through 5-HT4 receptor signaling. Additional molecular, genetic and behavioral studies are needed to determine the precise mechanism(s) of dematuration and also to determine what role this process plays in the anti-depressant mediated behavioral response.

Discussion

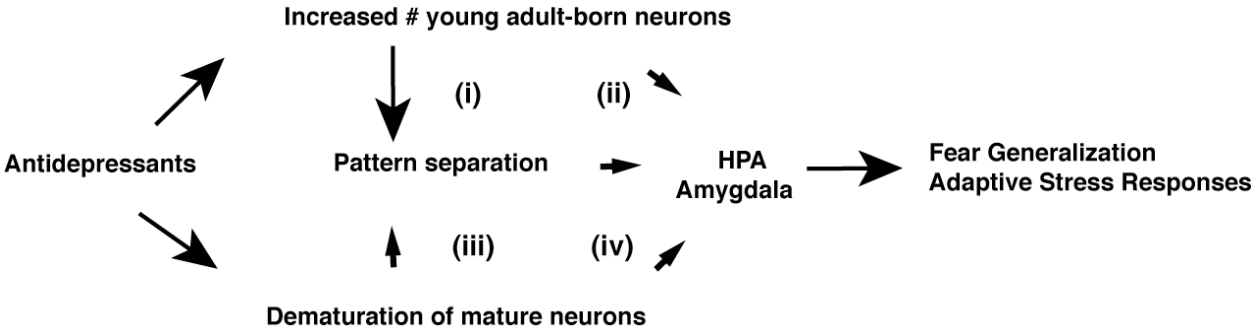
Anxiety disorders such as PTSD can be viewed as maladaptive responses involving dysregulation of neural circuitry that evolved to generate fearfulness. Healthy individuals are able to regulate activation of fear and neuroendocrine responses as a function of their environments. In contrast, individuals with PTSD exhibit heightened neuroendocrine (hyperarousal,) and behavioral responses (fear, avoidance) to neutral

stimuli resembling the aversive event even in presence of cues that convey safety. Efforts to delineate mechanisms underlying PTSD have implicated deficits in extinction learning, associative learning, extinction learning recall, fear inhibition and consolidation (Johansen et al., 2011; Jovanovic and Ressler, 2010; Kearns et al., 2012). However, much less is known about encoding mechanisms that underlie the overgeneralization of fear. We recently proposed that an imbalance in pattern separation and pattern completion may result in overgeneralization of fear (Sahay et al., 2011a; Sahay et al., 2011b). Specifically, failure to distinguish between perceptually similar environments may result in excessive pattern completion whereby minimal cues may trigger full and unusually vivid recall of the traumatic episodic memory, together with the associated emotional responses. The over-activation of the stress response in a similar "safe" environment may arise from a failure to suppress the HPA axis once the previous aversive memory is retrieved. Short periods of intense stress or trauma, a known risk factor, for PTSD, may modify the connectivity of the DG-CA3 circuit so as to produce an imbalance between pattern separation and pattern completion. Thus, increasing the number of young-adult born neurons may enhance pattern separation to modulate the excessive generalization seen in PTSD (Figure 1).

In thinking about how antidepressants recruit adult-born neurons to mediate their behavioral effects, we must ask the following: How does the stimulation of neurogenesis by antidepressants give rise to changes in the PVN? It is tempting to speculate that new neurons might secrete growth factors that impinge upon interneurons (whose dendrites ramify across layers in the hippocampus), thereby affecting the properties of hippocampal sub regions such as the subiculum to regulate HPA functions. Does increasing adult neurogenesis modulate activity or plasticity in the subiculum or other nodes in the stress regulation pathway such as the bed nucleus of the stria terminals or the septum? Does improving pattern separation also produce similar changes in the ventral subiculum to impact the HPA axis through these nodes? Given the differences in connectivity of the hippocampus along its septohippocampal axis with limbic structures such as the amygdala, prefrontal cortex, hypothalamus, do the effects of modulating neurogenesis on mood differ depending on whether the septal or temporal DG is targeted (Sahay and Hen, 2007)? Furthermore, given that antidepressants on the one hand promote generation of new neurons while at the same time causing dematuration of mature granule cells, it is interesting to consider whether these seemingly disparate processes might converge at the level of HPA axis regulation (Figure 1). Should dematuration turn out to be a robust AD induced effect, then one must ask whether dematuration of old (mature) dentate granule neurons makes them more similar to young adult-born neurons with regards to stress responsiveness and HPA modulation? The predicted effects of dematuration of mature neurons on pattern separation are not clear-cut: On one hand, dematuration may diminish pattern completion and enhance pattern separation by making the older neurons more juvenile-like. On the other hand, since dematuration results in decreased facilitation of mossy fiber-CA3 synapses, contextual encoding may be impaired. If so, it may be that antidepressants engage pattern separation independent mechanisms to produce changes in mood.

