NEUROBIOLOGY

Assembling the brain from deep within

Stellate cells appear to drive the maturation of the entorhinal-hippocampal network

By Flavio Donato

As anyone who has ever shopped at IKEA knows, assembling flat-packed furniture can be a daunting task. You start with a box and a collection of independent components that remotely resemble that lovely cabinet you hope to build. Every part has to be positioned into the proper slots in the correct order so that those independent components can work together for a specific purpose.

Building up a brain has striking resemblances to that process: A bunch of components (neurons) belonging to different functional units (cortical areas) must be connected in the proper sequence to produce extended neural circuits that can support sophisticated cognitive functions. In building neural circuits, as in building furniture, function emerges through assembly, and in most cases it is defined by the assembly process (1–3).

SETTING UP CIRCUITS DEEP IN THE BRAIN

For the sensory part of the brain, the developmental instruction manual consists of both genetically encoded molecules and sensory-derived signals (3), with waves of coordinated activity that spread sequentially from sensory organs to cortical areas orchestrating the maturation of microcircuits underlying perception (4, 5). In sensory circuits, the same sensory organs that tie our brain to reality are also the driving forces behind maturation (6).

Circuits that lie farther away from sensory inputs, however, must operate via a different mechanism. An example of such a network lies in the medial temporal lobe and is involved in building an abstract representation of space and helping with navigation and the creation of memories (7, 8). This network is characterized by multiple cell types, connected together in a sequence that goes from the entorhinal cortex to the hippocampus and back to the entorhinal cortex (9). Different cells in each of these structures respond to specific features of the environment (e.g., a border or a specific location) or self-motion (e.g., heading direction or speed) by ramping up their firing activity (10). However, how these circuits come together or produce spatially tuned firing patterns is not yet known, and the driving forces for maturation in such circuits remain to be determined.

ACTIVITY DRIVES MATURATION OF THE ENTORHINAL-hippocampal NETWORK

With this in mind, we sought to determine how neurons influence each other’s maturation across the entorhinal-hippocampal network. In our first set of experiments, we followed the development of the circuit in Principal neuronal subpopulations in layer 2 of the medial entorhinal cortex. Stellate (magenta) and pyramidal (cyan) neurons are identified, based on the expression of molecular markers (Reelin and Calbindin, respectively), and analyzed by confocal microscopy. Cells sharing the same birthdate are identified by immunodetection of BrdU (yellow), a thymidine analog injected during embryonic development.
mice by monitoring the expression of molecular markers associated with maturation in specific cell types of each subdivision of the network from postnatal day (P) 5 to P30. Surprisingly, we found that maturation progressed sequentially through the circuit, in an order that recapitulated the flow of information in the adult brain (9, 11).

But do these neurons need to “talk” to each other during development to mature? To answer this question, we used chemogenetics to silence excitatory activity in specific populations of neurons at every stage of the circuit. In a striking resemblance to the sensory systems, we observed that an activity-dependent instructive signal spreading synthaptically through the network was necessary to drive maturation. In fact, silencing specific populations of neurons in the network stopped this signal and arrested the maturation of those neurons that were downstream in the sequence (11).

STELLATE CELLS: DRIVERS OF MATURATION?

In contrast to the sensory systems, the source of the instructive signal seemed to originate deep within the brain, in layer 2 of the medial entorhinal cortex (MEC). Among the cell types found in this area, stellate cells seemed ideal candidates for this task because they were the first ones to mature and their maturation progression was cell-autonomously correlated with their birthdate (11). In addition, the topographical distribution of stellate cells born at the same time mirrored the topographical maturation of layer 2.

To figure out which role stellate cells play in this process, we first blocked the activity of their main inputs and determined that their maturation was not affected, indicating that these cells likely follow an intrinsic program for maturation (11). Then, to target subpopulations of stellate cells born on the same day, we developed a novel viral-based strategy using a virus that did not integrate into the cells’ genome and injecting it into the developing ventricle of the embryonic brain under ultrasound guidance. When stellate cells were silenced, the rest of the neurons in the network did not progress through maturation, suggesting that the activity of the stellate cells was necessary to initiate the maturation of the whole sequence in the circuit.

STELLATE CELLS AND DEVELOPMENT

For the first time, a population of neurons located deep in the brain was shown to behave as an intrinsic driver for the maturation of a neural network. Could associational cortical areas rely on a few of these intrinsic driving forces during development to give rise to neural networks processing cognition, and do these cells maintain their driving role in the adult brain? If so, they might be critically important for the brain’s computational activity, in both health and disease.

Due to their local and long-range connectivity, stellate cells in the medial entorhinal cortex have long been hypothesized to be a key component of the network producing the regular pattern of the grid cell firing (12). Because its hexagonal regularity does not have any physical correlate in the sensory world, it has been suggested that the firing pattern of the grid cells arises as a network phenomenon, constructed entirely by the entorhinal-hippocampal circuit itself (13, 14). Extrapolating from our own observations, it seems possible that stellate cells could drive the creation of this abstract firing pattern.

STELLATE CELLS AND DISEASE

Stellate cells seem to be selectively vulnerable to intracellular accumulation of amyloid plaques in rat models of Alzheimer’s disease (15). The accumulation starts in the MEC and spreads sequentially to the rest of the network (16), resulting in impaired cognitive functions, such as spatial orientation and memory problems. Understanding how stellate cells influence the assembly and maintenance of a functional network in the entorhinal-hippocampal system might therefore be fundamental to understand how the brain generates cognition and behavior.

Through such studies, we might one day hope to understand what happens when this neural circuit becomes deranged. And, finally, we may even learn how to fix it.  

REFERENCES


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