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The Adult Brain Makes New Neurons, and Effortful Learning Keeps Them Alive

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Abstract

The brain continues to produce new neurons throughout life. For instance, the hippocampus (a brain region necessary for select learning processes) produces thousands of new neurons each day. However, a significant number of them die and do so within just a few weeks of their birth. Laboratory animals that are trained to learn a new skill between one and two weeks after the new cells are generated retain most cells that would have otherwise died. The types of skills that keep new cells alive are not limited to those that depend on the hippocampus but rather include those that are effortful to learn, requiring more training trials or time spent training. Importantly, training alone is not sufficient to increase cell survival; animals that are trained but do not learn do not retain more cells than animals that are not trained. Therefore, learning increases the survival of newly generated cells in the hippocampus as long as the learning experience is new, effortful, and successful. Once rescued, the vast majority of these cells differentiate into neurons, thereby forming synapses and generating action potentials as they become incorporated into the existing architecture and functional circuitry of the adult brain.

Keywords

neurogenesis, cell survival, associative learning, physical-skill learning, hippocampus, memory, effortful learning, stem cell, exercise, classical conditioning

The adult brains of nonhuman and human animals can produce thousands, even tens of thousands, of new cells each day, many of which differentiate into mature functional neurons (Fig. 1; Eriksson et al., 1998; Gould, Beylin, Tanapat, Reeves, & Shors, 1999; Kempermann, Wiskott, & Gage, 2004; Manganas et al., 2007). A great number of new neurons are generated in the dentate gyrus of the hippocampus, a brain region necessary for select processes of learning. Given these relationships, scientists have focused on the putative role of new neurons in learning and memory, and numerous studies have reported that these cells are involved in behavioral processes that support learning (Kempermann et al., 2004; Kheirbek, Klemenhagen, Sahay, & Hen, 2012; Shors, Anderson, Curlik, & Nokia, 2012; Shors et al., 2001).

In the present review, I focus on a different relationship between neurogenesis and learning—namely, how learning influences the survival of newly generated neurons in the hippocampus. Even though thousands accrue each day, a significant number of them die within weeks. If an animal acquires a new skill just before the new cells begin to die, many of them survive and mature into functional neurons (Gould et al., 1999). This survival effect is attributed to learning and not simply training, because animals that are trained but fail to learn do not retain more cells than animals that are not trained (Fig. 2a). In experiment after experiment, my colleagues and I have observed significant correlations, typically r = ~.60, between performance on a given task and the number of surviving neurons (Curlik & Shors, 2011; Dalla, Bangasser, Edgecomb, & Shors, 2007; Leuner et al., 2004; Waddell & Shors, 2008). When learning does occur, most of the cells that would otherwise have died reside in the hippocampus for months (Leuner et al., 2004; Waddell & Shors, 2008), by which time they have acquired synaptic connections and electrical properties necessary to generate action potentials (van Praag et al., 2002).

