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What is the functional role of new neurons in the adult dentate gyrus?

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Summary

The exponential growth in research results on the regulation of adult hippocampal neurogenesis, the life-long addition of new neurons to the hippocampal dentate gyrus, is paralleled by an increasing puzzlement about the potential function of these new cells. But to determine the functional relevance of these new neurons several fundamental problems have to be overcome. Two of them are discussed here. First, it will remain impossible to define the functional contribution the new neurons in the dentate gyrus make to hippocampal function as long as it is unknown how the dentate gyrus itself contributes to hippocampal function. Our hypothesis is that adult hippocampal neurogenesis serves in avoiding a stability-plasticity dilemma between learning new information and preserving old information, by allowing the dentate gyrus to adapt to new input pattern statistics while preserving the ability to process old patterns appropriately. Second, it is still not known, whether in adult neurogenesis the structural alteration follows a specific functional stimulus and serves to consolidate a functional change triggered by that stimulus, or if less specific stimuli of novelty or complexity induce more general structural changes that prophylactically prepare the grounds to better process information in similar novel or more complex situations in the future. Here our experimental findings and theoretical considerations argue for the latter possibility.

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Discussing the rapidly growing knowledge about the regulation of neurogenesis in the adult hippocampus a recent commentary in Science magazine was titled "Newborn neurons search for meaning" and wondered, whether in all the "hubbub surrounding the field" the crucial fact that the function of the new neurons is still not known has not been lost (Barinaga, 2003). This is of course not the case, but the pointed statement nevertheless elucidates the state in the field. Against this criticism one could argue how it should be possible to know what the function of new neurons in the adult dentate gyrus might be, if there is still no clear concept of what the dentate gyrus itself is good for in the first place. Despite years of fruitful research no unifying theory of hippocampal function exists that would integrate all the different aspects that various experiments have brought up. One thing that most scientists working on the hippocampus however will agree on is that the role of the dentate gyrus within hippocampal function is even more mysterious than hippocampal function altogether. The idea of this article here is not to prematurely take sides in these discussions, but to briefly review some principal problems that we are facing when we try to find out what the functions of new neurons in the adult dentate gyrus might be. After all, the attempt to understand the function of new hippocampal neurons means entering the venerable discussion on hippocampal function by the back-door.

The pessimistic assumption that adult neurogenesis were merely an atavism in a brain region that somehow missed the transition into adulthood has constantly lost ground, because adult hippocampal neurogenesis produces new granule cells in a suggestive activity- and somehow function-dependent manner. Adult neurogenesis correlates with parameters describing the acquisition of the Morris water maze task, a hippocampus-dependent learning test (Kempermann and Gage, 2002). This makes intuitively sense, given the fact that at least to some degree the hippocampus has to be considered a machinery necessary for learning and that is for the acquisition of memories. The often used term of the "gateway to memory" indicates just this. The hippocampus is considered to play a prime role in the formation and consolidation of declarative memory, whereas non-declarative memory does not require processing in the hippocampus. Spatial memory, as it is necessary to successfully navigate the Morris water maze, is a form of declarative memory that can be assessed in rodents. Memories themselves are generally thought to be stored in the associative areas of the neocortex and not the hippocampus, because damage to the hippocampus does not abolish the ability to recall memories stored before the damage occurred. Accordingly, in our experiments adult neurogenesis did not show correlation with any parameters used to describe the recall of learned information in the water maze task (Kempermann and Gage, 2002). These findings might be suggestive, but cannot prove a causal relationship.

A theoretically very straightforward way of assessing the function of new neurons within the context of hippocampal function would be to simply abolish all the new cells. Hippocampal function could then be tested in animals without new neurons by means of several classical behavioral tasks, including but not restricted to the Morris water maze. In practice it turned out that this experiment, which has been published by Elizabeth Gould and her group (Shors et al., 2001), was sensitive to confounding influences (in particular side effects of the cytostatic drug used) and has led to somewhat ambiguous and conflicting results. Killing progenitor cells in the dentate gyrus with a cytostatic drug did not affect learning the water maze (Shors et al., 2002), but affected a hippocampus-dependent (the "trace") form of eye-blink conditioning while sparing the hippocampus-independent ("delayed") form (Shors et al., 2001). It is not easy to understand, why neurogenesis would be necessary to mediate a rather simple conditioned reflex that probably requires minimal processing, to say nothing of structural reorganization in the hippocampus, but not for a complex hippocampal learning task with a long acquisition phase and the known ability to influence hippocampal morphology, including an induction of adult neurogenesis. Therefore, at present the most stringent conclusion from these experiments might be that more experiments are needed. One fundamental problem lies in the fact that the experimental procedure in the two published studies eliminated not new neurons, but the proliferating (progenitor) cells of the dentate

gyrus – and elsewhere. If one were interested in studying the role of the rooster in the chicken farm, smashing eggs might not be the way to go.

