Developing a sense of direction

Nervous systems continuously perform computations to create thoughts, feelings, and perceptions of the world. Circuits composed of neurons, which are the specialized cells of the nervous system, execute these calculations. To do so, neurons in a circuit receive input from the environment and then communicate with other neurons in the circuit through specialized structures called synapses. Synapses can relay either positive (excitatory) or negative (inhibitory) signals between neurons. Although excitatory synapses have been extensively studied, much remains to be discovered about how inhibitory synapses are established to ensure accurate neural computation.

The model we used to study inhibitory synapse development and neural computation was the direction selective circuit in the retina. The retina is the light sensitive neural tissue in the eye that extracts features of the visual world and outputs this information to the brain. Direction selective circuits in the retina are designed such that their output neurons to the brain, direction selective ganglion cells, respond only to objects moving in a particular direction, referred to as the preferred direction. An asymmetry in inhibitory signaling onto the direction selective ganglion cell produces this computation. These cells receive less inhibitory signal when objects move in the preferred direction and more inhibition when objects move in the opposite, or null, direction.

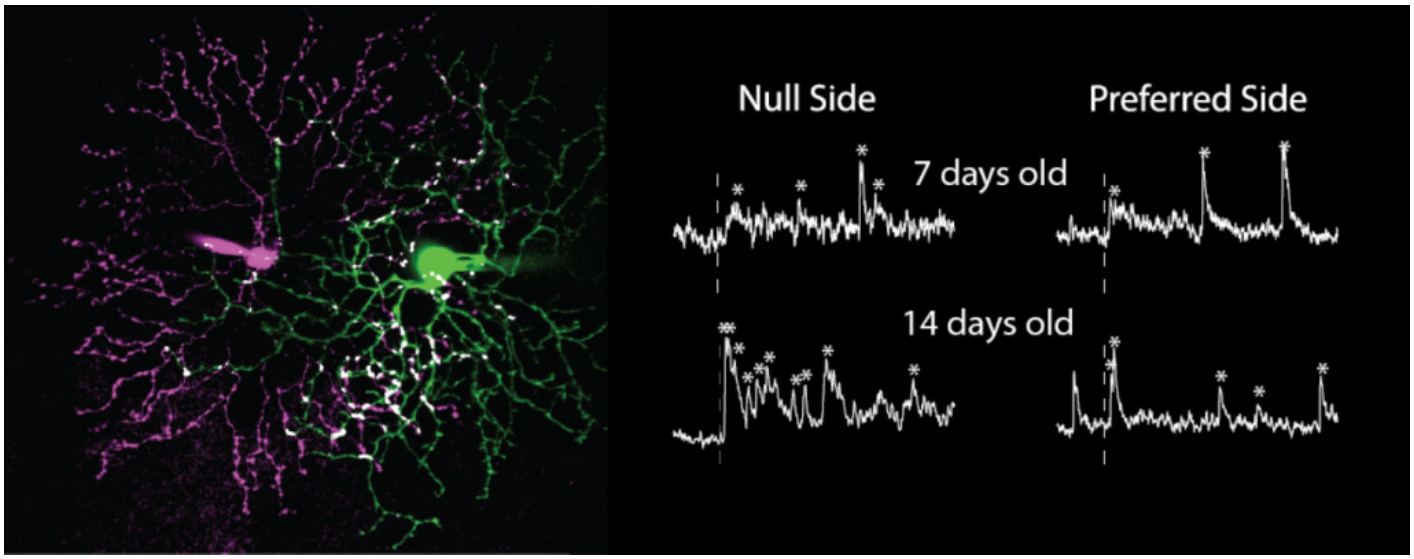

Fig. 1. Direction selective ganglion cell (green) and inhibitory neuron (magenta) with potential sites of inhibitory synapses (white). Right: Voltage clamp recordings from direction selective ganglion cell after stimulation of inhibitory neurons (dotted line). Synaptic currents are indicated by *, which increase in number during development when stimulating from the null side.

Although the direction selective circuit in adult animals is fairly well understood, how this wiring

emerges during development remained unknown. Two possibilities existed; inhibitory synapses from neurons on the null side of a direction selective ganglion cell either 1.) became stronger during development or 2.) increased in number. To answer this question, we turned to a mouse model. Mice are born with a premature visual system -- they do not open their eyes until two weeks after birth -- allowing us to study the early development of retinal circuits.
We measured the strength and number of synapses during development using the voltage clamp technique. This technique allows one to record the electrical current generated in a neuron upon activation of synapses. To conduct a voltage clamp recording, a glass needle with a microscopic tip is filled with a salt solution and carefully lowered to the cell. The outside of the cell is then sucked into the needle and the surface of the cell within the needle is broken, allowing for measurement of current flow across the cell's membrane.

To determine whether direction selectivity arises from an increase in synapse number or strength, we recorded synaptic currents from direction selective ganglion cells in response to stimulation of inhibitory neurons located on their preferred and null sides at both seven and fourteen days old, which is the developmental window when the asymmetry in inhibitory wiring occurs. We found that during this time only inhibitory neurons on the null side significantly increase the number of synapses they make onto a direction selective ganglion cell, while the synaptic strength remains constant. By analyzing the speed and timing of the electrical signals recorded in the direction selective ganglion cell, we also noticed that inhibitory synapses from null side neurons are formed closer to the center of the direction selective ganglion cell than inhibitory synapses from preferred side neurons.

In summary, we discovered that a specialized increase in inhibitory synapse number underlies the development of direction selectivity in the retina. This mechanism is likely to be essential for the formation of other neural circuits that rely upon a precise wiring of inhibitory synapses, such as those regulating learning and fear responses. Thus, the techniques and analysis described here can now be used to study the development of a variety of neural circuits in the nervous system.

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