Researchers deconstruct the 'biological clock' that regulates birdsong

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A team of researchers from Penn State and New York University has deconstructed an important "biological clock" in the zebra finch brain and found that the 'wires' between neurons, called axons, play a critical role in the precise timing of the birds' courtship song. Credit: Christopher Auger-Dominguez

The precise timing of a bird's complex song is driven in part by the often-ignored "wires" connecting neurons in the bird's brain, according to a new study. A team of researchers from Penn State and New York University has deconstructed an important 'biological clock' that regulates birdsong and other behaviors, leading to new ways of thinking about the function of neuronal networks.

"Many complex, learned behaviors, like hitting a golf ball or playing the violin, require incredibly precise timing at the level of neural firing," said Dezhe Jin, associate professor of physics at Penn State and an author of the paper. "But how the brain seamlessly regulates our muscles in such a precise way remains unclear. In this study, we created a model based on years of experimental observations which revealed that delays within the circuits of neurons play a critical role in the timing of their firing. We then pinpointed the source of the delays to the wires, or axons, that connect neurons."

In a paper appearing Oct. 15 in the journal *Cell*, Jin and colleagues address behavioral timekeeping using the zebra finch, a small Australian songbird capable of learning a courtship song with the skill of a master instrumentalist. To enable this vocal display, finches have a dedicated 'clock'—called HVC—in their brains that regulates the timing of the song. In HVC, groups of neurons fire in a predictable sequence that correspond to the performance of the song.

"HVC is often thought of as a clock because it controls a very complicated movement—the song—where precise timing is so critical," said Robert Egger, a postdoctoral fellow at the NYU School of Medicine and lead author on this study. "We used cutting-edge methods to measure the simultaneous activity of up to 70 neurons within HVC during singing. In the past, we had to measure each neuron one by one and align their activity to the song."

To explore how a circuit can be so precise, Jin and his graduate student Eugene Tupikov developed a series of large-scale computational models describing the neuronal circuit. In one case, a cluster of neurons fires at the same time which triggers the next cluster of neurons that fire at the same time, triggering the next cluster, like falling dominos, in what researchers call a synfire chain. In an alternative model, delays in the wires allow neurons to fire at slightly different times. The result is a more precise clock.

"We used to think of each group of neurons firing together as a separate, discrete tick of the second hand," said Michael Long, associate professor of neuroscience and physiology at the NYU School of Medicine and corresponding author of the paper. "But what we actually see is more like a second hand that moves smoothly and continuously. The distribution of delays among the wires allows for higher resolution because you don't get these tick points."

The team found a wide distribution of delays in the circuit, meaning some signals reach other neurons very quickly and some take much longer.

"We knew that delays in neuronal circuits were important over a large distance, but within local circuits, they were thought to be negligible, and for that reason were often ignored," said Jin, who led the modeling effort. "These results suggest that axons play a critical role in the timing of neuronal circuits and should be incorporated into future models."

To determine if axonal delays may play a role in other brain networks, the researchers estimated the delays in an area of the rodent brain used to sense their environment while they move their whiskers.

"Our results were consistent with the delays we saw in the songbird, which suggests that axonal delays may play an important role in shaping neuronal activity across a range of complex behaviors," said Jin. "We need to incorporate axon delays into how we think about the brain and how it works."

More information: Robert Egger et al, Local Axonal Conduction Shapes the Spatiotemporal Properties of Neural Sequences, *Cell* (2020). DOI: 10.1016/j.cell.2020.09.019