

New neurons in old brains: learning to survive?

William T. Greenough, Neal J. Cohen and Janice M. Juraska

Two studies examine how experience regulates neurogenesis in the adult rodent hippocampus. Although their conclusions appear contradictory, they may in fact be reconcilable.

It has been known for many years that in rodents, neurons continue to be produced in the dentate gyrus of the hippocampus throughout adult life^{1,2}. This finding generated considerable interest when it was first reported, not least because of its possible implications for brain repair. This initial excitement was tempered by the failure to detect neurogenesis in adult macaques³, but within the last two years the field has been revived by reports of neurogenesis in the dentate gyrus of marmosets⁴, macaques (M. Fallah, E. Fuchs, P. Tanapat, A.J. Reeves, E. Gould, *Soc. Neurosci. Abstr.* 24, 796.9, 1998) and even humans⁵. Moreover, a recent study⁶ reported that the survival of newly formed neurons in mice can be increased by exposure to a more complex environment, suggesting that neuronal replacement in adults may be regulated by experience.

Two papers in this issue, by Gould *et al.* (pages 260–265) and by van Praag *et al.* (pages 266–270), add to this growing body of evidence, in particular by demonstrating that both proliferation and survival of newly formed neurons can be affected by experience. Both studies seek to identify the aspects of experience that are essential to produce these effects, using learning tasks that either require or do not require the hippocampus. Yet, although they both use similar techniques, the two studies arrive at seemingly incongruent conclusions.

Gould *et al.* examined neuronal survival in the dentate gyrus after adult rats were trained in four different learning tasks. The first task was ‘trace’ associative eyeblink conditioning, in which a brief time interval separates the conditioned stimulus (CS; a burst of white noise) from the unconditioned stimulus (US; a shock to the eye). Performance on this task is

impaired by damage to the hippocampal formation. They compared this with ‘delay’ conditioning, which is similar to trace conditioning except that the US overlaps and coterminates with the CS; this task can still be learned after hippocampal lesions. In a second experiment, they compared ‘spatial’ learning in a water maze, in which the rat must learn to use distant cues to find the hidden platform, with a ‘local cue’ task, in which the rat learns to recognize the platform directly. As above, learning the first task requires an intact hippocampus, whereas learning the second task does not. In both experiments, the authors found that the survival rate of labeled neurons was more than two times greater in animals that had learned the hippocampus-dependent task than in those learning a similar but hippocampus-independent task.

Van Praag *et al.* examined both proliferation and survival of dentate gyrus neurons in response to a variety of experiences, including spatial navigation in a water maze as well as swimming, wheel running and housing in an ‘enriched’ laboratory environment. Consistent with earlier results from the same group⁶, the enriched environment enhanced the survival of newly formed neurons. The authors now find that running also enhances proliferation and, to a limited extent, survival, whereas—in contrast to the results of Gould *et al.*—navigational learning in the water maze produced no effect at all.

What are we to make of these apparently contradictory results? The most trivial possibility (which cannot be excluded) is that the results reflect either different measuring methods or the use of different subjects; Gould *et al.* used male rats, whereas van Praag *et al.* used female mice. However, there are also several more interesting possibilities that are suggested by differences in the experimental design of the two studies (Fig. 1).

It is important to distinguish between effects on the formation of new neurons

and effects on their subsequent survival. Gould *et al.*, by administering the label one week before training, examined only survival effects. In contrast, van Praag *et al.* tested the effect of experience both during and after the labeling period; by counting labeled neurons immediately after the labeling period, they measured the formation of new neurons, and then by counting several weeks later, they also measured the survival of these newly formed neurons.