As these questions are addressed, results should be considered in the context of their relevance to depressive illness. For example, depression is not a hippocampal specific disorder, but is associated with alterations in many brain regions, including prefrontal cortex, hypothalamus, amygdala and nucleus accumbens (Krishnan and Nestler, 2008), and it will be important to discern what role hippocampal neurogenesis plays in regulation of these regions. Additionally, in some individuals with depression, alterations in HPA axis regulation are not observed. Whether or not new neurons and antidepressant treatment play roles outside of stress response regulation to benefit these individuals will be important to determine. Despite these remaining questions, existing data provide insight into the role of adult-born neurons in regulation of mood, and pinpoint the stress response pathway as one important means by which adult-born neurons may exert their effect. Understanding how adult-born neurons contribute to pattern separation and regulation of the stress response system is likely to provide a conceptual framework upon which to think about how the DG modulates mood. Gaining such an understanding holds the promise of development of novel therapeutic strategies to target depressive and anxiety disorders.

Figure 1. Schematic showing the relationship between adult neurogenesis, antidepressants, dematuration, pattern separation and mood regulation. Adult-born neurons may modulate fear generalization and adaptive stress responses through pattern separation dependent and independent mechanisms (i and ii). The behavioral effects of antidepressants may require both increased adult hippocampal neurogenesis and dematuration of the mature DG neurons and these effects may be mediated independent of pattern separation (iii and iv). Large arrows convey established links whereas small arrows indicate relationships to be tested.



References

Adachi, M., Barrot, M., Autry, A.E., Theobald, D., and Monteggia, L.M. (2008). Selective loss of brain-derived neurotrophic factor in the dentate gyrus attenuates antidepressant efficacy. Biol Psychiatry *63*, 642-649.

Aimone, J.B., Deng, W., and Gage, F.H. (2011). Resolving new memories: a critical look at the dentate gyrus, adult neurogenesis, and pattern separation. Neuron *70*, 589-596.

Appleby, P.A., Kempermann, G., and Wiskott, L. (2011). The role of additive neurogenesis and synaptic plasticity in a hippocampal memory model with grid-cell like input. PLoS computational biology *7*, e1001063.

Bakker, A., Kirwan, C.B., Miller, M., and Stark, C.E. (2008). Pattern separation in the human hippocampal CA3 and dentate gyrus. Science *319*, 1640-1642.

Becker, S., Macqueen, G., and Wojtowicz, J.M. (2009). Computational modeling and empirical studies of hippocampal neurogenesis-dependent memory: Effects of interference, stress and depression. Brain Res *1299*, 45-54.

Bonaguidi, M.A., Wheeler, M.A., Shapiro, J.S., Stadel, R.P., Sun, G.J., Ming, G.L., and Song, H. (2011). In vivo clonal analysis reveals self-renewing and multipotent adult neural stem cell characteristics. Cell *145*, 1142-1155.

Chen, A.C., Shirayama, Y., Shin, K.H., Neve, R.L., and Duman, R.S. (2001). Expression of the cAMP response element binding protein (CREB) in hippocampus produces an antidepressant effect. Biol Psychiatry *49*, 753-762.

Clelland, C.D., Choi, M., Romberg, C., Clemenson, G.D., Jr., Fragniere, A., Tyers, P., Jessberger, S., Saksida, L.M., Barker, R.A., Gage, F.H.*, et al.* (2009). A functional role for adult hippocampal neurogenesis in spatial pattern separation. Science *325*, 210-213.

David, D.J., Samuels, B.A., Rainer, Q., Wang, J.W., Marsteller, D., Mendez, I., Drew, M., Craig, D.A., Guiard, B.P., Guilloux, J.P.*, et al.* (2009). Neurogenesis-dependent and -independent effects of fluoxetine in an animal model of anxiety/depression. Neuron *62*, 479-493.

Dranovsky, A., and Hen, R. (2006). Hippocampal neurogenesis: regulation by stress and antidepressants. Biol Psychiatry *59*, 1136-1143.

Dranovsky, A., Picchini, A.M., Moadel, T., Sisti, A.C., Yamada, A., Kimura, S., Leonardo, E.D., and Hen, R. (2011). Experience dictates stem cell fate in the adult hippocampus. Neuron *70*, 908-923.

