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Bonding networks: fMRI reveals functional connectivity in prairie vole brains

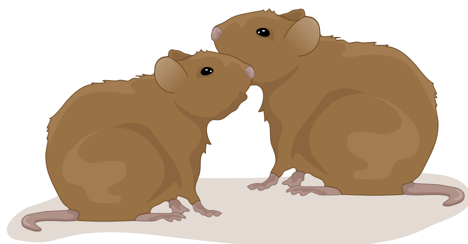
López-Gutiérrez, M.F. et al. *eLife* https://doi.org/10.7554/eLife.55081 (2021)

When one prairie vole catches the eye of another, the two will very often mate for life. That monogamous pair bonding, as well as other aspects of the prairie vole's prosocial behavior such as bi-parental care, has also caught the eyes of researchers. There is a small but growing community of scientists that have adopted prairie voles as models to study social behavior (and impairments) in an animal whose relationships are more akin to those that people experience than those of other lab rodents, such as mice and rats.

That community includes a colony of *Microtus ochrogaster* based in Querétaro, Mexico, set up five years ago by Wendy Portillo with prairie voles from Larry Young's lab at Emory University in Atlanta. Portillo, a neuroscientist at Universidad Nacional Autónoma de México (UNAM) Instituto de Neurobiología, is using the animals to study pair bonding and the influence of parental care on the social behavior of offspring.

Prior work in prairie voles has revealed potential roles for neurochemicals such as oxytocin and dopamine in the formation of pair bonds, and several neuroscience studies have established various functional connections between different areas of the brain. For example, work from Elizabeth Amadei and colleagues at Emory combining electrophysiology and optogenetic techniques detailed a link between the medial prefrontal cortex, an area of the brain involved in decision making, and the nucleus accumbens, part of the brain's reward system, as female prairie voles bonded with their mates. But as the community has identified more and more of the individual components at play in prairie vole pair bonding, questions remained about the bigger picture.

"We wanted to find out how these interactions were happening at a larger scale," says Fernanda Lopez, a graduate student at UNAM working with Portillo and neuroimaging specialist Sarael Alcauter, whose prior work had focused on humans and rats. Their new work published in *eLife* takes a wider look at the prairie vole brain, exploring the larger functional connectivity networks involved in pair bond formation and how those networks change and relate to social behavior in the animals.



Prairie voles display unique prosocial behavior, including monogamy and bi-parental care. Credit: Marina Spence / Springer Nature

To do so, Lopez and her colleagues used resting state functional magnetic resonance imaging (rsfMRI), a non-invasive neuroimaging approach commonly used in primates, including humans. Special magnetic resonance sequences are used to detect changes in oxygen concentration in the blood, an indirect measure of brain activity; as animals are scanned, signals recorded from different regions of their brains can then be correlated together to suggest functional connections. rsfMRI is a noisier technique than electrophysiology, explains Alcauter, but it can cover the whole brain of an animal instead of just a few regions at a time, and the approach enables longitudinal studies in which animals can be repeatedly imaged to look for changes over time.

Adapting the technique to a less traditional animal took some tweaking. Before any images can be recorded, you need to find an appropriate anesthetic that won't interfere with brain activity, says Alcauter. A mixture of isoflurane and dexmedetomidine has done the trick in mice and rats, but prairie voles aren't exactly either. As wild-caught animals from North American grasslands, they can be a little less docile and little more nervous with handling than their lab-bred cousins, says Lopez, so it took time to figure out the appropriate anesthetic dosages and administration routes. Size-wise they fall in between that of a mouse and a rat, so the available fMRI machinery and image collection pipelines had to be modified as well. And unlike the more common laboratory rodents, prairie voles don't yet have freely available brain atlases to reference once images are collected, so Lopez had to map out the different regions of the brain by hand. "We have to manage with the tools that we had available," she says.

But once the protocol was prepared for the prairies voles, imaging as well as behavioral studies could begin. "We were very confident that we would see changes in time – that we would find changes before and after pair bonding in functional connectivity," says Lopez. "But I actually was skeptical that the technique would be sensitive enough to see individual variation between subjects, and that it would correlate with behavior." The results were a pleasant surprise.

Sixteen male and sixteen female prairie voles were imaged before pairs were bonded and again after 24 hours and 2 weeks of cohabitation. Lopez mapped out 16 different regions of interest, including the nucleus accumbens and medial prefrontal cortex, and the team identified functional connectivity networks in the prairie vole brains that changed over time and that correlated with different measures of bonding, such as huddling latency when the pairs first started cohabitating and partner preference tests after bonds were formed.

The results replicate previous findings, including the detailed electrophysiological work, but they extend that knowledge to the level of the brain as a whole and reflect the variability observed in social behavior.

"Even though the nucleus accumbens, for example, has been characterized as the most relevant, all the regions are necessary," says Lopez. "We were able to confirm that these regions interact with each other, and they all contribute in a dynamic way…. I think this is very promising for future experiments with social behavior."

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