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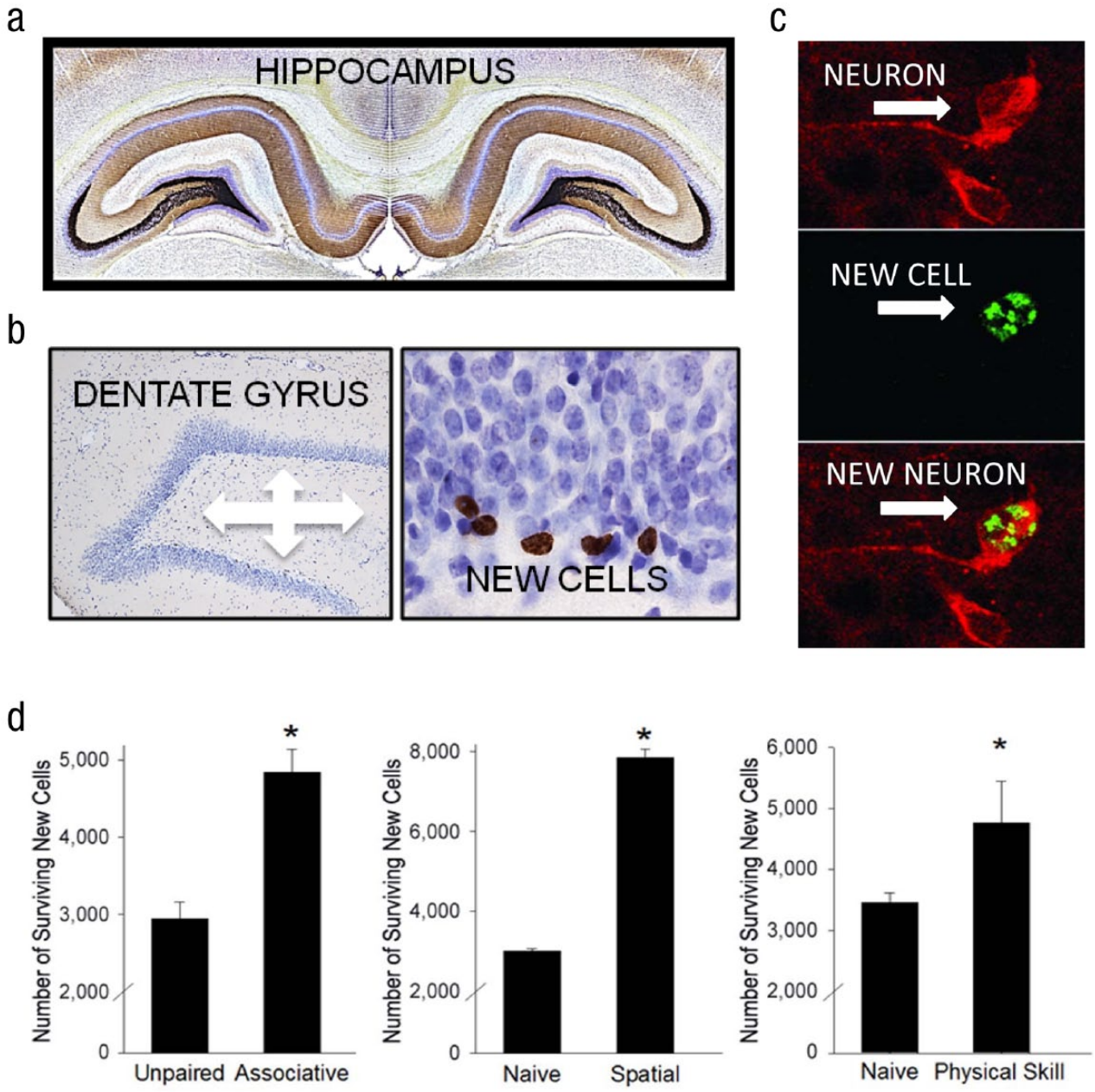

Fig. 1. Learning and the survival of new neurons in the adult hippocampus. Panel (a) shows the hippocampus (stained with Timm), a brain region in which thousands of new neurons are generated each day. Panel (b) shows, at left, the dentate gyrus of the hippocampus (indicated with arrows) and, at right, a higher magnification of new cells labeled with bromodeoxyuridine (BrdU), which denotes a newly generated cell. Panel (c) shows, at top, a cell stained with doublecortin, which denotes a neuron; at center, the same cell labeled with BrdU; and, at bottom, a cell stained with both markers, which signifies a newly generated neuron. Panel (d) presents results illustrating that learning an associative-memory task, a spatial-maze task, or a physical motor skill keeps cells alive that would have otherwise died. Error bars represent standard errors of the means. Asterisks indicate a significant advantage of trained groups (associative, spatial, and physical-skill conditions) over relevant untrained (naïve condition) control groups (data drawn from Curlik and Shors, 2011—left graph; Gould, Beylin, Tanapat, Reeves, & Shors, 1999—middle graph; and Curlik et al., 2013—right graph). Panels (a) and (b) are adapted from "Mental and Physical (MAP) Training: A Neurogenesis-Inspired Intervention That Enhances Health in Humans," by T. J. Shors, R. Olson, M. E. Bates, E. A. Selby, and B. L. Alderman, *Neurobiology of Learning and Memory*, advance online publication, doi:10.1016/j.nlm.2014.08.012. Copyright 2014 by Elsevier. Adapted with permission. Panel (c) is adapted from "Neurogenesis and the Spacing Effect: Trials Distributed Over Time Enhance Memory and Predict Cell Survival," by H. Sisti, A. Glass, and T. J. Shors, 2007, *Learning & Memory, 14*, p. 370. Copyright 2007 by Cold Spring Harbor Laboratory Press. Adapted with permission.

