New Neurons Maintain Efficient Stress Recovery

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Adult neurogenesis has been the focus of intense investigation, but the function of new neurons remains elusive. Snyder et al. (2011) report that new neurons in the hippocampus play an important role in appropriate shut-off of the stress response.

Despite decades of debate and controversy, it is now generally accepted that the hippocampus produces many new neurons in adulthood. The mystery that remains concerns the function of these adult-born neurons. While countless studies have linked new neurons to the learning and memory capabilities of the hippocampus, a resolution on their specific contribution has not been reached. New evidence from Snyder et al. (2011) identifies a novel and unexpected function for adult neurogenesis by demonstrating that new neurons play a crucial role in a lesser-known function of the hippocampus—shutting off the stress response. These findings pave the way for integrative hypotheses on the nature of stress and cognition.

In their groundbreaking recent study, Snyder and colleagues show that new neurons in the hippocampus are necessary for the efficient recovery of the hypothalamic pituitary adrenal (HPA) axis. This hormone system relies on the hippocampus for a shut-off signal. When receptors for glucocorticoids, the main stress hormone, are activated in the hippocampus, circuitry is engaged that inhibits the hypothalamus from further activating the HPA axis, thereby restoring glucocorticoid levels to baseline (Herman et al., 1992). Using two adult neurogenesis ablation strategies, transgenic destruction of mitotic cells and local X-ray irradiation, Snyder et al. showed that new neurons are required for the efficient shut-off of the HPA axis. Without new hippocampal neurons, circulating glucocorticoid levels were slower to recover to baseline levels than in controls after both single and repeated exposure to restraint stress. Adult mice without new neurons showed abnormal behavioral responses after stress and also showed signs of depression in tests of despair and anhedonia, as well as a depressive phenotype in the dexamethasone suppression test, an HPA axis negative feedback test that reveals impaired performance in a subset of human patients with depression. These findings strongly suggest that new neurons play a crucial role in resetting stress hormone systems back to normal and preventing the emergence of stress-related mood disorders. The results may also help to explain the mechanism underlying HPA axis dysregulation sometimes seen with aging, a process that is accompanied by diminished adult neurogenesis (Montaron et al., 2006).

When placed in the broader context of the literature aimed at elucidating the learning and memory functions of new neurons, these findings raise many questions. New neurons have been implicated in a variety of cognitive functions ranging from context fear learning to spatial memory. How can immature neurons in the same brain region be involved in cognition and stress regulation—functions that seem so disparate? Does a common computation underlie both the cognitive and stress regulatory functions of new neurons? Alternatively, do immature neurons behave differently when the hippocampus becomes engaged under low-stress learning conditions as opposed to high-stress conditions? Answers to these questions will require much additional experimentation, but some hints may be obtained by comparing the findings of Snyder and colleagues with the literature linking new neurons to learning and memory.

New neurons in the hippocampus are added to a subregion called the dentate gyrus. This area is known to be involved in pattern separation, a computational process wherein neuron firing patterns become more dissimilar as they move through the circuitry (O'Reilly and McClelland, 1994). In other words, the input firing patterns to the dentate gyrus are more similar than the output firing patterns. This process is thought to help in distinguishing memories. The contribution of new neurons to pattern separation has been supported with behavioral data—stimulation of adult neurogenesis improves behavioral tasks that require remembering subtle differences between spatial and contextual stimuli rather than larger differences, for which mature neurons are sufficient (Clelland et al., 2009; Sahay et al., 2011). Adult-born neurons are more excitable than mature neurons and they exhibit heightened synaptic plasticity with varying characteristics displayed as the cells mature (Wojtowicz, 2011). Because of these attributes, the young neurons may be involved in encoding additional information that, along with the information encoded by their mature counterparts, produces a richer data store with which the hippocampus can discriminate among stimuli and situations. Such a scenario has been proposed to explain cognitive deficits associated with new neuron depletion. Can impaired pattern separation also account for the inability of animals without new neurons to efficiently transition from a stressed to an unstressed state? A definitive answer to this question remains unknown, but a broader look at the functions of the hippocampus suggests it is possible.