The newly generated neurons of the adult dentate gyrus are granule cells, but do they differ from older granule cells? Are there functionally two types of granule cells, one larger population that is generated during development and early postnatally and one generated during adulthood (Wang et al., 2000)? Obviously, an activity- and function-dependent production of new neurons can only take place when the individual is capable of activity. This alone sets adult neurogenesis apart from embryonic neurogenesis, where the amount of activity is nil, limited or at least qualitatively different. Also, the population of progenitor cells, from which the new cells are derived in adult neurogenesis appears to be distinct. While during embryogenesis the dentate gyrus is formed from the side that later becomes the molecular layer, adult neurogenesis originates from stem or progenitor cells in the subgranular zone towards the hilus. But these factors notwithstanding, by all standards the new granule cells appear to become indistinguishable from older granule cells. They express the same mature markers, in particular calbindin (Kuhn et al., 1996), they extend their axon along the mossy fiber tract (Stanfield and Trice, 1988; Hastings and Gould, 1999; Markakis and Gage, 1999), and they have electrophysiological characteristics very similar to older granule cells (van Praag et al., 2002). Particularly with regard to the last criteria, however, the matter is complicated. In their landmark study, van Praag and coworkers had labeled new neurons with a retrovirus carrying the green-fluorescent protein (GFP) and used the patchclamp technique to analyze the new and the neighboring older granule cells (van Praag et al., 2002). However, with this approach the population of new cells could not be studied exhaustively. Therefore the question remained unanswered whether the new granule cells functionally mirror the range defined by the granule cell layer in general. Do the new cells reflect the local differences found in the granule cell layer (Wang et al., 2000)? Input to the granule cell layer varies considerably and granule cells receive afferents with different neurotransmitter systems (glutamatergic, dopaminergic, acetylcholinergic, and serotonergic) in a varying combination. The main (glutamatergic) input from the entorhinal cortex via the perforant path is not homogeneous either. Within the thickness of the granule cell layer, the electrophysiological properties of the granule cells change (Wang et al., 2000), potentially indicating that granule cells differ to some degree. New granule cells can be found in the entire granule cell layer with only minimal local preferences (slightly more new cells in the dorsal, suprapyramidal blade than in the ventral, infrapyramidal blade) (Kempermann et al., 2003). Moreover, it seems that within days or weeks during their development the new cells find their place within the granule cell layer (Kempermann et al., 2003). After that their distribution does not change over time. This could imply that the new granule cells acquire a locally specific functional phenotype. The alternative hypothesis is that the new cells are a class of their own, with subtle differences to all other granule cells and perhaps independent of their individual location. The answer to these questions will clearly influence the final interpretation of what adult neurogenesis is good for.

Adult hippocampal neurogenesis does not contribute vast numbers of new neurons. But there is increasing evidence that the granule cell layer grows measurably during those periods postnatally when adult neurogenesis shows a high rate. As adult neurogenesis declines with age to very low levels in old age the contribution becomes unmeasurable (Kempermann et al., 1998). A rough estimate is that the total growth of the dentate gyrus in adult mice is by about 10%, reflecting something like 30 000 neurons. These are too few cells to allow the build-up of entire new structures. There is no evidence, for example, that the adult dentate gyrus would be expanded in certain areas, in a continuation of late embryonic and early postnatal development. Most importantly, there is no indication of a turnover in the dentate gyrus (Biebl et al., 2000; Cooper-Kuhn et al., 2002). Also, the new cells appear rather evenly distributed throughout the rostro-caudal extension of the granule cell layer. However, a detailed analysis has not been conducted so far, so there still might be distributions not immediately obvious. The distribution within the thickness of the granule cell

layer, however, has been studied. The majority of new granule cells (50-60%) is found in the inner third of the granule cell layer and remains there (Kempermann et al., 2003). These finding suggest that function might be dependent on location (rather than age), but more detailed experiments are needed to confirm this idea. However, from such observation we have derived the hypothesis that the new neurons are unlikely to add bulk memory or multiply processing power but are strategically inserted into the neuronal network of the granule cell layer (Kempermann, 2002). The mossy fiber tract, which connects the dentate gyrus to area CA3 is one of the bottle necks within the information processing circuits of the hippocampus. Accordingly, the relative contribution of single new cells to overall function could be greatest at exactly this location. Information flows from cortical regions via the entorhinal cortex to the dentate gyrus, from there to CA3, onward through the Shaffer collaterals to CA1 (and the subiculum) and from there via the entorhinal cortex back out to the associative areas of the cortex (Amaral and Witter, 1989).

