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Invited review

Is structural remodeling in regions governing memory an univocal correlate of memory?

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ABSTRACT

Advances in our ability to visualize changes in single neuron morphology *during* or after *training* have largely contributed to renew the interest into the structural basis of memory. Nevertheless the idea that structural alterations in memory-specific neural circuits can be univocally considered as correlates of memory needs to be carefully considered in view of evidence showing that a variety of sensorial/motor/emotional stimuli also alter the morphology of neurons in those circuits. The aim of this review is to examine the respective impact of memory vs other forms of experiences in triggering structural plasticity in the rodent brain, the challenge being to disentangle alterations due to the formation of declarative/relational memories from those developing in the same regions in relation to non-memory functions.

1. Introduction

Memory formation associates with re-arrangements of synaptic connectivity at brain sites that are specific to the nature of the memory. Synaptic re-arrangements occur at the level of dendritic spines that change in number, volume, and shape in response to stimuli. This morphological plasticity is supported by the dynamic properties of the spine actin cytoskeleton that regulate the trafficking and anchoring of AMPA receptors at the level of synaptic membranes. Changes in neuronal connectivity therefore associate with changes in the amount of excitatory neurotransmission in memory-activated circuits. Nevertheless, several brain regions governing specific forms of memory are also activated and remodeled following exposure to a variety of sensorial/motor/emotional experiences, making it difficult to identify the function at the origin of the remodeling. Here we review the literature describing structural changes that occur following memory and non-memory experiences, with the aim of isolating remodeling criteria specific to the formation of declarative/relational memory.

2. Declarative relational memory associates with structural remodeling in limbic and cortical circuits

Declarative memory, the memory of facts and events, largely relies on the formation of flexible relational representations among the constituent elements of a specific experience (Cohen, Poldrack, & Eichenbaum, 1997; Konkel & Cohen, 2009). Neural traces of these associations are formed and stored in limbic and cortical circuits.

The first evidence of hippocampal remodeling following spatial training was provided by O'Malley et al. (2000) who detected an augmentation of dendritic spines by electron microscopy in the dentate middle molecular region of rats 6 h following water maze training. This increase was, however, transient as the number of spines returned to control levels 72 h post-training. These data were then confirmed by Hongpaisan and Alkon (2007) who combined scanning confocal and electron microscopy to concurrently estimate the density and the morphology of spines. Specifically these authors reported that, two days following completion of water maze training, mushroom spines, but not of filopodia, stubby, or thin spines were increased in CA1 pyramidal cells of trained rats compared to swimming controls. Then, by imaging spines by DIL dye staining 6 h following radial maze training, Mahmmoud et al. (2015) observed an augmentation of total and mushroom spines in apical and basal dendrites of CA1, but also

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of CA3, and in the molecular cell layer of the dentate gyrus indicating that multiple hippocampal regions are remodeled following spatial learning.

Using the eyeblink conditioning paradigm, a hippocampus-dependent associative task in which a neutral stimulus (e.g. tone) is paired with an air puff (unconditional stimulus) until the tone alone provokes a conditioned nictitating reflex, Leuner, Falduto, and Shors (2003) observed an increase in dendritic spines in CA1 basal dendrites 1 d after rats acquired the conditioning. Disrupting acquisition by injecting a competitive NMDA receptor antagonist prevented the increase in spines suggesting that a causal relationship exists between learning performance, excitatory neurotransmission, and enhancement of synaptic connections in the hippocampus. Similarly, Knafo, Ariav, Barkai, and Libersat (2004) reported an augmentation in CA1 spines 3 d after rats were trained to discriminate positive cues across pairs of odors for a water reward. Because the length and the diameter of dendritic segments was unchanged following training, the increase in spine density was considered as reflecting a net augmentation in the number of hippocampal excitatory synapses. Indeed, given the olfactory nature of the conditioned stimuli, spines were also more numerous in the piriform cortex therefore showing that structural remodeling occurs along the entire anatomical circuit supporting olfactory memory (Knafo, Grossman, Barkai, & Benshalom, 2001). Finally, studying structural synaptic plasticity in inbred mice with inherited differences in hippocampus function (Matsuyama, Namgung, & Routtenberg, 1997; Nguyen, Abel, Kandel, & Bourtchouladze, 2000) and hippocampus-dependent learning performance (Ammassari-Teule & Caprioli, 1985; Ammassari-Teule, Passino, Restivo, & de Marsanich, 2000; Upchurch & Wehner, 1989) was taken as an opportunity to confront spines deriving from spontaneous differences in memory scores. C57BL/6J (C57) and DBA/2J (DBA) mice were trained to discriminate between two odors simultaneously delivered, and to associate the positive odor with the position of a water reward. Results showed that only C57 mice learned to identify the positive odor and exhibited a post-training increase in spine density on apical, oblique, and basal dendrites of CA1 pyramidal cells (Restivo, Roman, Ammassari-Teule, & Marchetti, 2006). Interestingly, maze running time over training, an index of procedural learning, was found decrease in the same fashion in all groups, thereby confirming that strain differences in hippocampal spines were selectively reflecting differences in associative memory.