The ventral part of the hippocampus has been implicated in regulation of the HPA axis and mood (Herman et al., 1992; Bannerman et al., 2003). The ventral hippocampus further differs from the dorsal hippocampus, which encodes spatial information, in that its neurons seem more tuned to information about landmarks and cues that signal emotional valence (Royer et al., 2010). Although most pattern separation studies on the

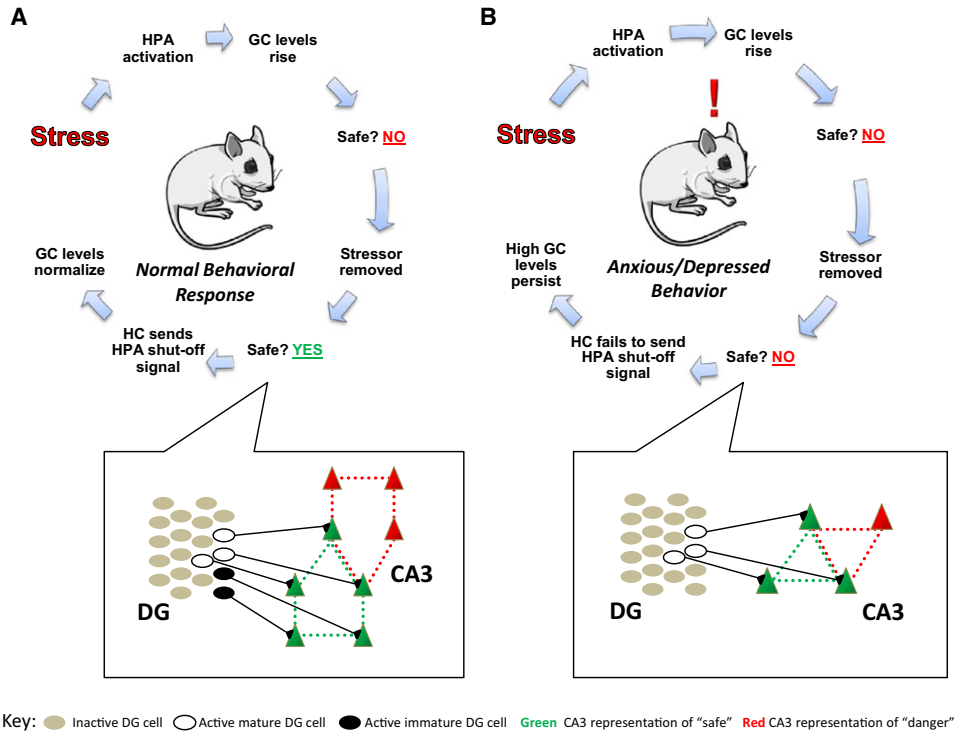

Figure 1. Young Neurons May Facilitate HPA Axis Shut-Off by Increasing Pattern Separation
With new neurons (A), richer representations of different states may be formed in area CA3 (inset A). After a stressor, young neurons in the dentate gyrus (DG) may prevent interference between patterns that signal safety and those that signal danger. Without new neurons (B), discrimination is impaired, as CA3 activation patterns are formed from fewer granule cells that produce greater overlap in representation between safety and danger (inset B). Transition from danger to safety is delayed—signals from the hippocampus (HC) to shut off the HPA axis are not sent, glucocorticoids (GC) remain elevated, and symptoms of depression emerge.

dentate gyrus have focused on functions attributed to its dorsal component, it remains possible that new neurons in the ventral component perform similar pattern separation computations about information that is emotionally salient. Along these lines, the ventral hippocampus lacking new neurons may have reduced pattern separation capabilities that make it unable to process information about safety quickly enough to transition from a stressed to an unstressed state—an inability to rapidly recognize that danger has ended may produce prolonged activation of the HPA axis (Figure 1). This possibility is consistent with findings linking the presence of new neurons in the hippocampus to learned safety and antidepressant responses (Pollak et al., 2008).

Whether common or unique mechanisms underlie the cognitive and stress regulatory functions of new neurons remains unknown. Like all good studies, the exciting new paper from Snyder and colleagues raises more questions about adult brain plasticity than it answers. Although a unifying functional theory of adult-born neurons may be a long-term goal, this study has immediate clinical implications: the identification of new neurons as a useful substrate for stress resilience and mood regulation will surely encourage new studies aimed at understanding and developing more effective therapies for treating mood disorders.

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