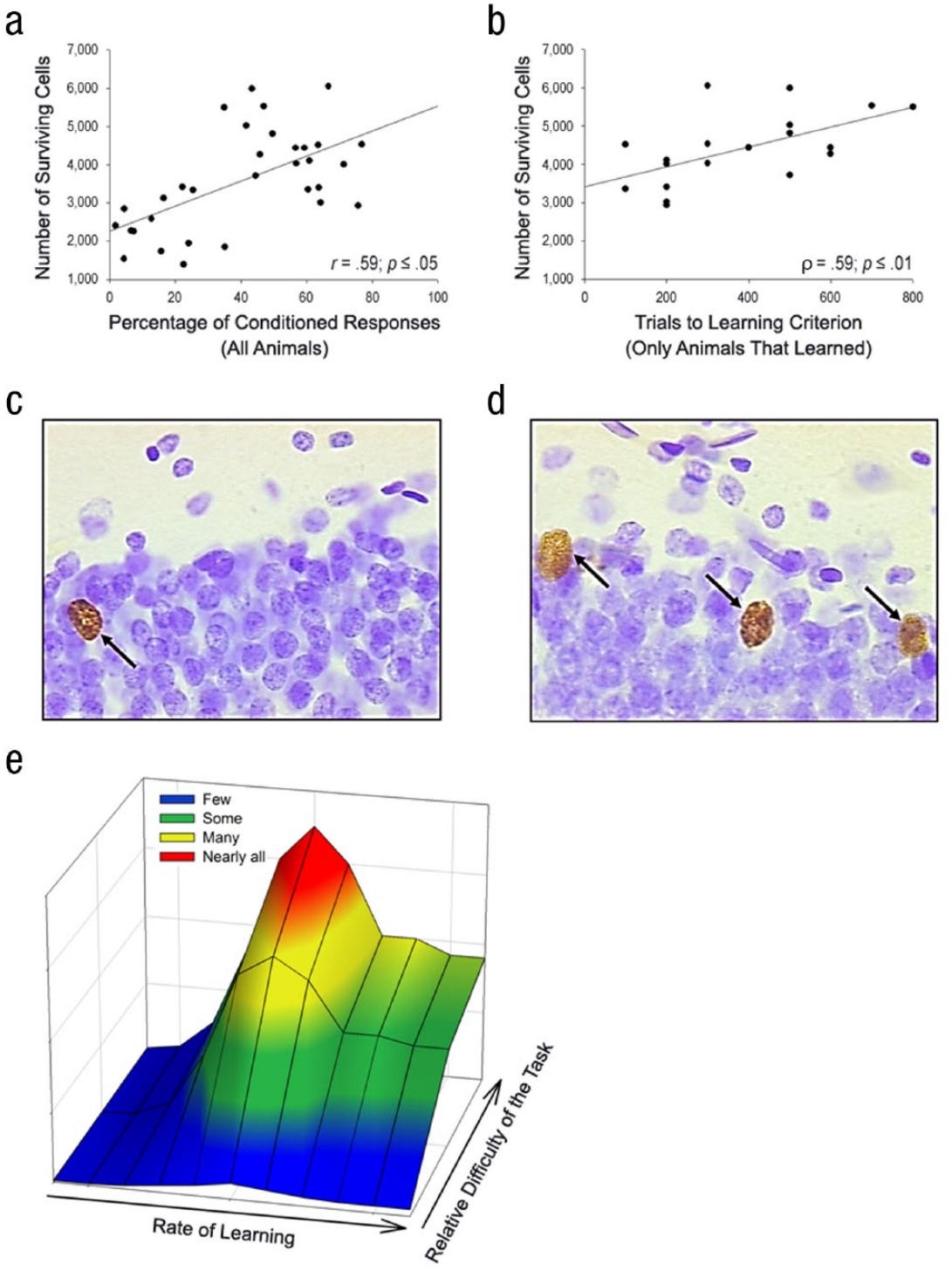

Fig. 2. Results from Curlik and Shors (2011) showing individual differences in learning and the survival of new neurons. Learning, as indexed by the percentage of conditioned responses during trace conditioning, was correlated ($p < .05$) with the number of new cells surviving in the hippocampus (a). Animals that learned but required more trials of training to do so retained more new cells (b). Brain slices show new cells that were present in the hippocampus of an animal that did not learn (c) and an animal that did learn (d). These findings indicate relationships among the rate of learning, the difficulty of the training task, and the number of surviving neurons (ranging from few to nearly all; e). Adapted from "Learning Increases the Survival of Newborn Neurons Provided That Learning Is Difficult to Achieve and Successful," by D. M. Curlik and T. J. Shors, 2011, *Journal of Cognitive Neuroscience, 23*, pp. 2166 (a), 2165 (b), 2167 (c, d), and 2168 (e). Copyright 2011 by MIT Press. Adapted with permission.

Dissociating Hippocampal Dependence From Cell Survival

Not all types of learning rescue new neurons from death. Over the past decade, we have identified some of the critical features that ensure their survival. First, the learning experience must be a new one. If an animal is simply retrained on a task that it has already learned, the cells within the animal's hippocampus are no more likely to survive than if the animal were not trained at all. Therefore, acquisition of a new skill or memory is necessary to rescue new neurons from death (Anderson, Sisti, Curlik, & Shors, 2011). Second, the new cells respond especially well to training experiences that depend on the hippocampus for learning. For example, they survive in response to learning a hippocampal-dependent task referred to as *trace eyeblink conditioning*. During training, an animal learns to associate a conditioned stimulus (typically a tone) with an unconditioned stimulation of the eyelid, which occurs after a temporal gap and causes the animal to blink. Learning is indexed by the number of blinks that occur during the trace interval in response to the conditioned stimulus.

Cell survival also increases in response to spatial-navigation training, another type of learning that depends on the hippocampus. During one such task, known as the *Morris water maze*, the animal must use spatial cues in its environment to escape from a pool of water onto a hidden platform. The new cells do not survive after training with tasks that are similar in procedure but do not depend on