PERSPECTIVE

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Potential role for adult neurogenesis in the encoding of time in new memories

James B Aimone, Janet Wiles & Fred H Gage

The dentate gyrus in the hippocampus is one of two brain regions with lifelong neurogenesis in mammals. Despite an increasing amount of information about the characteristics of the newborn granule cells, the specific contribution of their robust generation to memory formation by the hippocampus remains unclear. We describe here a possible role that this population of young granule cells may have in the formation of temporal associations in memory. Neurogenesis is a continuous process; the newborn population is only composed of the same cells for a short period of time. As time passes, the young neurons mature or die and others are born, gradually changing the identity of this young population. We discuss the possibility that one cognitive impact of this gradually changing population on hippocampal memory formation is the formation of the temporal clusters of long-term episodic memories seen in some human psychological studies.

The past decade has seen a dramatic increase in our understanding of the mechanisms involved in, and the extent of, the continuing addition of new neurons in the adult brain[1,2]. The persistent lifetime incorporation of new granule cells into the dentate gyrus has been demonstrated in rodents, primates and humans[3,4]. The effects of environment and behavior on the dynamics of the neurogenesis process are being revealed[5–7], but animal studies focusing on the impact of neurogenesis on behavior have been inconclusive[8].

In this Perspective, we have taken a somewhat different approach to investigating the function of adult neurogenesis. By applying recent findings about the developmental properties of newborn granule cells to what is known about the surrounding circuit, we have developed an idea for one role that continuous neurogenesis could have in the function of the dentate gyrus. Mounting evidence that immature granule cells are possibly more 'excitable', with a stronger propensity for long-term potentiation (LTP) than fully mature neurons, suggests that these cells may have a unique role in the processing of the dentate gyrus circuit[9,10]. By considering the dentate gyrus's theorized role in hippocampal processing, we are able to make specific predictions about how immature neurons may be affecting hippocampus-dependent learning and memory formation[11,12].

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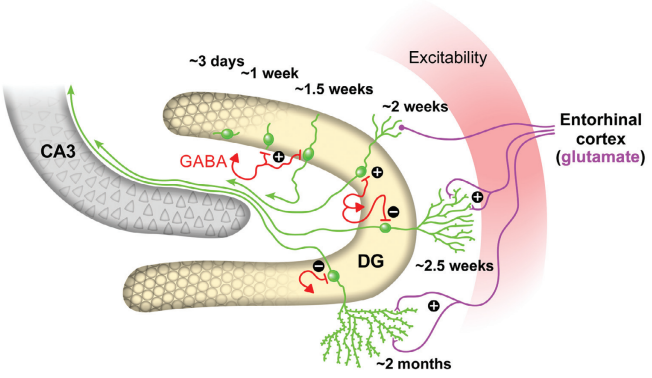

Figure 1 Growth and maturation of adult newborn granule cells. At 3 d, newborn cells have few projections and are migrating to their final location. At 1 week, early nonoriented dendrites appear, coupled with the onset of somatic GABA inputs (red neurons), and by 1.5 weeks, the primary apical dendrite extends to the molecular layer. Two-week-old neurons have aspiny, developed dendritic arborizations with extensive GABA input. By 2.5 weeks, spines have begun to appear, indicating the onset of entorhinal input, though not at the densities seen in fully mature cells. By 2 months, neurons have arborizations and electrophysiology similar to mature neurons. GABA is excitatory in immature neurons but becomes inhibitory around the time the excitatory glutamatergic synapses are established. The bar labeled excitability indicates the time period in which immature neurons have a distinct physiology, such as more depolarized resting potentials, and demonstrate increased LTP. Modified from ref. 30.

Notably, new neurons do not integrate into a cell layer thought to be involved in memory storage, but rather into a hippocampal structure with the theoretically straightforward role of pattern separation. Although there are many hypotheses about how the hippocampal circuit functions in memory formation, storage and retrieval, the idea that the dentate gyrus provides distinct codes to the network via the granule cells' mossy fibers has been one of the least controversial[13–15]. This function seems computationally inevitable, due to its highly divergent input structure (~200,000 entorhinal cortex cells project to >1 million dentate gyrus granule cells in the rat) and the sparse, powerful mossy fiber projection to the CA3 (refs. 16,17). Sparse activity in the dentate gyrus following exposure to spatial environments has been observed experimentally with both implanted electrodes[18] and in an immediate-early gene study[19], with the latter suggesting that different sets of granule cells are activated in response to exposure to two distinct environments.

