Feed-forward inhibition promotes circuit and network mechanisms supporting memory consolidation

D13

Hannah Twarkowski[1,2,3], Victor Steininger[1,2,3,4], Min Jae Kim[1,2,3,6] and Amar Sahay[1,2,3,5]

1) Center for Regenerative Medicine, Massachusetts General Hospital (MGH), Boston, Massachusetts, USA; 2) Harvard Stem Cell Institute, Cambridge, Massachusetts, USA; 3) Department of Psychiatry, Massachusetts General Hospital, Harvard Medical School, Boston , Massachusetts, USA;.
4) Brain Mind Institute, Ecole Polytéchnique Fédérale de Lausanne (EPFL), Lausanne, Switzerland; 5) BROAD Institute of Harvard and Massachusetts Institute of Technology (MIT), Cambridge, Massachusetts, USA; 6) Department of Biomedical Engineering, John Hopkins University, Baltimore, MD, USA

KEY FINDINGS

- **Contextual learning induces lasting, experience specific neuronal ensembles in the hippocampus 1 day after learning that decay over time**
- **Increasing feed-forward inhibition (FFI) prevents time-dependent decay of experience specific ensembles in CA1**
- **FFI facilitates cross-region communication prior to learning & the formation of context specific ensembles in CA1 following learning**
- **CA1 ensemble dictates context specificity of neuronal maps in ACC at remote time points and may function as an Index**

Contact

Htwarkowski@gmail.com @Twarkowski

More findings can be found here in my eLife article

Motivation

Understanding circuit changes that occur during learning and memory consolidation is a key element towards circuit-based approaches to improve cognition in memory and psychiatric disorders. Alterations in GABAergic interneurons (INs) are thought to contribute to development of different psychiatric disorders as well as age-related memory impairments and may represent a shared neural substrate across diagnostic criteria.

Upon learning, feed-forward inhibition (FFI) in the dentate gyrus – CA3 circuit is temporarily increased. Previously, we identified a specific molecular regulator, Ablim3, mediating this change. In aged rodents with impaired memory this mechanism fails but can be restored by viral manipulation of Ablim3. Moreover, alterations in Ablim3 levels in humans are suggested to serve as a biomarker for memory loss in aging.

Here, we asked **how increased FFI in DG – CA3 influences network properties and ensemble dynamics during memory consolidation** in the hippocampal – cortical network.

Methods

2-3 month old C57Bl6J mice were bilaterally injected in dorsal CA1 with a lenti-virus short-hairpin construct to **downregulate ablim3 in hippocampal DG** neurons.

Mice for electrophysiological recordings were implanted with tetrodes in dorsal CA1 and ACC. Mice for calcium imaging were further injected with AAV1.CamKII.GCaMP6f and implanted with a GRIN lens in CA1 (1mm) or in ACC (0.5mm).

Lenti-virus mediated upregulation of feed-forward inhibition (FFI) through PV interneurons

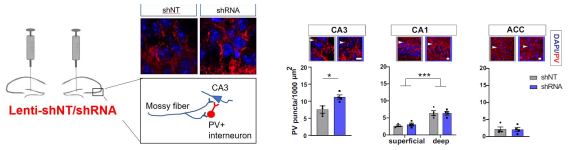
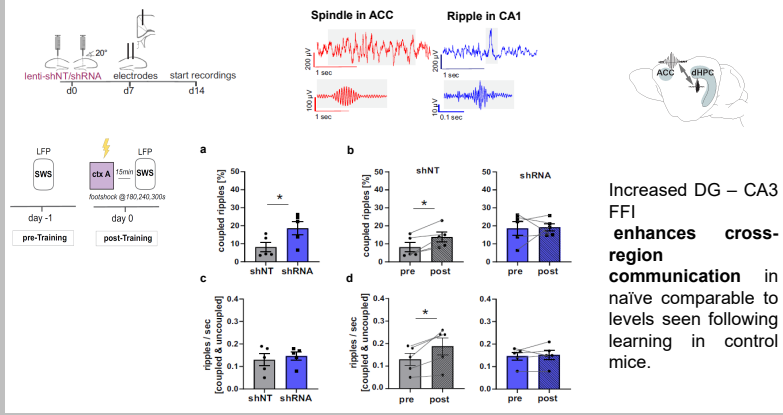
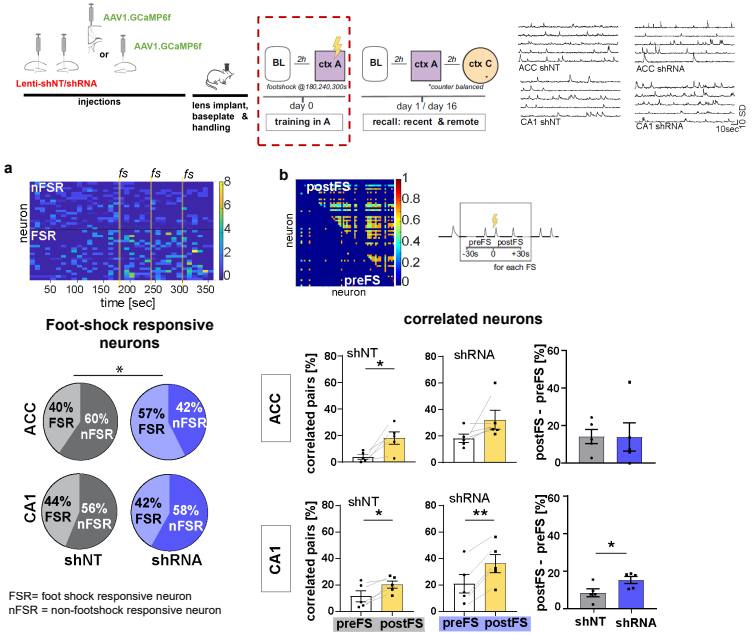