the hippocampus. For example, they do not survive when animals are trained to navigate a water maze with a clearly visible escape platform—a task that does not require the use of spatial cues and in which learning is not dependent on the hippocampus. Nor do the cells survive when animals are trained with classical conditioning tasks known as *delay-conditioning tasks*, in which the conditioned and unconditioned stimuli overlap in time and learning also does not depend on the hippocampus.

The results presented thus far suggest that new neurons in the hippocampus's cells respond preferentially and perhaps even exclusively to learning skills that depend on the hippocampus. However, we have dissociated hippocampal dependence from the increase in cell survival in a number of ways. For instance, animals that are trained with a trace eyeblink conditioning task in which the temporal gap is very short (250 milliseconds instead of the standard 500 milliseconds) do not retain more of the new cells even though learning this task does depend on the hippocampus (Waddell, Anderson, & Shors, 2010). Therefore, training conditions do exist that depend on the hippocampus but do *not* rescue new neurons from death.

An exclusive relationship between cell survival and hippocampus-dependent learning can also be refuted from the other angle: In some instances, engaging in tasks that do *not* depend on the hippocampus for learning can rescue new neurons from death. Take, in this case, gross-motor-skill training with the *rotarod task*. During this task, an animal learns to balance itself on a large rod that rotates in space. Learning the skill does not depend on the hippocampus, and training on a "simple" version of the task, in which the rod slowly rotates at the same speed, does not keep the new cells alive. However, if the rod moves faster and faster during each trial, the task becomes more effortful and difficult to master. Animals that learned this more effortful motor skill retained significantly more new neurons than animals that did not learn the skill or that were not trained (Curlik, Maeng, Agarwal, & Shors, 2013). Because animals can learn the skill without an intact hippocampus, these data dissociate hippocampal dependence, per se, from the effects of learning on cell survival in the hippocampus. We know from studies using classical conditioning that learning engages the hippocampus, even if learning itself does not depend on it (Miller & Steinmetz, 1997). Thus, the new cells are likely influenced by learning experiences of many sorts, only a few of which stimulate them to survive.