The necessity of sparse, orthogonal (distinct) inputs into the hippocampus has been well described computationally[20], and it has been suggested biologically that the powerful dentate gyrus projection drives how the CA3 responds to its entorhinal and recurrent inputs[21,22]. Behaviorally, there is evidence that dentate gyrus–specific lesions can disrupt the acquisition of some spatial memories, despite the remaining direct entorhinal to CA3 input[23,24]. However, it is most likely that neurogenesis knockdowns are not the equivalent of a full dentate gyrus lesion, and there is no reason to believe that neurogenesis is required for the dentate gyrus to produce sparse codes. Notably, the dentate gyrus was considered to be the hippocampus's source of sparse code generation long before the existence of adult neurogenesis was widely recognized[20]. Consistent with the idea that neurogenesis may not be required for all dentate gyrus functions, experiments that repress neurogenesis have generally failed to show the same short-term acquisition deficits that dentate gyrus lesions show[25].

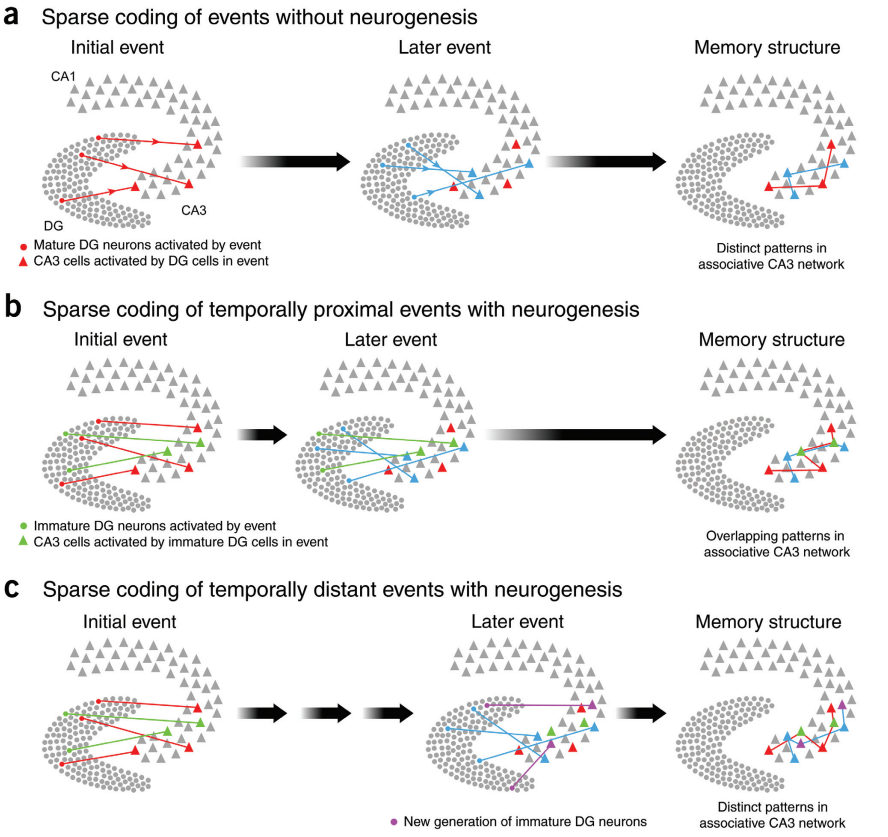

Figure 2 Schematic showing how newborn granule cells may encode temporal memories in the hippocampus. (**a**) Without neurogenesis, two distinct events would activate separate sparse populations of dentate gyrus granule cells (red and blue). These patterns would result in two highly distinct CA3 patterns (red and blue). (**b**) With neurogenesis, two events that occur at about the same time (for example, within a week of each other) would activate the same population of newborn neurons (green) in addition to the distinct patterns (red and blue) formed within the mature granule cell population. As a result, the CA3 patterns for the two memories, although different, now partially overlap. (**c**) Events that are temporally remote would encounter different populations of newborn neurons (green and purple). As a result, the memories formed within the CA3 no longer overlap.

