Article

Neuron

Hippocampal Somatostatin Interneurons Control the Size of Neuronal Memory Ensembles

Highlights

- Active neuronal populations inhibit non active neurons during memory formation
- Optogenetic activation of GCs creates an artificial memory and abolishes natural recall
- Non active neurons are excluded from the memory trace via lateral inhibition
- Excitatory neurons activate SST+ interneurons and engage dendritic lateral inhibition

Authors

Thomas Stefanelli, Cristina Bertollini, Christian Lüscher, Dominique Muller, Pablo Mendez

Correspondence

pablo.mendez@unige.ch

In Brief

Stefanelli et al. show that the size of the cellular engram is determined by a competitive process in which active neurons inhibit the recruitment of neighboring cells by engaging somatostatin-expressing dendrite-targeting interneurons.

Stefanelli et al., 2016, Neuron *89*, 1074–1085
March 2, 2016
http://dx.doi.org/10.1016/j.neuron.2016.01.024

CellPress

CellPress

Neuron
Article

Hippocampal Somatostatin Interneurons Control the Size of Neuronal Memory Ensembles

Thomas Stefanelli,[1] Cristina Bertollini,[1] Christian Lüscher,[1,2] Dominique Muller,[1,3,4] and Pablo Mendez[1,4,*]
[1]Department of Basic Neurosciences, Faculty of Medicine, University of Geneva, Michel-Servet 1, 1211 Geneva-4, Switzerland
[2]Service of Neurology, Geneva University Hospital, Gabrielle-Perret-Gentil 4, 1211 Geneva-4, Switzerland
[3]Deceased, April 29, 2015
[4]Co-senior author
*Correspondence: pablo.mendez@unige.ch
http://dx.doi.org/10.1016/j.neuron.2016.01.024

SUMMARY

Hippocampal neurons activated during encoding drive the recall of contextual fear memory. Little is known about how such ensembles emerge during acquisition and eventually form the cellular engram. Manipulating the activity of granule cells (GCs) of the dentate gyrus (DG), we reveal a mechanism of lateral inhibition that modulates the size of the cellular engram. GCs engage somatostatin-positive interneurons that inhibit the dendrites of surrounding GCs. Our findings reveal a microcircuit within the DG that controls the size of the cellular engram and the stability of contextual fear memory.

INTRODUCTION

Memory acquisition starts when exploration of a new environment drives synaptic activity in a small fraction of hippocampal neurons, triggering synaptic plasticity mechanisms that are believed to underlie long-term storage of memory (Martin et al., 2000; Malenka and Bear, 2004; Matsuzaki et al., 2004). Although synaptic plasticity occurring during memory formation has been extensively investigated in many brain areas (Whitlock et al., 2006; Maren and Quirk, 2004; Frankland et al., 2001; Nabavi et al., 2014), it remains unknown how memory is assigned to selected populations of neurons. How neuronal ensembles are chosen to encode a particular memory has implications for stability and specificity of memory and ultimately determines the storage capacity of neuronal networks (Olshausen and Field, 2004).

Excitatory neurons in the mouse dentate gyrus (DG) are essential for memory formation and retrieval (Pierson et al., 2015; Kheirbek et al., 2013). The immediate early gene *cFos* has widely been used as a marker for neuronal activity in this brain region (Smeyne et al., 1992; Reijmers et al., 2007; Morgan and Curran, 1991) since its rapid and transient upregulation correlates with experience driven synaptic activity. New environment exploration induces the formation of an active neuronal ensemble defined by cFos expression in a distinct fraction of granule cells (GCs) (Deng et al., 2013; Tashiro et al., 2007; Liu et al., 2012). When associated with an aversive stimulus such as in fear conditioning paradigms, retrieval of the contextual memory requires the reactivation of the cFos-expressing ensemble of neurons (Tayler et al., 2013). As context information is permanently stored, the active neuronal ensemble that emerged during the exploration becomes both necessary and sufficient for the mnemonic representation of the context (Ramirez et al., 2013; Tanaka et al., 2014; Denny et al., 2014) and is then referred to as the cellular engram.

The mechanisms ruling how fear memory is assigned to excitatory neurons in the amygdala involve the activity of the transcription factor cAMP response element-binding protein (CREB) that modulates cellular excitability ultimately governing memory allocation (Han et al., 2007; Yiu et al., 2014). Although much evidence has identified cell autonomous mechanisms that regulate the selection of neuronal ensembles (Rogerson et al., 2014), network mechanisms may also contribute to the formation of the cellular engram. Do active ensembles of neurons interact with silent neurons during memory acquisition? What factors limit the size of the engram? What are the consequences of this restricted recruitment for memory stability?

The activity of hippocampal excitatory projection neurons is controlled by a diverse population of inhibitory interneurons (INs) (Markram et al., 2004). For example, parvalbumin (PV)-expressing inhibitory cells target soma and axon initial segment and thus control the action potential output of excitatory cells (Freund and Katona, 2007). In contrast, somatostatin (SST)-expressing INs target dendrites and filter synaptic input to principal cells (Miles et al., 1996; Maccaferri, 2005). Recent work has proposed a role of inhibition in the neuronal computations performed in the hippocampus during fear memory formation (Lovett-Barron et al., 2014). Dendritic- and somatic-targeting INs are ideally situated to control synaptic activity flow in the hippocampal network (Mendez and Bacci, 2011), yet whether they play a role in determining the cellular engram and by extension in memory formation, remains elusive.

Here we investigate network mechanisms that govern the formation of the cellular engram and test its effects on memory stability. We find that memory is assigned to hippocampal GC populations by an activity-dependent process that regulates the size of the cellular engram and the stability of the associated memory. Active neurons engage local INs and inhibit surrounding projection neurons excluding them from the engram. Altogether, our results reveal a role of specific inhibitory circuits in the network plasticity responsible for contextual fear memory.