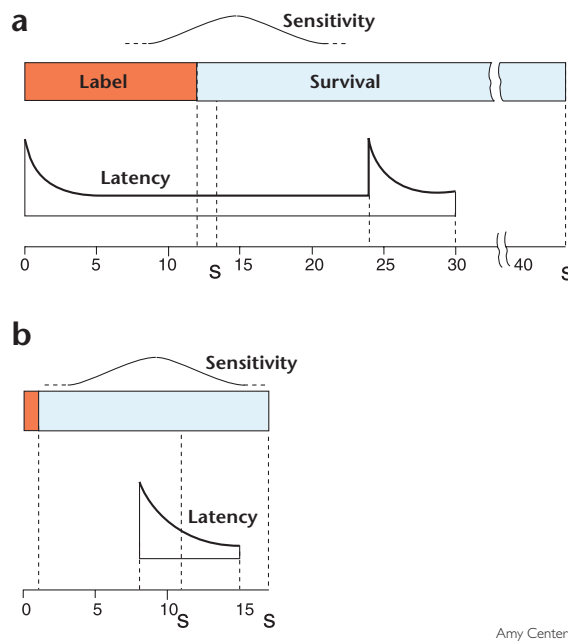
Focusing first on survival, the results of Gould *et al.* suggest that hippocampal learning is important. New neurons may be more sensitive than more mature neurons to the effects of activity, and it is possible that the period of maximum sensitivity may begin shortly after the neuron is formed. Gould *et al.* suggest that the initial postproliferative period is critical to the survival of newly generated neurons because this is when their axons emerge from the dentate gyrus and begin to contact target cells in hippocampal subfield CA3.

If there is a period of sensitivity of this sort, then the results of the studies may be reconcilable after all. Van Praag *et al.* did not observe any effect of water-maze learning on either proliferation or survival. Their water-maze procedure, however, produced very rapid learning, such that the mice were already approaching their asymptotic level of performance before the labeling was complete. Thus, much of the learning may have been completed before most of the neurons entered their period of maximum sensitivity. In contrast, Gould *et al.* administered water-maze training one week after the neurons were already labeled. These newly labeled neurons might be among those most affected by experience, because the experience occurred during their period of maximum sensitivity. The trace conditioning in the Gould *et al.* study may likewise have been given at the time of maximum effectiveness relative to the sensitivity of the newly formed neurons. A further difference between the two studies is that the animals used by van Praag *et al.* learned with fewer trials than those used by Gould *et al.*; it is possible that the more difficult task in the latter study may have placed a greater load on the hippocampus and therefore produced a stronger survival-promoting effect.

The major positive finding of the van Praag *et al.* study, which the other study does not contradict, is that wheel running leads to enhanced labeling immediately after the BrdU incorporation phase. The

The authors are at the Department of Psychology and the Beckman Institute, University of Illinois, 405 N. Mathews Ave., Urbana, Illinois 61801, USA.
e-mail: Greenough@uiuc.edu

Fig. 1. Time course of the water-maze experiments. In both studies, dividing cells were labeled by BrdU injection, and animals were subsequently sacrificed on the days indicated (S) and examined for labeled neurons in the dentate gyrus. Some animals were trained in a water maze (learning is manifested as reduced latency). Control animals were compared with animals that had undergone spatial learning. **(a)** van Praag *et al.* administered BrdU daily between days 1 and 12 and counted labeled neurons after one day (day 13, assumed to reflect proliferation) or four weeks (day 43, assumed to reflect survival). Mice were trained daily for 30 days beginning at the start of the labeling period, with the platform location reversed at day 24. Most of the initial learning occurred early in the labeling period, and learning of the reversed platform condition occurred two weeks after labeling. **(b)** Gould *et al.* administered BrdU for one day only, and counted neurons on day 11 or 17 (reflecting survival in both cases). Training began one week after labeling, and continued for one week. The discrepancy between the two studies could be explained if we assume that newly formed neurons go through a transient period of sensitivity to the survival-promoting effect of learning (shown by the curve at the top of each panel). In the van Praag *et al.* study, learning (and presumably elevated hippocampal activity) would occur mainly before and after the sensitive period, whereas in the Gould *et al.* study, it would occur during this period.



Amy Center

authors' interpretation is that exercise increases the proliferation of neuronal precursor cells. It is curious that the animals in the enriched environment cages, which appear from the figure to include similar exercise wheels, show no increase in proliferation. Rather, they show an increase in subsequent neuronal survival that is considerably greater than the survival effect found in the exercise group. There is evidence that BrdU administration may have toxic effects on cell proliferation⁷, and it is possible that exercise—which has been shown to increase vascularization and presumably blood flow⁸, as well as the expression of trophic factors⁹, in some brain areas—could offset this toxicity.