Effortful learning increases neuronal survival

Given these dissociations between hippocampal dependence and neurogenesis, one wonders what it is about learning that keeps new neurons alive. Very generally, it appears to be the effort involved in learning: Tasks that keep new neurons alive tend to be more difficult to acquire than those that do not and thus require more effort to learn. Such "effortful" tasks include trace eyeblink conditioning, spatial-navigation learning, and training with the accelerating version of the rotarod task, all of which require more trials of training to acquire than their counterparts, which do not keep the new cells alive: short-trace eyeblink conditioning, delay eyeblink conditioning, training with a visible platform in a water maze, and training on a slowly moving rotarod. We have also found that increasing the interval between the onset of the conditioned stimulus and that of the unconditioned stimulus during a standard delay-conditioning task (in which the stimuli overlap in time) increases effort by increasing the number of trials necessary to learn; animals trained to learn this "long-delay" task retain more new neurons than animals that are not trained (Leuner, Waddell, Gould, & Shors, 2006).

Perhaps most compelling are the data that address individual differences in learning. Within a given training

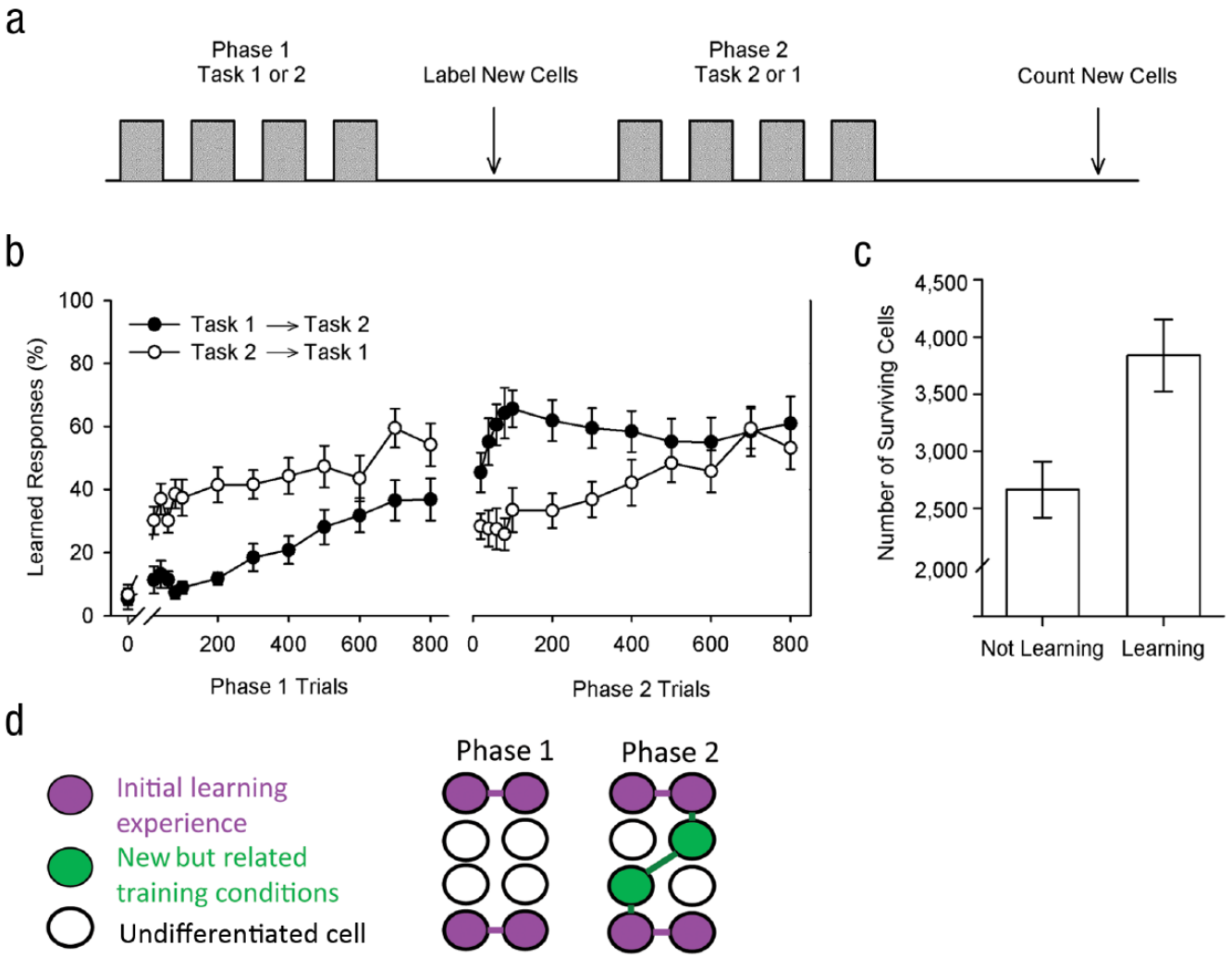

Fig. 3. "Learning to learn" paradigm and results from Nokia, Sisti, Choski, and Shors (2012). Groups of animals were trained on two tasks that rescue new neurons from death: trace eyeblink conditioning and very-long-delay eyeblink conditioning. Training took place during two phases (one for each task, with task order counterbalanced between subjects) that were separated by a few weeks; new cells were labeled after Phase 1 and counted after Phase 2 (a). Learning during Phase 1 increased performance during Phase 2 (b). Cells not yet born during Phase 1 were more likely to survive in animals that were learning during both phases of training than in those that were not learning (c). Error bars represent standard errors of the means. Panel (d) illustrates a hypothesis explaining these results: Neurons rescued from death by learning under one condition (purple circles) activate or otherwise influence neurons that are born and then rescued during learning of a new but related skill (green circles). Connections and/or circuits (colored lines) among cohorts of cells are then used to calculate similarities and differences among learned experiences. Panels (a) through (c) are adapted from "Learning to Learn: Theta Oscillations Predict New Learning Which Enhances Related Learning and Neurogenesis," by M. S. Nokia, H. M. Sisti, M. Choski, and T. J. Shors, 2012, *PLoS ONE,* 7, Article e31375. Copyright 2012 by the authors.

condition, animals that require more trials of training to learn, provided that they do learn, retain more new neurons than animals that learn very quickly (Fig. 2b). For example, during trace eyeblink conditioning, an animal might require as many as 500 trials or as few as 100 trials to learn to emit a well-timed conditioned response to the conditioned stimulus. As long as it learns, however, the animal that takes longer to train will retain more neurons (Curlik & Shors, 2011; Leuner et al., 2004; Waddell & Shors, 2008). Together, the data suggest that some degree of effort is necessary to engage the neurons to survive and that more effort is necessary to learn a more difficult task (Figs. 2c–2e).

