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Neurogenesis interferes with the retrieval of remote memories: Forgetting in neurocomputational terms

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A B S T R A C T

In contrast to models and theories that relate adult neurogenesis with the processes of learning and memory, almost no solid hypotheses have been formulated that involve a possible neurocomputational influence of adult neurogenesis on forgetting. Based on data from a previous study that implemented a simple but complete model of the main hippocampal circuitry (Weisz & Argibay, 2009), we now test this model under different situations to better study the case of remote memories. The results of this work show that following neurogenesis, the new, ongoing memories in the hippocampus are better retained than when no neurogenesis occurs at all, while the older memories are affected (to a lesser extent) by a special type of interference that is different from interference that occurs with an increasing number of memories *per se*. This work adds a new point of analysis in support of the interference view that might lead to the forgetting of memories in the hippocampus as they are transferred to neocortex for long-term storage, consistent with the Complementary Learning Systems models of system-level consolidation. Attention should be directed to the specific causes of interference; the results of this work signal a type of distortion of remote memories that is produced by the birth and the growth of new processing units, which results in a subtly impoverished retrieval as new neurons become active. The proposals of this model fit well with some empirical findings that are related to the issue.

In the future, as new evidence emerges, we believe that this biological process, which is largely related to learning and memory, will also help to shape our ideas about normal forgetting and its possible contributions to system consolidation.

1. Introduction

According to Dudai (2002), forgetting can be defined as the following:

1. The loss of learned information.
2. The inability to retrieve learned information.
3. A deterioration in the correspondence between the memory retrieved and the memory acquired.

In the present work, we take definition "2" from above, mainly because of different previous psychological theories that assume that it is difficult to probe the loss of learned information (definition "1"). Moreover, from a neurocomputational point of view, facts stored in the form of symbols in matrices persist, and forgetting is mainly the inability to perform partial or total retrieval of the stored information.

It is almost universally accepted that the hippocampus, a bilateral archicortical structure that is interconnected with multiple subcortical and cortical areas, plays an important

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role in certain types of memory and in specific steps of memory formation (reviewed in Zola-Morgan, Squire, & Amaral, 1986). The intrinsic circuitry, consisting of the successive projections from the entorhinal cortex to the dentate gyrus (perforant pathway), from the dentate gyrus to CA3 (mossy fibres) and from CA3 to CA1 (Schaffer's collateral pathway), is commonly named the "trisynaptic pathway".

Adult hippocampal neurogenesis refers to the production of new granule cells in the dentate gyrus (Kempermann, 2006), the initial station for relay in the architectural network of the hippocampus. The new neurons that are generated daily in the hippocampus are integrated into existing neuronal circuits through the integration of the axons to the mossy fibre connections (Ide et al., 2008). Numerous neurocomputational models have been designed to address the role of adult hippocampal neurogenesis, and based on these models, new theories have emerged (Aimone, Deng, & Gage, 2010a, 2010b; Becker, MacQueen, & Wojtowicz, 2009; Garthe, Behr, & Kempermann, 2009; Weisz & Argibay, 2009). At present, most of the models agree in terms of the participation of hippocampal neurogenesis in the processes of learning and memory. The results of experimental data and of mathematical simulations suggest that the new granule cells might be involved in computational functions, such as pattern separation, to avoid overlapping of similar information, and pattern integration to introduce a degree of similarity to the encoding of events that occur closely in time (Aimone, Wiles, & Gage, 2009; Deng, Aimone, & Gage, 2010).

Recently, some advances expanded the functional roles for new neurons to systems consolidation (Inokuchi, 2011). According to the standard model of system-level consolidation, the hippocampus is required for the formation and retrieval of certain types of memories. However, this hippocampus dependence decays gradually over time, which is associated with a progressive increase in the requirements for extra-hippocampal regions, such as the neocortex, for memory retention (Frankland & Bontempi, 2005). Following the pioneering computational study by Marr (1971), who formulated the first model to account for system consolidation, McClelland et al., in what was an influential work, investigated the computational properties of these two levels and suggested a functional explanation about why both levels would be necessary for the integration of memories into structured neocortical memory systems, formulating the so-called Complementary Learning Systems theory. Central to this model is that changes in the strength of the connections between the hippocampal system and the different cortical areas are rapid and transient, whereas changes in the cortical connections are slow and long-lasting (McClelland, McNaughton, & O'Reilly, 1995).

The increased attention to models, such as those from McClelland et al., as well as recent work in, e.g., language learning (Davis & Gaskell, 2009), indicates a strong current interest in the field of consolidation. A necessary component of most contemporary consolidation models is that redundant memories must be routinely cleared from the hippocampus, in consideration of its finite storage capability. This scenario is generally assumed, but little is known about how memories are erased (Frankland & Bontempi, 2005; McClelland, McNaughton, & O'Reilly, 1995). In contrast to models and theories that relate adult neurogenesis to the processes of learning and memory, almost no solid hypotheses have been formulated that relate a possible neurocomputational influence of adult neurogenesis on hippocampal forgetting. In the context of system consolidation, a new challenge for theories of adult hippocampal neurogenesis and the processes of learning and memory is to understand how coping with novelty (i.e., acquiring new memories) is related to or balanced with the processes of forgetting old information.

In the past, when working with a model of neurogenesis in the hippocampus that is based on biologically plausible hippocampal circuits, we found that neurogenesis increases the network's capacity for new information while increasing the forgetting of old information (Weisz & Argibay, 2009). Based on these data and on new information that is obtained through the implementation of new experimental conditions with the model, we now propose a working hypothesis: In neurocomputational terms, the addition of new neurons in the hippocampus during adult life not only contributes to a successive and dynamic adaptation to the environment based on mechanisms of pattern integration of temporally adjacent events and pattern separation for events separated in time but also constitutes a mechanism of interference with the retrieval of old memories, thus being part of a mechanism of forgetting. We later discuss that this mechanism might be helpful to the process of system consolidation.

We implemented a simple but complete model of the main hippocampal circuitry, experimenting with several conditions to explore the role of neurogenesis in hippocampal forgetting.

2. Materials and methods

2.1. Hippocampal model

An artificial neural network that models the memory function of the hippocampus has been previously described (Weisz & Argibay, 2009). Briefly, this hippocampal model has 4 sub-networks in view of the different regions that are modelled (EC, DG, CA3 and CA1). We assumed different functional roles for each network, as proposed by Treves and Rolls (1994) (Fig. 1):

- EC (simulated with 600 neurons), the neural group for presenting inputs to and outputs from the hippocampus.
- DG (simulated with 1000 neurons), supporting a pattern separation function.
- CA3 (simulated with 1000 neurons), the region that presumably "stores" the different patterns or memories.
- CA1 (simulated with 1000 neurons), supporting a categorisation function that enables remapping and reorganising of the patterns.
- Input pathways to CA3: The patterns to be stored would be presented through the mossy fibres (from DG) and the cue initiating memory retrieval would enter through the perforant path (from EC) (Rolls & Kesner, 2006; Treves & Rolls, 1992).