It is interesting to speculate about the possible adaptive significance of this proliferative effect. Intense exercise in a natural environment may be associated with a need for increased navigation skills. It might therefore be beneficial to produce more neurons in anticipation of greater hippocampal use during a period of active exploration. One should be cautious, however, about accepting such interpretations, particularly given that some

exogenous effects on brain plasticity seem difficult to explain in adaptive terms. For instance, the number of dendritic spines in area CA1 is increased¹⁰, and long-term potentiation more readily induced¹¹, during proestrus when estrogen and progesterone levels are high. Yet during this period, performance on several hippocampus-dependent tasks is slightly impaired, whereas performance on similar but hippocampus-independent tasks is unaffected^{12,13}. In other words, plasticity may be manifested even when it is not needed or used.

Nevertheless, given that the hippocampus has this unique capability of regulating the production of new neurons from a continuously generated population of precursors, it seems important to consider the possible implications for hippocampal function. It also seems important to ask what is unique about the hippocampus, in other words why other parts of the brain do not seem to exploit the possibility of continuous neurogenesis. One proposal comes from analyzing the different ways in which the brain must process and store information. Studies of information storage in

model neural networks have shown that adding new learning sequentially to the network can result in 'catastrophic interference'¹⁴. That is, the changes induced by encoding new information into the network can obscure previously stored information. McClelland *et al.*¹⁵ proposed that the hippocampus protects against this by forming a very rapid and relatively short-lived form of representation that permits reactivation of representations in the cerebral cortex, so that those long-term representations in cortex can be learned in an interleaved fashion. In this way, although new information arrives sequentially, the reactivation of all related information in cortical long-term memory, mediated by the connection to hippocampus, results in the whole set of representations being rehearsed together. But, if the hippocampus protects the cerebral cortex from catastrophic interference, in the way just described, what protects the hippocampus itself? McClelland *et al.*¹⁵ say rather little about this, suggesting only that the hippocampal representation is a sparse one, so that there is relatively little interference.

On the other hand, what if the hippocampus stored its memories differently from the cerebral cortex, by adding neurons that can deal with new information and deleting those that encode obsolete information, rather than changing connections? It is the changing of connections that produces catastrophic interference. If new memories got new neurons with new connections, catastrophic interference might be avoided. The hippocampus could aid the cerebral cortex in developing functional interleaving of memories and throw out the information that was needed to do this, once successful cortical storage was achieved.

If such a mechanism operates in the hippocampus, why does it not exist in the cortex too? McCloskey and Cohen¹⁴ and McClelland *et al.*¹⁵ suggested that the connectivity changes that produce catastrophic interference are the same changes that provide the ability to generalize from one set of observations to another, and to generate abstract representations of information. That is, the strength of a fully distributed representation system, in which an integrated set of connections stores all the knowledge in a given domain (as is thought to occur in cortex), is its ability to support generalization and abstraction. The flip side is that such a system cannot learn sequentially without risking catastrophic inter-

ference. Adding a 'front end' mechanism—the hippocampal temporary organizer—might offer the virtues of distributed representation while protecting against the negative consequences.

1. Kaplan, M. S. & Hinds, J. W. *Science* **197**, 1092–1094 (1977).
2. Bayer, S. A. *Exp. Brain Res.* **46**, 315–323 (1982).
3. Eckenhoff, M. F. & Rakic, P. *J. Neurosci.* **8**, 2729–2747 (1988).
4. Gould, E. *et al. Proc. Natl. Acad. Sci. USA* **95**, 3168–3171 (1998).

5. Eriksson, P. S. *et al. Nat. Med.* **4**, 1313–1317 (1998).
6. Kempermann, G., Kuhn, H. G. & Gage, F. H. *Nature* **386**, 493–495 (1997).
7. Pollard, D. R., Baran, M. M. & Bachvarova, R. *J. Embryol. Exp. Morphol.* **35**, 169–178 (1976).
8. Isaacs, K. R., Anderson, B. J., Alcantara, A. A., Black, J. E. & Greenough, W. T. *J. Cereb. Blood Flow Metab.* **12**, 110–119 (1992).
9. Neeper, S. A., Gomez-Pinilla, F., Choi, J. & Cotman, C. *Nature* **373**, 109 (1995).
10. Woolley, C. S., Gould, E., Frankfurt, M. & McEwen, B. S. *J. Neurosci.* **10**, 4035–4039 (1990).