Fear conditioning (FC) requires to form an association between a neutral stimulus (e.g. a tone or a context) and an aversive unconditioned stimulus (e.g. electric foot-shock). Investigations of the neural basis of FC have shown that the basolateral amygdala (BLA) is required for tone (TFC) and contextual (CFC) fear conditioning (LeDoux, 2000; Phillips & LeDoux, 1992) while the hippocampus is required only for CFC (Anagnostaras, Maren, & Fanselow, 1999; Maren, Anagnostaras, & Fanselow, 1998; Matsuo, Reijmers, & Mayford, 2008). Accordingly, BLA spines were found to be increased following TFC and CFC, and CA1 spines following CFC (Giachero, Calfa, & Molina, 2013; Restivo, Vetere, Bontempi, & Ammassari-Teule, 2009). Nevertheless, when C57 mice were used as subjects, more spines with large head diameters were observed in BLA and CA1 neurons 24 h following both CFC and TFC (Pignataro, Middei, Borreca, & Ammassari-Teule, 2013), in line with the view that these mice form contextual representations in any situation they face. Interestingly, the observation that the majority of newly formed spines have a large head diameter (Pignataro & Ammassari-Teule, 2015) is consistent with the previous observation that BLA spines selectively formed following TFC have a larger PSD area (Fitzgerald et al., 2015; Lamprecht, Farb, Rodrigues, & LeDoux, 2006). Only Sanders, Cowansage, Baumgärtel, and Mayford (2012) reported a decrease in hippocampal spines following CFC. Spines, however, were counted in transgenic mice expressing the GluR1 subunit fused to green florescent protein with a c-fos promoter, and imaged by measured GluR1 insertion on active neurons. Because AMPA receptors are the primary mediators of fast action neuronal transmission, the minor number of GluR1 positive spines in active neurons observed after CFC might depict an initial state of circuit remodeling before NMDARs activate GTPases pathways, phosphorylate scaffolding proteins, and remodel the cytoskeleton (Kasai, Matsuzaki, Noguchi, Yasumatsu, & Nakahara, 2003).

While the formation of recent memory traces principally depends on the hippocampus, it is now well demonstrated that their long term storage requires extra-hippocampal structures including anterior cingulate, limbic, prelimbic, entorhinal and retrosplenial cortices (Frankland & Bontempi, 2005; Squire & Alvarez, 1995; Squire & Bayley, 2007; Squire, Stark, & Clark, 2004). In line with this view, examination of spine density at training-to-test intervals ranging from 7 to 30 days revealed a progressive increase in spine density in layer V pyramidal aCC (Aceti, Vetere, Novembre, Restivo, & Ammassari-Teule, 2015; Restivo et al., 2009) and in infra-limbic (ILC) and prelimbic (PLC) neurons (Vetere et al., 2011). Importantly, when spine growth was detected in the neocortex, hippocampal spines were returned to pre-training levels (Restivo et al., 2009). Then to verify whether the spines formed in aCC neurons were actually supporting remote fear memory, Vetere et al. (2011b) increased transcription of the myocyte enhancer factor 2 (MEF2), a negative regulator of spinogenesis, in the aCC immediately after CFC. Results showed that the treatment concurrently blocked remote memory expression and remote formation of aCC spines. In the same line, mice lacking the guanylate kinase domain of PSD 95 were found to exhibit normal recent, but defective remote, memory. Interestingly, this defect was associated with an hypoactivation of the ILC and a selective blockade of dendritic spines formation in the ILC. Indeed because sensorial stimuli elicit structural plasticity in primary sensorial cortical regions, spines were increased in the mouse primary auditory cortex following TFC, and a fraction of these newly formed spines persisted in the network at most remote time points (Moczulska et al., 2013).

3. Multiple experiences trigger structural remodeling in declarative/relational memory circuits

3.1. Formation of contextual representations increases dendritic spines in the hippocampus

Extensive evidence indicates that independently from its role in declarative/relational memory (Dusek & Eichenbaum, 1997) the hippocampus governs the formation of non-associative contextual representations (Smith & Bulkin, 2014). Thus, whether hippocampal spines formed following CFC training are partly or exclusively imputable to the formation of the contextual representation associated with the footshock is undetermined. To investigate the possibility that hippocampal remodeling might vary according to the nature (associative vs non-associative) of the contextual representation, Restivo et al. (2009) compared CA1 dendritic spine growth after exposing mice to CFC training or pseudo-training. Interestingly, the spine scores of pseudo-trained mice, i.e., mice placed in the conditioning chamber without experiencing any shock, were intermediate between those of trained mice and those of naïve mice. Confirming the intermediate status of hippocampal remodeling in pseudo-trained mice, comparison of cumulative frequencies of spines among the three groups showed that both trained and pseudo-trained mice exhibited an increase in spines on the majority of sample neurons, even though more neurons were remodeled in the mice that formed an aversive memory.