Effects of neuron addition on coding

Several recent studies have looked at the computational effects of neurogenesis within the biological context of the hippocampus[26,27]. Mathematically, it is unclear what effect the continuous addition of neurons to a sparsification layer would have on the structure of codes produced by the dentate gyrus, but it has been suggested that the increased number of possible distinct codes would ultimately increase hippocampal memory capacity[27] or reduce interference between existing memories[26]. Whereas these functions are plausible implications of replacing neurons in this circuit, the increasing evidence suggesting that these new neurons are not functionally identical to the existing granule cells during their development has additional implications for their function within the dentate gyrus (ref. 28 and **Fig. 1**). Although it is still unknown when or how these new neurons begin to influence CA3 pyramidal neurons, it is known that they form mossy fiber connections onto the CA3 early in development[29,30] and exhibit action potentials within 3 weeks[31]. On the other hand, the new neurons' electrophysiological properties appear to remain different from those of mature granule cells even when they are over a month old[32]. Newborn granule cells have lower activation thresholds, higher resting potentials and increased levels of LTP compared to fully developed granule cells[9,10]. Furthermore, immediate-early gene studies (an indicator of cellular activity) suggest that these cells are more responsive to new environments (H. Makino, A. Tashiro and F.H.G., *Soc. Neurosci. Abstr.* 141.3, 2005).

What would this increased activity of new cells mean for the sparsification performed by the dentate gyrus? Immediately, the activity patterns of the dentate gyrus would become somewhat less sparse, as there would be several thousand new neurons responding to a wider range of inputs. Presumably, the function of the dentate gyrus is to provide not just sparse codes, but codes that are orthogonal, or distinct, to the CA3 (ref. 20). However, the inclusion of neurogenesis might have the opposite effect on the separation of two events. If the newborn neurons are more likely to fire than mature cells, they would provide a disproportionately larger part of the dentate gyrus's sparse code. Two unique and new events would have the same subset of neurons disproportionately represented in their sparse codes. The production of fewer sparse codes by the newborn neurons would result in more overlap in their outputs in response to different events. As a result, the overall overlap between codes for two distinct events would be substantially increased.

For example, when a new event occurs, a sparse subset of neurons (referred to here as a 'pattern') in the dentate gyrus will respond (**Fig. 2a**, left). These granule cells in turn project to a limited set of CA3 pyramidal neurons, which are connected to one another and form a new CA3 pattern. According to conventional hippocampal theory, a different new event will then induce a different pattern of dentate gyrus granule cells, which in turn will create a new pattern in the CA3 (**Fig. 2a**, center). Now these two events are encoded in highly independent patterns by the recurrent network in the CA3 (**Fig. 2a**, right). This creation of distinct patterns within the CA3 has long been the assumed role of the dentate gyrus[20].

The inclusion of more responsive new neurons would alter this mechanism. When the dentate gyrus responds to a new event, young neurons are included in the sparse pattern that is generated (**Fig. 2b**, left). However, these same young neurons are likely to be included in the coding for the other events as well (**Fig. 2b**, center). Because these new cells also have connections to the CA3, a subset of CA3 pyramidal cells exists that would be included in both events. As a result, the patterns generated within the CA3 are no longer independent; rather, they overlap because each event's pattern includes the pyramidal cells activated by the newborn neurons (**Fig. 2b**, right).

This rough analysis would suggest that neurogenesis is detrimental to the proposed goal of separating similar inputs into distinct codes for the hippocampus. But this would only be the case transiently. It is important to consider that these newborn neurons make up a dynamic, constantly changing subset. The neurons mature out of this group, ultimately becoming less active and almost indistinguishable from the other granule cells[31]. New neurons are constantly being born, forming unique downstream connections, and passing through periods of higher activity compared to more mature cells. Eventually, those that survive are destined to become sparse coders themselves. Therefore, although newborn neurons may be included in encoding a new event (**Fig. 2c**, left), those neurons will mature or die and a different set of newborn neurons (with different CA3 projections) will be involved in the encoding of different events that occur at later times (**Fig. 2c**, center). As a result, two events that occur far apart in time will not form the same degree of overlap as two events that occur close in time (**Fig. 2c**, right).

From these empirical observations and analytical conclusions, we are able to hypothesize that there are two functional populations of granule cells. One is the set of mature granule cells, creating highly sparse representations of entorhinal inputs and, in so doing, providing distinct codes to the downstream CA3. The other group is a constantly changing set of newborn neurons that respond to entorhinal inputs in a less discriminatory manner, thus adding a component of temporal similarity to the codes sent to the CA3. The CA3, driven by mossy fiber input, may not distinguish between these two populations. The implications of such a hypothetical binding are substantial. It is plausible that these similarities in dentate gyrus outputs would result in a parallel subset of recurrently connected pyramidal cells in the CA3 and that this subset would in turn be included in the CA3 representations of the events that are occurring. As the subset of immature granule cells changes, so would the CA3 subset. Once such codes exist in the CA3, this effect would theoretically propagate to downstream regions—the CA1, subiculum and ultimately back to the deep layers of the entorhinal cortex. In this manner, time-associated patterns could become fully integrated into the hippocampal processing based on temporal information provided not by sensory information, but by the intrinsic rate of neurogenesis.