11. Warren, S. G., Humphreys, A. G., Juraska, J. M. & Greenough, W. T. *Brain Res.* **703**, 26–30 (1995).
12. Warren, S. G. & Juraska, J. M. *Behav. Neurosci.* **111**, 259–266 (1997).
13. Markus, E. J. & Zecevic, M. *Psychobiology* **25**, 246–252 (1997).
14. McCloskey, M. & Cohen, N. J. in *The Psychology of Learning and Motivation: Advances in Research and Theory* vol. 24 (ed. Bower, G. H.) 109–165 (Academic, New York, 1989).
15. McClelland, J. L., McNaughton, B. L. & O'Reilly, R. C. *Psychol. Rev.* **102**, 419–457 (1995).

Now you see it: frontal eye field responses to invisible targets

John Assad

Neurons in the frontal eye field respond even when a visual target is perceptually masked, but small variations in their activity predicts whether a monkey will respond to the stimulus.

Over the past several decades, neurophysiologists have made significant progress toward understanding the chain of neuronal processing linking sensation to action. However, like excavators slowly converging from opposite sides of a tunnel, their efforts have focused largely on the extremes of the problem—the initial sensory input and final motor output. For eye movements made to visual targets, we understand in detail both the early visual analysis occurring in the retina, thalamus and primary visual cortex and the brainstem mechanisms controlling eye movement. Yet, the sheer complexity and flexibility in our responses to visual stimuli argue that numerous stages of neuronal processing must intervene. On page 283 of this issue, Thompson and Schall¹ provide an intriguing glimpse into how one likely site of such processing, the frontal eye field (FEF), uses visual information to control a decision about whether to move the eyes. Under masking conditions that make the target's visibility unreliable, the authors report that FEF neurons reliably respond

to the target whether or not the monkey perceives it, but that small variations in the magnitude of their response predict very accurately whether an eye movement will be made.

David Ferrier first described the FEF in 1875 as the area in frontal cortex that most readily elicited eye movements when electrically stimulated. Many lesion and inactivation studies have supported this view, and tracer and stimulation experiments have revealed strong projections from the FEF to areas involved in generating saccades, such as the superior colliculus and pontine oculomotor nuclei². In addition to these motor functions, the FEF also seems to be a site of visual integration, in that it receives inputs from a vast swath of extrastriate visual cortex. The FEF thus seems ideally positioned at the confluence of visual inflow and motor outflow to mediate visual-motor interactions. Consistent with this view, single-unit recording

in monkey FEF has revealed neuronal signals related to both sensory stimuli and saccades, sometimes in the same neuron. In a typical experiment, a spot of light is flashed in the visual periphery, and the monkey is required to saccade to the location of the target. Many FEF neurons discharge shortly after the presentation of the stimulus, and then also around the time of the eye movement³. Given this dual nature of FEF responses, it seems reasonable that the FEF might be an important center for integrating visual input to control eye movement—a sort of decision point or dispatcher.

Thompson and Schall varied the usual saccade task by using backward masking to make the stimulus sometimes perceptually invisible. If a brief target is immediately followed by another stimulus (the mask), humans will report that

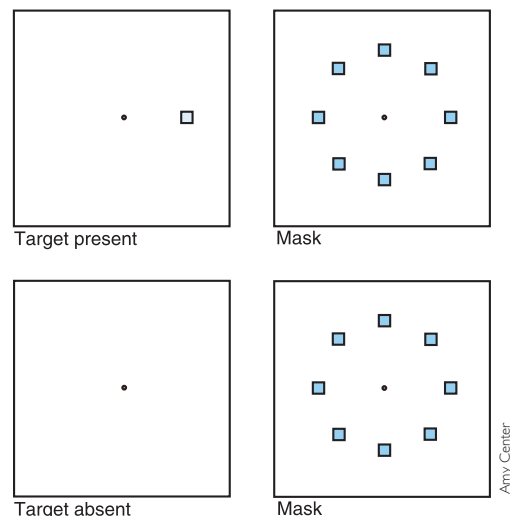


Fig. 1. Stimuli for the backward-masking protocol. A dim target appears at one of eight positions on some trials, but not on others. On all trials, eight bright masking stimuli then appear, which can prevent the monkey from perceiving the target.

John Assad is in the Department of Neurobiology, Harvard Medical School, 220 Longwood Ave., Boston, Massachusetts 02115, USA. email: jassad@hms.harvard.edu