Duman, R.S., and Monteggia, L.M. (2006). A neurotrophic model for stress-related mood disorders. Biol Psychiatry *59*, 1116-1127.

Ge, S., Yang, C.H., Hsu, K.S., Ming, G.L., and Song, H. (2007). A critical period for enhanced synaptic plasticity in newly generated neurons of the adult brain. Neuron *54*, 559-566.

Gilbert, P.E., Kesner, R.P., and Lee, I. (2001). Dissociating hippocampal subregions: double dissociation between dentate gyrus and CA1. Hippocampus *11*, 626-636.

Herman, J.P., Cullinan, W.E., Morano, M.I., Akil, H., and Watson, S.J. (1995). Contribution of the ventral subiculum to inhibitory regulation of the hypothalamo-pituitary-adrenocortical axis. J Neuroendocrinol *7*, 475-482.

Herman, J.P., Dolgas, C.M., and Carlson, S.L. (1998). Ventral subiculum regulates hypothalamo-pituitary-adrenocortical and behavioural responses to cognitive stressors. Neuroscience *86*, 449-459.
Herman, J.P., and Mueller, N.K. (2006). Role of the ventral subiculum in stress integration. Behav Brain Res *174*, 215-224.
Holsboer, F., Gerken, A., Stalla, G.K., and Muller, O.A. (1987). Blunted aldosterone and ACTH release after human CRH administration in depressed patients. Am J Psychiatry *144*, 229-231.
Hunsberger, J.G., Newton, S.S., Bennett, A.H., Duman, C.H., Russell, D.S., Salton, S.R., and Duman, R.S. (2007). Antidepressant actions of the exercise-regulated gene VGF. Nat Med *13*, 1476-1482.
Imayoshi, I., Sakamoto, M., Ohtsuka, T., Takao, K., Miyakawa, T., Yamaguchi, M., Mori, K., Ikeda, T., Itohara, S., and Kageyama, R. (2008). Roles of continuous neurogenesis in the structural and functional integrity of the adult forebrain. Nat Neurosci *11*, 1153-1161.
Johansen, J.P., Cain, C.K., Ostroff, L.E., and LeDoux, J.E. (2011). Molecular mechanisms of fear learning and memory. Cell *147*, 509-524.
Jovanovic, T., and Ressler, K.J. (2010). How the neurocircuitry and genetics of fear inhibition may inform our understanding of PTSD. Am J Psychiatry *167*, 648-662.
Kearns, M.C., Ressler, K.J., Zatzick, D., and Rothbaum, B.O. (2012). Early Interventions for Ptsd: A Review. Depression and anxiety.
Kesner, R.P. (2007). A behavioral analysis of dentate gyrus function. Prog Brain Res *163*, 567-576.
Kobayashi, K., Ikeda, Y., Haneda, E., and Suzuki, H. (2008). Chronic fluoxetine bidirectionally modulates potentiating effects of serotonin on the hippocampal mossy fiber synaptic transmission. J Neurosci *28*, 6272-6280.
Krishnan, V., and Nestler, E.J. (2008). The molecular neurobiology of depression. Nature *455*, 894-902.
Lacefield, C.O., Itskov, V., Reardon, T., Hen, R., and Gordon, J.A. (2010). Effects of adult-generated granule cells on coordinated network activity in the dentate gyrus. Hippocampus.
Lacy, J.W., Yassa, M.A., Stark, S.M., Muftuler, L.T., and Stark, C.E. (2011). Distinct pattern separation related transfer functions in human CA3/dentate and CA1 revealed using high-resolution fMRI and variable mnemonic similarity. Learning & memory (Cold Spring Harbor, NY *18*, 15-18.
Lagace, D.C., Donovan, M.H., DeCarolis, N.A., Farnbauch, L.A., Malhotra, S., Berton, O., Nestler, E.J., Krishnan, V., and Eisch, A.J. (2010). Adult hippocampal neurogenesis is functionally important for stress-induced social avoidance. Proc Natl Acad Sci U S A *107*, 4436-4441.
Lee, J.S., Jang, D.J., Lee, N., Ko, H.G., Kim, H., Kim, Y.S., Kim, B., Son, J., Kim, S.H., Chung, H.*, et al.* (2009). Induction of neuronal vascular endothelial growth factor expression by cAMP in the dentate gyrus of the hippocampus is required for antidepressant-like behaviors. J Neurosci *29*, 8493-8505.
Leutgeb, J.K., Leutgeb, S., Moser, M.B., and Moser, E.I. (2007). Pattern separation in the dentate gyrus and CA3 of the hippocampus. Science *315*, 961-966.

