Exploring the origins of excitatory and inhibitory neuronal tuning in the postsubiculum

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Action potentials from dozens of individual neurons recorded in mouse postsubiculum. Credit: Adrian Duszkiewicz.

Brain cells can be broadly divided into two categories: inhibitory and excitatory neurons. Excitatory neurons are cells that support the
generation of electrical impulses in postsynaptic neurons, thus prompting the activation of cells in specific brain regions. Inhibitory neurons, on the other hand, contribute to inhibiting these electrical impulses and thus reducing activity in specific brain regions.

The balance between inhibition and excitation contributes to the healthy functioning of the brain. While the neurobiological processes underpinning the fine-tuning of excitatory neurons are now well understood, those underlying the fine-tuning of inhibitory neurons remain elusive.

Researchers at McGill University and University of Edinburgh carried out a study aimed at better understanding the principles governing the fine-tuning of both excitatory and inhibitory neurons in the mouse postsubiculum, a region in the brain's medial temporal lobe known to support spatial navigation and memory.

Their findings, published in *Nature Neuroscience*, validate the hypothesis that the equivalent tuning of excitatory and inhibitory neurons is an intrinsic property of local cortical networks.

"Our laboratory is interested in how information about the outside world is reflected in the activity of individual brain cells," Adrian J. Duszkiewicz, lead author of the paper, told Medical Xpress. "The mammalian brain is made of millions of brain cells, called neurons, forming billions of connections, and cracking its code knowing the activity of only a fraction of those brain cells is a challenging task. Still, in some parts of the brain activity of individual neurons is relatively straightforward to interpret, and if we study such circuits in detail we may discover some more general principles of how activity of individual brain cells relates to the outside world."
Cells that engage in fairly straightforward patterns of activity include neurons in the primary visual cortex, which become active in response to visual stimuli. Other examples of these cells are place cells in the hippocampus and grid cells in the medial entorhinal cortex, both of which exhibit patterns of activity that are closely related to an animal's location in its surrounding environment.

The existence of grid cells was first unveiled almost two decades ago and the team who discovered them received the 2014 Nobel Prize in Physiology/Medicine.

"Both place cells and grid cells belong to the class of 'excitatory' cells, that is, brain cells that activate other brain cells they connect to," Duszkiewicz explained. "Such cells constitute a majority of neurons in the cerebral cortex (~85%), while remaining neurons largely belong to another cell class, called 'inhibitory' cells, which decrease the activity of cells they connect to."

Past studies have found that the activity of excitatory cells, including neurons in the primary visual cortex and place cells, is closely connected to environmental features. Inhibitory cells, on the other hand, tend to be permanently active and their activity can only be slightly modulated by external/environmental events.

The primary objective of the recent work by Duszkiewicz and his collaborators was to better understand the origin of inhibitory cell activity. Specifically, the team set out to determine whether the activity of these cells is really random, or whether it follows a particular pattern.

"To do this, we turned to another part of cerebral cortex—a brain area called postsubiculum, that is dedicated to the sense of orientation in space," Duszkiewicz said. "Excitatory cells in postsubiculum are called 'head-direction cells' because each of them is active when the animal is
facing a particular direction, and together they form the brain's equivalent of a compass, accurately tracking the animal's orientation in the environment."

The researchers decided to focus their efforts on the mouse postsubiculum because this brain region is known to have a very simple neural code. The simplicity of its code allowed them to map out the activity patterns of individual neurons simply by tracking the direction in which a mouse was moving while it was exploring a box.

"We used miniature electrode arrays that we implanted into the brains of mice and aimed at the postsubiculum," Duszkiewicz said. "This technique allowed us to track activity of dozens of individual neurons, up to 180 at a time, while the mice were foraging for cereal in a large box."

Most of the neurons examined by the researchers, namely the mice's excitatory head-direction cells, were only active when the mice were facing a specific direction. The team also observed some inhibitory neurons that were active all the time and yet appeared to prefer seemingly random sets of directions.

"When we took a closer look at activity patterns of neurons in postsubiculum, or their 'tuning' to the animal's direction, we realized that tuning of inhibitory neurons was not exactly random," Duszkiewicz said. "By looking at their activity alone we were able to determine which way the mouse is currently looking, with similar accuracy to excitatory cells, which means that their activity was meaningful. But more importantly, their activity patterns looked as though they summed the activity of all neighboring excitatory neurons—the canonical head-direction cells."

Interestingly, the researchers found that the patterns of activity of inhibitory neurons did not appear to be at all influenced by inputs
originating from other brain areas. In contrast, they appeared to be entirely determined by the tuning of nearby excitatory neurons.

Duszkiewicz and his colleagues defined this interplay between the tuning patterns of excitatory and inhibitory activity as "excitatory/inhibitory equivalence." Specifically, their findings show that the tuning patterns of excitatory and inhibitory cells are comprised of the same components and inhibitory patterns are the sum of excitatory patterns.

"We think that this finding brings us closer to understanding how the two neuron classes, the excitatory and inhibitory cells, work together to create a mental map of the outside world inside the brain," Duszkiewicz said. "This could be particularly important in the age of artificial neural networks, as it puts some constraints on how individual nodes of artificial neural networks should map to the external world if those networks are to model the activity inside real brains."

The results gathered by Duszkiewicz and his collaborators shed some new light on the local origins of excitatory and inhibitory tuning in the mammalian brain. While their recent study focused on the postsubiculum, the team hopes to soon broaden their investigation and examine other brain regions.

"Up until now, we have only focused on one neural circuit, the postsubiculum, because its activity patterns are relatively easy to understand," Duszkiewicz added.

"Yet now that we know what to look for, we want to confirm that this excitatory/inhibitory tuning equivalence can be observed in brain areas with more complex activity—such as the grid cells in the medial entorhinal cortex. Another avenue we will pursue in our future work is looking more closely at different sub-classes of inhibitory neurons (of which there are many), to see if they show any differences in their
tuning to the animal's orientation."


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