Our theory is that adult neurogenesis allows the hippocampus to adapt the first of its three processing modules to the level of complexity and novelty frequently encountered by the animal (Kempermann, 2002). Thus adult neurogenesis would modify the network by inserting relatively few new neurons rather than primarily increasing its size. Increasing processing power of a computer by ten percent would be ineffective. The main effect of adult neurogenesis will be qualitative and not quantitative. And it will be cumulative, improving the quality of the network with increasing age. Old animals which have very low levels of adult neurogenesis would not need as substantial adaptations as younger ones. Our studies have shown, however, that in old animals neurogenesis can be stimulated to a much larger relative degree than in younger animals (Kempermann et al., 1998; Kempermann et al., 2002), suggesting that upon functional challenge the hippocampus recruits the maximum of new cells available to cope with the new needs. Feng et al. have proposed that adult neurogenesis provides a means of erasing old memories and preparing the dentate gyrus for new information (Feng et al., 2001). We would argue that the fact that there is no obvious turnover of cells and that the increase in neuron numbers is incremental, slow and relatively modest in absolute terms argues against this idea. Also, old animals learn hippocampal tasks not as poorly as the low level of adult neurogenesis at old age would suggest.

There is no indication that the dentate gyrus would store memories. This role is usually assigned to CA3, which has strong recurrent connectivity. CA3 is commonly conceptualized as a so-called Hopfield-network (Treves and Rolls, 1994), a type of recurrent artificial neuronal network that can store patterns quickly and recall them in an auto-associative fashion, meaning that even a partial cue can retrieve a complete pattern. Hopfield-networks work particularly efficiently if the patterns to be stored are uncorrelated or orthogonal (Hertz et al., 1991). Thus, orthogonalizing the input patterns could be an important function of the dentate gyrus to increase storage capacity of the CA3-network and, more importantly, to reduce interference between different patterns. One can think of this orthogonalization as a transformation that removes common features and emphasizes differences to make the transformed patterns maximally unrelated. This can be achieved only in a statistical sense, of course, and not for each pattern individually. This is important, because it would help to understand, why not for each new information a quantity of new neurons is needed.

One way of orthogonalizing patterns is to make their representations sparse (Hertz et al., 1991), and in fact, the dentate gyrus is known to have a very sparse neural activity (Barnes et al., 1990). Maximizing sparseness is closely related to independent component analysis (ICA), which attempts to decompose patterns linearly into statistically independent components. Sparseness and ICA have been suggested as important coding principles in primary visual (Bell and Sejnowski, 1997; Olshausen and Field, 1997) and auditory cortex (Lewicki, 2002) and ICA has been demonstrated to be advantageous also for pattern discrimination (Bartlett et al., 2002). Thus we follow the hypothesis that orthogonalization is achieved by sparsification (Barnes et al., 1990; Treves and Rolls, 1994) and assume that this is related to an implicit independent component analysis.

But why might neurogenesis be required for this function? The transformation necessary to

orthogonalize input patterns depends on the statistics of the patterns. Assume the dentate gyrus of a mouse has developed an orthogonalizing transformation for a given range of input patterns, let say for a given environment the mouse lives in. Then the mouse is transferred into a qualitatively different environment. The dentate gyrus now has to orthogonalize a different range of input patterns and should learn a new adapted transformation. However, since the transformation is not only necessary for storage but also for recall, the mouse also needs the old transformation, otherwise it could not recall memories from the old environment. This is a classical stability-plasticity dilemma. Part of our hypothesis is that neurogenesis is one way of solving this dilemma. Intuition would suggest that instead of adapting all synaptic weights in the dentate gyrus network, which would erase the old transformation, the old synaptic weights were kept fixed and new neurons with new synaptic connections were added. This is somewhat in the spirit of the cascade-correlation learning architecture (Fahlmann and Lebiere, 1990) with the difference that it must be possible to eliminate or separate the effect of the new neurons if old patterns have to be processed. These new neurons would add to the transformation what is needed to orthogonalize the new patterns and the old transformation is still available. The new neurons would literally add new (orthogonal) dimensions to the representation that have not been present or important in the old environment. This would also explain why neurogenesis may decrease with increasing age, because the effect of adding new dimensions to the representation accumulates and tends to saturate. Notice that our hypothesis that neurogenesis serves learning of new transformations while preserving old transformations does not depend on whether CA3 is considered a permanent storage or an intermediate one (see below), as long as the time of storage is longer than the timescale on which the animal has to adapt to qualitatively new environments.

