Journal Club

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A Critical Time for New Neurons in the Adult Hippocampus

Benedetta Leuner,[1] Erica R. Glasper,[1] and Christian Mirescu[2]

[1]Department of Psychology, Princeton University, Princeton, New Jersey 08544, and [2]Helen Wills Neuroscience Institute, University of California, Berkeley, Berkeley, California 94720

Review of Tashiro et al. (http://www.jneurosci.org/cgi/content/full/27/12/3252)

Despite the vast literature on adult neurogenesis in the mammalian hippocampus, the function of these new neurons remains unclear. New neurons are generated in the dentate gyrus with estimates ranging on the order of thousands added per day in rodents. These newly born cells can differentiate into mature neurons and integrate into existing hippocampal networks (Hastings and Gould, 1999; Ge et al., 2006), but a substantial proportion have only a transient existence. The loss of adult-generated cells can be reduced by experiences such as environmental enrichment and hippocampal-dependent learning (Kempermann et al., 1997; Leuner et al., 2004, 2006). In a recent paper in *The Journal of Neuroscience*, Tashiro et al. (2007) identify a critical period in the life of an adult-generated neuron during which experience is necessary for its survival. Using the induction of immediate early genes as an indicator of neuronal activity, they also demonstrate that experience during this time window increases the number of new neurons activated by exposure to the same experience in the future. In doing so, Tashiro et al. (2007) provide new insights into how newly generated neurons may contribute to hippocampal function.

The authors first address whether a time period exists during which the survival of new neurons is maximally sensitive to experience. At 1 week intervals after administration of the DNA synthesis marker bromodeoxyuridine (BrdU), mice were housed in an enriched environment for 7 d. Relative to cage controls, environmental enrichment increased the number of new neurons in the dentate gyrus coexpressing the neuronal marker NeuN (Fig. 1) [Tashiro et al. (2007), their Figs. 2*c* (http://www.jneurosci.org/cgi/content/full/27/12/3252/F2), 4*c* (http://www.jneurosci.org/cgi/content/full/27/12/3252/F4)]. Importantly, this increase was restricted to new neurons that underwent mitosis between 1 and 3 weeks before enrichment, suggesting that the survival of new neurons is only influenced by the environment during a narrow temporal window shortly after new cells are produced. These data are generally consistent with the time period when newly generated neurons are extending their axons (Hastings and Gould, 1999), receiving GABA-mediated excitatory synaptic inputs, and beginning to receive glutamatergic contacts (Ge at al., 2006), factors that likely promote survival and aid in functional integration.

The authors then examine whether long-term survival of new neurons requires continual behavioral stimulation. New neurons rescued by exposure to enriched environments during this critical period were stable for extended periods of time, regardless of the interim housing conditions [Tashiro et al. (2007), their Fig. 5*b* (http://www.jneurosci.org/cgi/content/full/27/12/3252/F5)]. Specifically, neuronal survival was enhanced in mice that were housed in enriched conditions for 3 weeks after BrdU injection, as well as in mice that were housed in enriched conditions for 3 weeks and then placed in standard cages for 4 months thereafter. Such observations indicate that once cells outlive the critical period, survival is ensured. This finding is consistent with the long-lasting increase in the survival of adult-born neurons after training on the hippocampal-dependent task of trace eyeblink conditioning (Leuner et al., 2004). Thus, persistence of new neurons after environmental enrichment may result from learning opportunities that are inherent to a complex environment.

Last, Tashiro et al. (2007) address whether enriched environment-induced modifications in adult neurogenesis alter the subsequent response of these cells to experience. To explore this issue, expression of the immediate early gene products, c-fos and Zif268, was measured in new neurons after reexposure to the same enrichment experience 6 weeks after BrdU injections (Fig. 1). In this case, increased BrdU+/NeuN+/c-fos+ cells were observed but were highest in cells that were labeled at 2 weeks of age [Tashiro et al. (2007), their Fig. 3*b* (http://www.jneurosci.org/cgi/content/full/27/12/3252/F3)]. This effect required reexposure to enrichment, because c-fos expression

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Correspondence should be addressed to Dr. Benedetta Leuner, Department of Psychology, Princeton University, Green Hall, Princeton, NJ 08544. E-mail: bleuner@princeton.edu.

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levels did not increase in mice that were only given the initial exposure (Tashiro et al., 2007). In addition, water maze training (rather than environmental enrichment) did not result in an increased density of new neurons expressing Zif268, confirming that although the effect generalizes to other immediate early genes, the response is selective to a specific environment [Tashiro et al. (2007), their Fig. 4*d* (http://www.jneurosci.org/cgi/content/full/27/12/3252/F4)]. Thus, the authors suggest that experience-induced immediate early gene expression reflects neuronal activation resulting from previous memory processing.