Li, Y., Luikart, B.W., Birnbaum, S., Chen, J., Kwon, C.H., Kernie, S.G., Bassel-Duby, R., and Parada, L.F. (2008). TrkB regulates hippocampal neurogenesis and governs sensitivity to antidepressive treatment. Neuron *59*, 399-412.
Malberg, J.E., Eisch, A.J., Nestler, E.J., and Duman, R.S. (2000). Chronic antidepressant treatment increases neurogenesis in adult rat hippocampus. J Neurosci *20*, 9104-9110.
Marr, D. (1971). Simple memory: a theory for archicortex. Philosophical transactions of the Royal Society of London *262*, 23-81.
Maya Vetencourt, J.F., Sale, A., Viegi, A., Baroncelli, L., De Pasquale, R., O'Leary, O.F., Castren, E., and Maffei, L. (2008). The antidepressant fluoxetine restores plasticity in the adult visual cortex. Science *320*, 385-388.
McEwen, B.S. (2001). Plasticity of the hippocampus: adaptation to chronic stress and allostatic load. Ann N Y Acad Sci *933*, 265-277.
McHugh, T.J., Jones, M.W., Quinn, J.J., Balthasar, N., Coppari, R., Elmquist, J.K., Lowell, B.B., Fanselow, M.S., Wilson, M.A., and Tonegawa, S. (2007). Dentate Gyrus NMDA Receptors Mediate Rapid Pattern Separation in the Hippocampal Network. Science *317*, 94-99.
Mirescu, C., and Gould, E. (2006). Stress and adult neurogenesis. Hippocampus *16*, 233-238.
Myers, C.E., and Scharfman, H.E. (2008). A role for hilar cells in pattern separation in the dentate gyrus: A computational approach. Hippocampus.
Nakashiba, T., Cushman, J.D., Pelkey, K.A., Renaudineau, S., Buhl, D.L., McHugh, T.J., Rodriguez Barrera, V., Chittajallu, R., Iwamoto, K.S., McBain, C.J.*, et al.* (2012). Young dentate granule cells mediate pattern separation, whereas old granule cells facilitate pattern completion. Cell *149*, 188-201.
Nakazawa, K., Quirk, M.C., Chitwood, R.A., Watanabe, M., Yeckel, M.F., Sun, L.D., Kato, A., Carr, C.A., Johnston, D., Wilson, M.A.*, et al.* (2002). Requirement for hippocampal CA3 NMDA receptors in associative memory recall. Science *297*, 211-218.
Nemeroff, C.B., Widerlov, E., Bissette, G., Walleus, H., Karlsson, I., Eklund, K., Kilts, C.D., Loosen, P.T., and Vale, W. (1984). Elevated concentrations of CSF corticotropin-releasing factor-like immunoreactivity in depressed patients. Science *226*, 1342-1344.
Neunuebel, J.P., and Knierim, J.J. (2012). Spatial firing correlates of physiologically distinct cell types of the rat dentate gyrus. J Neurosci *32*, 3848-3858.
O'Reilly, R.C., and McClelland, J.L. (1994). Hippocampal conjunctive encoding, storage, and recall: avoiding a trade-off. Hippocampus *4*, 661-682.
Rolls, E.T., and Kesner, R.P. (2006). A computational theory of hippocampal function, and empirical tests of the theory. Prog Neurobiol *79*, 1-48.
Rudy, J.W., and O'Reilly, R.C. (1999). Contextual fear conditioning, conjunctive representations, pattern completion, and the hippocampus. Behav Neurosci *113*, 867-880.
Sahay, A., and Hen, R. (2007). Adult hippocampal neurogenesis in depression. Nat Neurosci *10*, 1110-1115.
Sahay, A., Scobie, K.N., Hill, A.S., O'Carroll, C.M., Kheirbek, M.A., Burghardt, N.S., Fenton, A.A., Dranovsky, A., and Hen, R. (2011a). Increasing adult hippocampal neurogenesis is sufficient to improve pattern separation. Nature *472*, 466-470.