Neurogenesis and learning to learn

I am often asked whether there is an upper limit on the number of cells that can be rescued from death by learning. We attempted to answer this question by training animals successively on two training tasks, both of which increase cell survival on their own (Fig. 3; Nokia, Sisti, Choski, & Shors, 2012).

In one training phase, animals were trained with trace eyeblink conditioning, in which they learned to associate a tone with eyelid stimulation across a temporal gap. In another training phase, the same animals were trained on a very-long-delay conditioning task in which the same stimuli overlapped but over a longer interval. The training phases for each task took place a few weeks apart (with task order counterbalanced between groups). Therefore, during the second phase of training, animals already knew the association but had to learn new temporal relationships between the conditioned and unconditioned stimuli. In general, training on the initial task facilitated learning during training on the second task. This was expected, because the stimuli were the same and the basic association had already been acquired during Phase 1. With respect to cell number, animals that learned well during training on the first task (Phase 1) learned even better during training on the second task (Phase 2) and thereby retained more new neurons (neurons that were not yet born during Phase 1 training) than animals that were trained on only one task or trained on the same task twice.

These data suggest that successful and successive learning experiences perpetually increase the number of neurons that survive in the future, primarily because they tend to increase future performance on related training tasks. They also suggest that a great number of neurons can be accrued by increasing the opportunities for learning to occur.

Hundreds of studies have reported that preventing neurogenesis interferes with select learning processes, many of which do depend on the hippocampus (Kempermann et al., 2004; Kheirbek et al., 2012; Shors et al., 2001). However, it is unclear how or even whether these new neurons, once rescued, contribute to processes of learning in the hippocampus. It may be that they are used to encode the "context" of the learning experience, even if that learning experience does not depend on the hippocampus. They may also be used to integrate experiences that do not depend on the hippocampus with those that do. Or they may simply reflect part of a neurobiological mechanism for increasing the number of new neurons in the brain, neurons that can be used for other purposes. It is tempting to propose that the new cells contribute to the memory of the event that was used to rescue them. However, the hippocampus itself is typically not integral to the long-term storage of memories or their recollections.