For how long would this time association occur within the sparse codes produced by the dentate gyrus? The maturation of newborn neurons takes approximately 1 to 2 months in rodents[33], but there are several phases of this maturation process[1]. The excitability of newborn neurons most probably decreases from the time spinogenesis begins (~16 days), which is around the same time GABA may begin to have an inhibitory influence on the neuron[31]. Whereas there are indications that newborn neurons remain more responsive than fully mature cells for some time[9], the maturation of dendritic arborizations and reduced spine formation by 1 month of age[30] probably make the neurons respond more selectively. Because the subset of newborn neurons is constantly changing, the similarity in coding would be greatest for events occurring at about the same time, when each event would activate a similar newborn neuron population (**Fig. 2b**). As days and weeks pass, the young neurons would mature or die and others would be born, changing the newborn neuron subset, thereby reducing the similarity between the two events. After several weeks, the population of young neurons would be completely different (**Fig. 2c**).

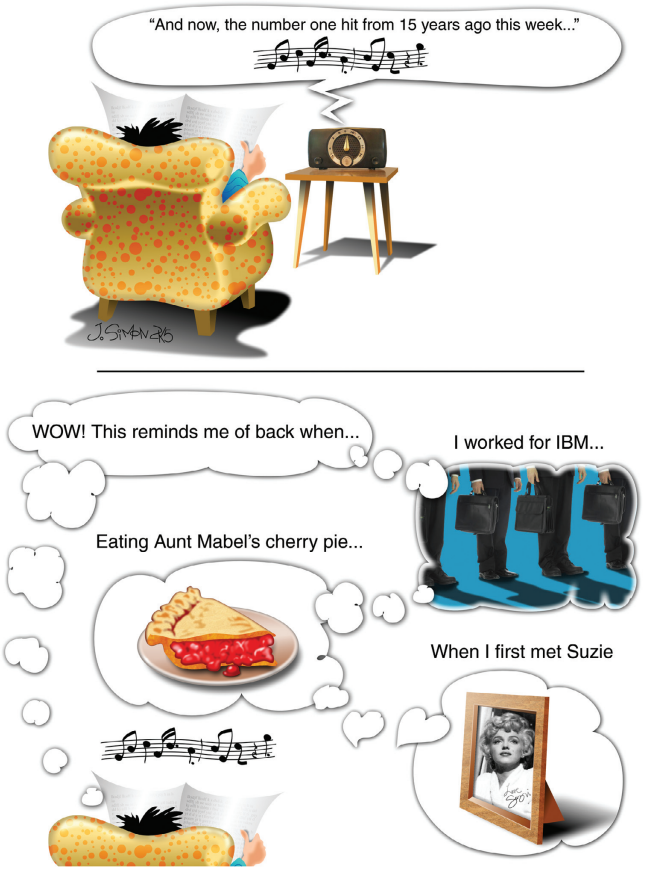

Figure 3 Cartoon example of how temporal associations may exist in long-term human memories. The reactivation of an old memory—such as hearing a hit song again years later—can induce the recollection of other memories that were formed at the same time. According to this hypothesis, these memories would have been originally encoded in part by the same set of young neurons, although this recall would most probably be hippocampus independent. Some memories may be general to the time of life—a summer internship, for example. Others may be repeated events that also occurred during that time period, such as visiting a relative. Finally, meaningful personal events may be recalled, such as meeting someone important for the first time.

Structure of temporal information in human memory

What we have described here is a biological mechanism by which temporal associations can form in the outputs of the dentate gyrus. Whereas the physical incorporation of such information into neural networks is a new concept biologically, the existence of 'time' in our memories has been debated for centuries. The actual manner in which long-term memories are associated has been a matter of contention psychologically for over a century and philosophically for much longer. Aristotle's *On Memory and Reminiscence*[34], for example, discusses the association of memories by time. However, although it has long been evident that human memories have a temporal component, it is not at all clear how this information is encoded.