Sahay, A., Wilson, D.A., and Hen, R. (2011b). Pattern separation: a common function for new neurons in hippocampus and olfactory bulb. Neuron *70*, 582-588.
Santarelli, L., Saxe, M., Gross, C., Surget, A., Battaglia, F., Dulawa, S., Weisstaub, N., Lee, J., Duman, R., Arancio, O*., et al.* (2003). Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. Science *301*, 805-809.
Sapolsky, R.M., Krey, L.C., and McEwen, B.S. (1984). Glucocorticoid-sensitive hippocampal neurons are involved in terminating the adrenocortical stress response. Proc Natl Acad Sci U S A *81*, 6174-6177.
Saxe, M.D., Battaglia, F., Wang, J.W., Malleret, G., David, D.J., Monckton, J.E., Garcia, A.D., Sofroniew, M.V., Kandel, E.R., Santarelli, L*., et al.* (2006). Ablation of hippocampal neurogenesis impairs contextual fear conditioning and synaptic plasticity in the dentate gyrus. Proc Natl Acad Sci U S A *103*, 17501-17506.
Schloesser, R.J., Lehmann, M., Martinowich, K., Manji, H.K., and Herkenham, M. (2010). Environmental enrichment requires adult neurogenesis to facilitate the recovery from psychosocial stress. Mol Psychiatry *15*, 1152-1163.
Schloesser, R.J., Manji, H.K., and Martinowich, K. (2009). Suppression of adult neurogenesis leads to an increased hypothalamo-pituitary-adrenal axis response. Neuroreport *20*, 553-557.
Schmidt, B., Marrone, D.F., and Markus, E.J. (2012). Disambiguating the similar: the dentate gyrus and pattern separation. Behav Brain Res *226*, 56-65.
Shirayama, Y., Chen, A.C., Nakagawa, S., Russell, D.S., and Duman, R.S. (2002). Brain-derived neurotrophic factor produces antidepressant effects in behavioral models of depression. J Neurosci *22*, 3251-3261.
Snyder, J.S., and Cameron, H.A. (2012). Could adult hippocampal neurogenesis be relevant for human behavior? Behav Brain Res *227*, 384-390.
Snyder, J.S., Kee, N., and Wojtowicz, J.M. (2001). Effects of adult neurogenesis on synaptic plasticity in the rat dentate gyrus. J Neurophysiol *85*, 2423-2431.
Snyder, J.S., Soumier, A., Brewer, M., Pickel, J., and Cameron, H.A. (2011). Adult hippocampal neurogenesis buffers stress responses and depressive behaviour. Nature *476*, 458-461.
Son, H., Banasr, M., Choi, M., Chae, S.Y., Licznerski, P., Lee, B., Voleti, B., Li, N., Lepack, A., Fournier, N.M*., et al.* (2012). Neuritin produces antidepressant actions and blocks the neuronal and behavioral deficits caused by chronic stress. Proc Natl Acad Sci U S A *109*, 11378-11383.
Song, J., Zhong, C., Bonaguidi, M.A., Sun, G.J., Hsu, D., Gu, Y., Meletis, K., Huang, Z.J., Ge, S., Enikolopov, G*., et al.* (2012). Neuronal circuitry mechanism regulating adult quiescent neural stem-cell fate decision. Nature *489*, 150-154.
Tashiro, A., Makino, H., and Gage, F.H. (2007). Experience-specific functional modification of the dentate gyrus through adult neurogenesis: a critical period during an immature stage. J Neurosci *27*, 3252-3259.
Toni, N., Laplagne, D.A., Zhao, C., Lombardi, G., Ribak, C.E., Gage, F.H., and Schinder, A.F. (2008). Neurons born in the adult dentate gyrus form functional synapses with target cells. Nat Neurosci *11*, 901-907.
Treves, A., Tashiro, A., Witter, M.E., and Moser, E.I. (2008). What is the mammalian dentate gyrus good for? Neuroscience *154*, 1155-1172.

Tronel, S., Belnoue, L., Grosjean, N., Revest, J.M., Piazza, P.V., Koehl, M., and Abrous, D.N. (2010). Adult-born neurons are necessary for extended contextual discrimination. Hippocampus.
Wang, J.W., David, D.J., Monckton, J.E., Battaglia, F., and Hen, R. (2008). Chronic fluoxetine stimulates maturation and synaptic plasticity of adult-born hippocampal granule cells. J Neurosci *28*, 1374-1384.
Wiskott, L., Rasch, M.J., and Kempermann, G. (2006). A functional hypothesis for adult hippocampal neurogenesis: avoidance of catastrophic interference in the dentate gyrus. Hippocampus *16*, 329-343.
Yassa, M.A., Mattfeld, A.T., Stark, S.M., and Stark, C.E. (2011). Age-related memory deficits linked to circuit-specific disruptions in the hippocampus. Proc Natl Acad Sci U S A *108*, 8873-8878.
Zhao, C., Teng, E.M., Summers, R.G., Jr., Ming, G.L., and Gage, F.H. (2006). Distinct morphological stages of dentate granule neuron maturation in the adult mouse hippocampus. J Neurosci *26*, 3-11.