HELLENIC REPUBLIC
MINISTRY OF EDUCATION, RESEARCH AND RELIGIOUS AFFAIRS
GENERAL SECRETARIAT FOR RESEARCH AND TECHNOLOGY

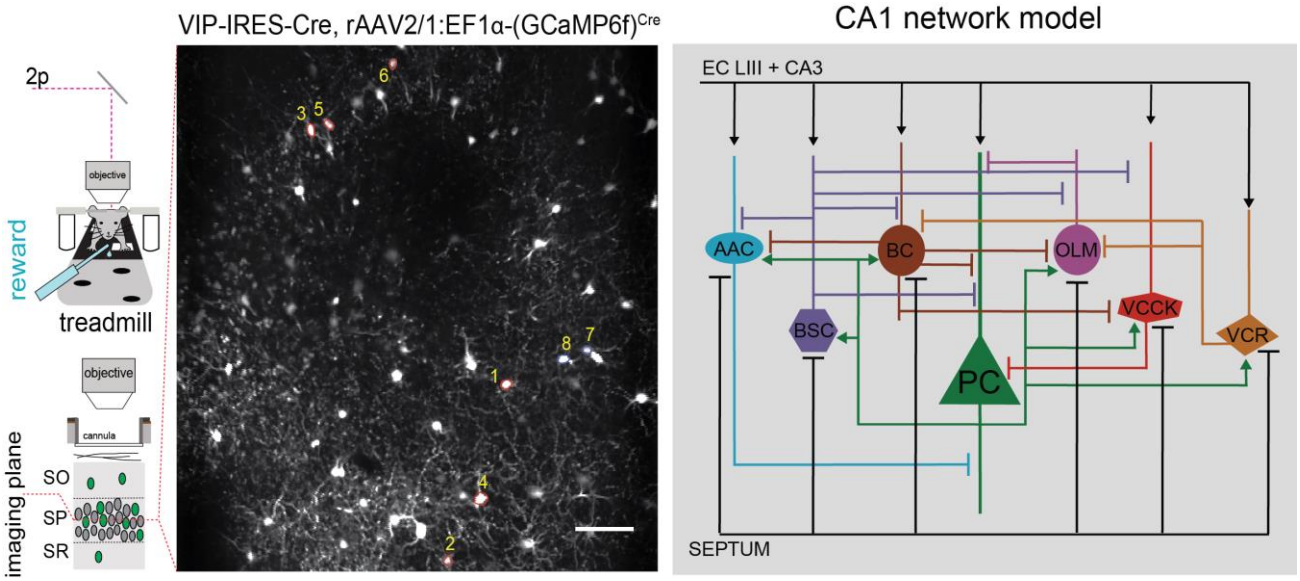
FOUNDATION FOR RESEARCH AND TECHNOLOGY-HELLAS
INSTITUTE OF MOLECULAR BIOLOGY AND BIOTECHNOLOGY

Heraklion 1/2/2019

PRESS RELEASE

SUBJECT: NEW PUBLICATION

IMBB and Columbia Researchers pinpoint the cells that control the brain's memory flow



The laboratories of Dr. Attila Losonczy (http://www.losonczylab.org/) at Columbia University in New York and Dr. Poirazi (www.dendrites.gr) at the Institute of Molecular Biology and Biotechnology (IMBB) of FORTH, joined forces in order to explain how neurons flexibly lay down or recall memories. The study is the first to provide visual evidence that a particular type of neurons – the so called VIP interneurons- makes this flexibility possible. The work is published in the scientific journal Neuron and is likely to have important implications for memory-related dysfunctions.

The brain's headquarters for learning and memory is the hippocampus, and it can be divided into distinct areas that process memory-related information. For this study, the researchers focused on area CA1, which encodes an animal's location -- as discovered by researchers who won the 2014 Nobel Prize. In 2016, Dr. Losonczy's lab found that CA1 neurons can act like a homing beacon; when a mouse looked for something, like water, neural activity spiked as the animal got close.

The current study investigated how this activity increased preferentially as the animal got closer to the reward. It did so using a battery of techniques, ranging from molecular, cellular, imaging and behavioral experiments to detailed computational modeling of different cell types found in this area.

Broadly speaking, neurons fall into two categories: excitatory and inhibitory. Excitatory neurons are the gas pedal; they drive the activity of other neurons. Inhibitory neurons, by contrast, are the brakes: they suppress neural activity.

The focus of this study was a particular type of CA1 inhibitory neurons called vasoactive intestinal polypeptide-expressing, or VIP, cells. Researchers had previously confirmed the existence of VIP cells, but had not examined them in the hippocampus of animals as they learned. Using a two-photon microscope, Dr. Losonczy and his team monitored the VIP-cell activity as the mice ran on treadmills laden with various sights and sounds, some familiar and others new. This allowed the researchers to examine how the animals' brains responded as they explored their surroundings, without a particular goal in mind. In second set of experiments, the mice were given a task: find a water reward that had been placed at a specific, unmarked location along the treadmill's path.

VIP-cell activity tended to spike during both sets of experiments: first as the animal ran aimlessly and then during goal-oriented learning when it sought the reward. Silencing these interneurons optogenetically affected the animal's ability to learn the reward location. However, the mechanism by which VIP cells excreted this action remained a mystery.

Computational modeling undertaken by the team of Dr. Poirazi at IMBB shed light on how VIP cells heavily influenced CA1 neural activity. Specifically, there are two types of VIP cells: those that directly inhibit (brake) excitatory neurons (the VIP-CR cells) and those that inhibit other inhibitory neurons that target excitatory cells (the VIP-CCK cells). Therefore, VIP cells could impact learning either directly, via their *inhibitory* effects onto pyramidal cells, or indirectly, via releasing the inhibition of other cells types that also inhibit pyramidal cells (*disinhibitory* effect). Discriminating between these two cell types / effects is challenging with current experimental techniques.

To answer this question, the IMBB postdoctoral fellow Spiros Chavlis developed a detailed model of the CA1 circuit of the hippocampus that incorporated VIP interneurons along with other cells found in this brain area. The model was calibrated to reproduce the increased spiking activity of excitatory neurons as a virtual mouse performed the same task in *simulated* experiments. The model also accounted for the two VIP cell types and their connectivity with both excitatory and inhibitory cells.

With the help of Ioanna Pandi, a Master student in the Poirazi lab, the IMBB team performed simulated lessoning of the two VIP interneuron subtypes in the model circuit. These *in computo* manipulations revealed that VIP interneurons influence behavior via their dis-inhibitory actions onto excitatory neurons. Disinhibition, although may seem counter-intuitive, appears to be an ingenious way in which excitatory neurons can -- in a roundabout way -- be activated. It offers a delicate and fine-tuned nature of learning. This added layer of complexity may have evolved to match the complex nature of memory. This complexity also gives the circuit added flexibility when choosing which groups of neurons get activated, thus providing an additional, subtle way of adjusting itself during learning.

Reference:

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Relevant links: https://www.cell.com/neuron/fulltext/S0896-6273(19)30010-8
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