However, there is a fundamental problem in the hypothesis that the new neurons participate in orthogonalization or any other similar processing step, if the input that is to be processed is the one that has to trigger neurogenesis to achieve successful processing. It takes weeks to perhaps months for a new neuron to become fully integrated and functional (van Praag et al., 2002). The input that will benefit from the increased number of neurons cannot be the same that has once triggered neurogenesis and thus provided the new neurons whose synaptic weights can now be altered. Thus, the situation is somewhat similar to data from research on long-term-potentiation (LTP), the putative electrophysiological mechanism underlying learning. There, measurable synaptic changes precede detectable structural changes, that is the formation of new dendritic spines (Engert and Bonhoeffer, 1999). Accordingly, there are two general options. Either adult neurogenesis is involved in consolidating an earlier functional change on a structural level, or adult neurogenesis is a non-specific preparatory step that allows the general adaptation of the system to experienced levels of complexity. Either structure follows function or function follows structure. Our hypothesis that old synaptic weights are fixed, however, tends to argue for the latter, which would also explain, why such unspecific stimuli such as physical activity (van Praag et al., 1999) trigger adult neurogenesis.

If adult neurogenesis is so crucial for the dentate gyrus, why would adult neurogenesis then not be required in CA1 as well, since CA1 also has to adapt to the new pattern statistics? In fact, if CA1 actually inverted the transformation carried out in the dentate gyrus, it would have to closely parallel the adaptation of the dentate gyrus. However, while the dentate gyrus has to take measures to preserve also the old transformation, CA1 does not have this constraint. CA1 simply has to follow the changes with the objective that it inverts the transformation performed by the dentate gyrus. This is similar to a so-called auto-encoder network (Hertz et al., 1991, p. 132) that is, for example, trained through backpropagation and where the encoding stage corresponded to the dentate gyrus and the decoding stage to CA1 – with the difference that the encoding stage had the additional objective of orthogonalizing the input patterns.

A retrograde amnesia found in patients with bilateral hippocampal damage has been interpreted as reflecting the period the hippocampus needs to consolidate the memory. However, what makes things considerably more complicated is the finding that whereas memories might still be retrievable

in subjects with hippocampal damage, this recalled information appears to be qualitatively altered. Also for some pieces of information the retrograde amnesia seems to extend much further into the past than for others. This could indicate a different speed of consolidation for different memories, but it might also argue in favor of the idea that in one sense or another the hippocampus could be involved in the retrieval of the already stored information or that it is the actual long-term storage site for some kinds of memories (Nadel and Moscovitch, 1997). It has also been suggested that stored memory contents might again become hippocampus-dependent during retrieval and thus vulnerable to alterations (Nadel and Land, 2000; Myers and Davis, 2002). Additionally, the hippocampus is profoundly involved in limbic system and presumably through these connections contributing to what we call "emotional memory" and to the affective contexts and tags we assign to new information.

In this brief discussion we have touched two of the main problems in recognizing the function of new neurons in the adult dentate gyrus. Both are fundamental issues: First, we have discussed the function of adult neurogenesis in the context of the function of the dentate gyrus. Under the assumption that the dentate gyrus performs a transformation of entorhinal input patterns to facilitate storage in CA3, we have hypothesized that adult neurogenesis allows the dentate gyrus to adapt to new input pattern statistics while preserving the ability to process old patterns appropriately. It would therefore provide a solution to the stability-plasticity dilemma between learning new information and preserving old information. Second, the question is whether adult neurogenesis acts post hoc to provide a structural consolidation of a specific functionally induced change, or prophylactically reacts to the more general experience of increased functional challenge, thereby allowing a long-term adaptation of the system to better cope with similar situations in the future. Our hypothesis that old synaptic weights should be kept constant would argue for the latter. Overall, we believe that the research on adult neurogenesis in the dentate gyrus is not only interesting in itself but provides a new avenue to the understanding of hippocampal function in general.

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