Fig 1: Increased DG-CA3 FFI strengthens cross-region communication similar to spatial learning



Increased DG – CA3 FFI **enhances cross-region communication** in naïve comparable to levels seen following learning in control mice.

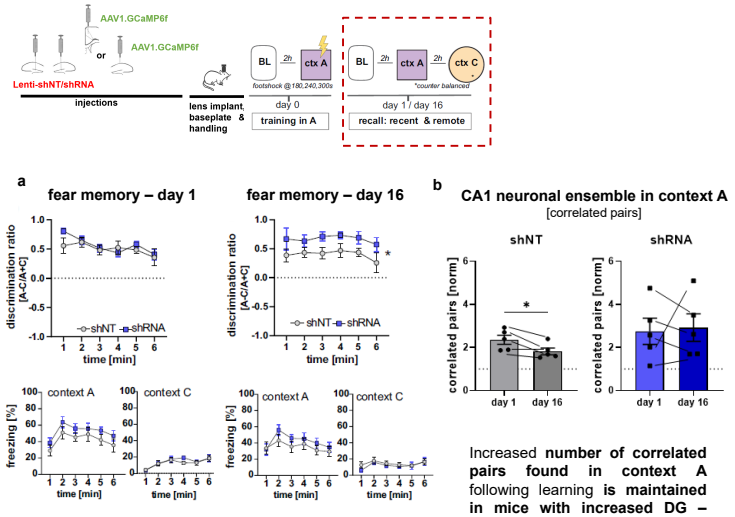
Fig 2: Increasing DG-CA3 FFI promotes the neuronal responses during foot-shock learning



FSR= foot shock responsive neuron
nFSR = non-footshock responsive neuron

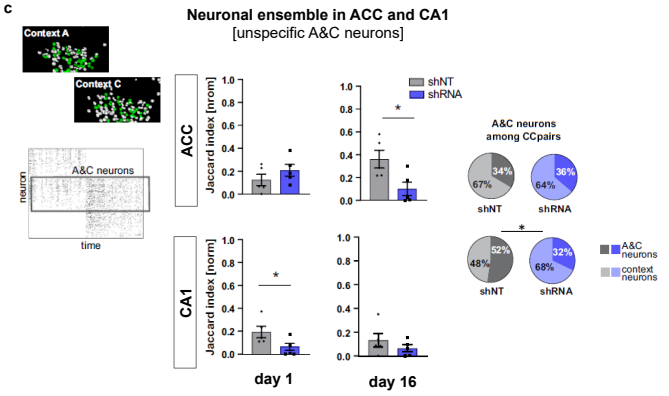
Increased DG – CA3 FFI **facilitates neuronal response** to the foot-shocks during spatial learning compared to control mice

Fig 3: DG-CA3 FFI dictates strength and specificity of CA1-ACC ensembles



Increased DG – CA3 FFI **increases long-term fear memory**

Increased **number of correlated pairs found in context A** following learning **is maintained in mice with increased DG – CA3 FFI**



Specificity of neuronal ensembles in CA1 is facilitated by increased FFI at both recent and remote recall (day 1 and day 16).

The **time-dependent increase in specificity found in ACC at day 16** indicates a role for DG – CA3 FFI in memory consolidation and a continuous role for CA1 in recall of remote events..