These findings raise numerous questions about the selectivity of responses of adult-generated neurons in general. First, do immature neurons preferentially respond to familiar experiences to which they were exposed during the critical period? For instance, if animals receive multiple experiences (such as environmental enrichment and specific learning tasks) during the critical time, would both experiences subsequently activate the new neurons? Also, it is important to point out that a substantial number of new neurons persisted even in control animals and that the majority of BrdU-labeled cells were not activated by the second exposure to the enriched environment. What are the response properties of new neurons that did not require environmental enrichment for their survival? Finally, are similar mechanisms, be they release of trophic factors or synaptic activation, responsible for promoting the survival of new neurons and their subsequent activation?

In summary, these experiments suggest that environmental enrichment during a critical period not only alters the number of new neurons, but also affects whether those cells will respond to the same event at a later time. Because the responsiveness of adult-generated neurons is greater than mature granule cells after spatial exploration and navigation learning (Ramirez-Amaya et al., 2006; Kee et al., 2007), new granule cells may contribute to learning and memory by creating a neural representation of previous experiences. In this way, Tashiro et al. (2007) add to a growing body of data (Snyder et al., 2005; Leuner et al., 2006) suggesting a role for adult-generated hippocampal neurons in the storage and long-term memory of experiences.

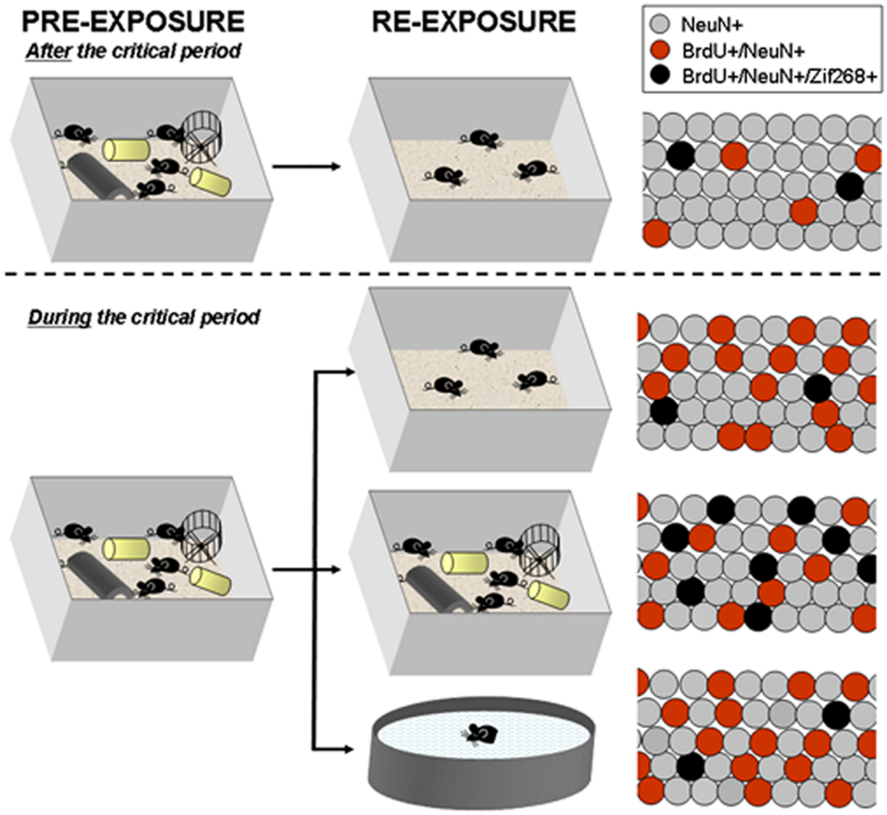

Figure 1. Simplified schematic diagram of the results presented by Tashiro et al. (2007). Exposure to environmental enrichment during a critical period (1–3 weeks after BrdU administration; bottom) increased the survival of new neurons in the dentate gyrus (BrdU+/NeuN+). In contrast, new neuron survival was not enhanced in mice exposed to an enriched environment after the critical period (top). The authors also demonstrated that reexposure to the same experience of environmental enrichment at a later time enhanced neuronal activation (BrdU+/NeuN+/Zif268+; bottom). Increased neuronal activation did not occur when mice were only given the initial exposure or were reexposed to a different experience of water maze training.

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