Because the cells are new, they process all experiences as new. Thus, one might imagine that one cohort of new neurons (those generated at the same time) constitute a cellular source for encoding events that occur at one moment in time. After they have been incorporated, these "time-stamped" neurons can interact with cells generated in the future and rescued from death by experiences occurring at that time. For example, in the study discussed above (Nokia et al., 2012; Fig. 3), neurons rescued from death during the first phase of trace conditioning would eventually mature and make synaptic contacts with other neurons, which could activate or otherwise influence newer cells that had just been born, as they become receptive to learning during Phase 2 of very-long-delay training. The coactivation of these time-stamped cell populations and their circuits could provide a means for establishing similarities and distinguishing differences between what we have learned in the past and what we are learning in the present, all with the goal of predicting what will happen in the future (Fig. 3d).

Production Versus Survival of New Neurons

At this point, the important, albeit fine, distinction must be made between cell production (i.e., proliferation) and cell survival. Many experiences and manipulations can alter the number of cells that are produced. For example, exercise, sexual activity, and antidepressants increase cell production, whereas stress, aging, and alcohol decrease cell production (for review, see Shors et al., 2012; Shors, Olson, Bates, Selby, & Alderman, 2014). However, learning exerts its effects on the cells that were already produced and present in the hippocampus at the time of training. In our studies with classical conditioning, learning did not increase the number of cells produced during training, and animals that tended to learn well did not begin training with more new cells (Anderson et al., 2011; Gould et al., 1999; Nokia et al., 2012). In contrast, physical exercise increases the production of new cells but does not necessarily keep alive the cells that are already present when exercise begins (Curlik et al., 2013; Pereira et al., 2007).

These and other data indicate a preferential effect of learning on the *survival* of cells that are new and already present when training begins. That said, the processes of proliferation and survival eventually interact with one another; making more new neurons provides a greater supply of neurons to rescue during learning. For example, the number of new cells increases in response to physical training with exercise. If these cells are present during some type of mental training, a greater number of them will survive to become mature neurons. We refer to this "ideal" combination of training conditions as "MAP" training because it combines mental and physical training experiences to optimally increase the number of surviving new neurons in the adult brain (Curlik & Shors, 2013; Shors et al., 2014).

Neurogenesis and Desirable Difficulties

Let us now consider how we, as individuals, can maximize the number of new cells that survive to become functional neurons in our hippocampi. How can we keep ourselves engaged in "desirable difficulties"—activities that make learning more effortful and ultimately enhance retention and recall? According to Bjork, Dullosky, and Kornell (2013), desirable difficulties include practices such as (a) spacing trials of training over longer periods of time, (b) self-testing, (c) varying the conditions of training, and (d) interleaving different topics and/or skills within the same training sessions. It is perhaps relevant that animals trained with spaced trials of training outperform those trained with massed trials and, as a result, retain more new neurons in their hippocampus (Sisti, Glass, & Shors, 2007). Also, as discussed, animals trained under varying training conditions (e.g., trained on two related tasks in succession; Fig. 3) learn especially well and retain more new neurons as a result (Nokia et al., 2012).

But these are laboratory studies. In our real lives, it is often less than desirable to engage in effortful learning practices. Indeed, humans prefer massed training over spaced training because it is easier, even though it results in weaker long-term retention (Bjork et al., 2013). And few of us attempt to learn a new language while simultaneously learning how to play a new instrument and a new sport. Even if we were to make the effort to learn all three skills at one time, most of us would reach an acceptable plateau, after which further training would be aversive (Ericsson, Nandagopal, & Roring, 2009). Nonetheless, we know that training experiences that challenge our capacity for learning produce superior levels of performance. The data presented here suggest that they also increase the number of neurons that reside in our brains.

Recommended Reading

Bjork, R. A., Dullosky, J., & Kornell, N. (2013). (See References). Discusses the most effective ways to study and learn in the classroom, based on information from the science of learning.

Ericsson, K. A., Nandagopal, K., & Roring, R. W. (2009). (See References). A review that discusses how deliberate and extended skill practice enhances performance and solidifies expertise.

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Declaration of Conflicting Interests

The author declared no conflicts of interest with respect to the authorship or the publication of this article.

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