Psychology research over recent decades has led to several distinct hypotheses of how time is associated with autobiographical memories[35]. Although these studies suggest that conventional dates are most

probably not 'tagged' onto most memories, there is increasing evidence that important events, or temporal landmarks, are either encoded with conventional dates[36] or have dates that are predictable, such as birthdays and holidays[37]. Furthermore, there is increasing evidence that proximal memories somehow remain associated with one another later in life (refs. 38, 39 and **Fig. 3**). Consistent with this finding, it seems that priming with an unrelated but proximal dated memory rapidly improves our ability to date less important autobiographical memories. For example, an individual may not be able to provide a date for a memory but may be able to use nearby memories with known dates to approximate an answer[37].

Most psychological theories that have shown that time is encoded into autobiographical memory are based on interviews and diary studies and do not focus on the biological mechanism by which this encoding takes place. Although there is little biological understanding of how specific mnemonic associations are formed, neurological observations over the past century have indicated where in the brain long-term memories are physically formed and eventually stored in humans[12,40], with the hippocampus being recognized as one of the critical structures in the establishment of long-term memories[41,42]. It is our hypothesis that an overlap in dentate gyrus sparse codes initiates these temporal associations in the hippocampus during early stages of memory formation. This temporal association memory may be permanently coupled with the sensory information to contribute to the formation of memories that are temporally tied into the individual's autobiography.

The dentate gyrus is presumably only involved in the initial encoding of information. Little is known about how memories are stored long term and retrieved, beyond the observation that, at some point, these new memories become independent of the hippocampus[12,40,43]. How information storage occurs remains unclear, though there is evidence that prefrontal cortical regions are involved in the consolidation, storage and retrieval of long-term memories, and it is likely that combinations of the prefrontal and other cortical regions are involved in the ability to recall remote memories[40,44]. If this temporal information is initially encoded by the hippocampus, as we are proposing, its long-term storage and eventual retrieval (as shown in **Fig. 3**) would most probably occur in other regions and would no longer involve the newborn neurons that originally took part in its encoding.

Future testing of temporal association memory hypothesis

The experimental observation of the process outlined here will probably not be a trivial task. Temporal associations in memories have been described mostly in humans, but our understanding of human neurogenesis is limited[4]. Human neurogenesis has only been definitively studied postmortem, and there has been no rigorous quantitative analysis of neurogenesis levels in young adults. One possibility is to look to several neurological observations as an opportunity to test this hypothesis, as there is a large body of research suggesting that neurogenesis levels are altered in numerous animal models of human conditions. Neurogenesis has been shown to decrease substantially in animal models of aging, depression and alcoholism[45–47]—conditions that have all been associated with memory loss in humans[48–50]. Although each of these conditions is associated with widespread neurological pathologies, with the role of neurogenesis in each being poorly defined, it would still be interesting to see if these conditions are also accompanied by a degraded ability to remember temporal associations in memories formed during putative low-neurogenesis periods. Not all neurological conditions exhibit a decrease in hippocampal neurogenesis—for example, some seizures and neurodegenerative disorders are accompanied by increased levels of neurogenesis[1]. It may also be interesting to monitor whether temporal association memory is enhanced in any such conditions that do not lead to general cognitive impairments.

Likewise, because neurogenesis has been characterized primarily in rats and mice, it would be beneficial to find an appropriate behavioral task that tests temporal associations in these animals. Testing rodents on complex memory tasks is difficult for numerous reasons[12], and to our knowledge temporal associations between tasks have never been studied at this level. It may be possible to design a behavioral protocol that relies on temporal associations between two hippocampus-dependent tasks in which the role of neurogenesis can be fully ascertained in conditions that either amplify or knock down neurogenesis.

It should also be emphasized that the hypothesis presented here focuses exclusively on newborn granule cells at the specific developmental time between their initial involvement in the network and full maturation. Determining when newborn neurons begin to communicate with the CA3 will be interesting, as it seems that their axons reach the CA3 when the GABAergic inputs are excitatory[30]—though there are indications that GABA-driven cells may not exhibit action potentials[31]. Fully characterizing the duration of maturation and whether it is behaviorally modulated will help us further understand the impact of developing new neurons. The long-term survival of adult-born granule cells suggests an additional long-term function for these cells, as once the excitability of newborn neurons returns to the level of 'mature' granule cells, the time coding function would presumably be complete. Therefore, it is likely that the long-term impact of these cells is quite different from that during their early period of increased excitability. Although this later function remains unclear, we feel that this early property of neurogenesis is a possible explanation of one of the long-standing problems facing our understanding of memory—how do we remember when things happened?

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COMPETING INTERESTS STATEMENT

The authors declare that they have no competing financial interests.

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