OPINION, **VIEWPOINT**

Rodent learning sheds light on missed social cues in autism

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"I could kill you," my wife told me when I drank the last cup of coffee in the house this morning. But does she really want to murder me?

From experience, I knew (or hoped) she wasn't serious. I might have thought a little harder if those words had come from a stranger after I'd finished off the free coffee at the auto repair shop. Like most people, I think I'm pretty good at reading people in such scenarios without really knowing how I do it.

But what if I couldn't? For many people with autism, this uncertainty defines their social encounters. Exciting studies with rodents are shedding light on the brain networks responsible for so-called 'social transmission' of information and how these networks may go awry in people with autism.

Generally defined, social transmission is the ability to glean information about one's surroundings from the behavior of another. Animals from tiny bugs to great apes depend on social transmission to survive in an environment full of predators and toxins. In people, social transmission has evolved into an often indispensable and sometimes rewarding part of daily experience.

The essence of social transmission is the automatic interpretation of social cues. In the auto repair shop, I infer a stranger's intent through facial expression, tone of voice and body posture. People with autism often have difficulty extracting information from those social cues. To understand why, we need to know more about the brain regions that help us interpret these cues and use them to guide behavior.

In the past two decades, scientists have begun to define a network of brain structures that work together to promote complex social skills. Sometimes called **the social brain network**, these regions show collective changes in activity during tasks that require social cognition[1]. They include

the amygdala, responsible for recognizing social cues and producing emotional responses; the insular cortex, which monitors how we feel; and the prefrontal and cingulate cortices, responsible for deciding on and guiding appropriate responses.

Imaging studies suggest that abnormal activity in this network might impair recognition of social cues and cause abnormal responses in people with autism[2,3]. Yet precisely how these brain regions interact to promote social skills, or how autism disrupts the process, has remained unclear. Human studies of this matter have not been an option, because of both the slow social maturation process and the need for invasive surgical methods to monitor and activate or inactivate brain regions.

Do as I do:

An idea on how to approach these questions came to me quite unexpectedly. Our lab uses rodents to study the biology of emotion. Like people, rodents engage in complex social behaviors, and when they do, they display rudimentary activation of the frontal cortex and amygdala, the same regions involved in the social brain network of primates[4,5].

A few years ago, an undergraduate student, Shabana Yusufishaq, with interests in teaching and biology came to my lab and posed a simple question: How do children learn from each other?

As we became more familiar with the field of social neuroscience (and the fact that such a thing as social neuroscience existed), that one question evolved into these: Does abnormal social development in children impair their capacity for social transmission of information — as in children with autism? And are the parts of the brain responsible for social transmission of information the same parts involved in the impairments characterizing autism?

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Rodent studies would let us tease apart the interplay between the nodes of the social brain network. All we would have to do is impair social development in rats, using mutations or environmental influences, assess their social transmission abilities and then try to determine which parts of the social brain are malfunctioning.

The approach has the advantage of speed; most social development in rodents occurs within the first six or seven weeks of life. **Rats would provide us with a model** to test whether abnormal social development can impair social transmission of information.

The ideal test for our purposes would be a behavioral task involving some of the social transmission skills that are impaired in people with autism, such as the ability to recognize and

respond to social cues. One activity that calls on both of these skills is social learning, in particular the learning of fear[6,7].

In a simple form of social fear learning, two rats are placed on either side of a chamber. A divider limits direct physical contact, but the rats can see, smell and hear each other. The experimenter plays an auditory cue (a long beep). Immediately after the cue, one of the rats receives an electric shock in the foot (a basic Pavlovian conditioning technique). The other rat doesn't get a shock, but can see, hear and smell the response of the shocked rat[8].

When the observing rat recognizes that its friend is having a bad experience and is manifestly distressed, it too will begin to display signs of distress. We found that the rat will also show signs of anticipating something bad as soon as it hears the beep, even if the shocked rat is no longer present.

These responses are evidence that the rat has recognized a social cue from a fellow rat and can generate an appropriate response. Social experience and genetic background influence similar types of social behaviors[9].

Spreading fear:

Our next step was to see if we could adapt this approach to study questions directly related to autism. This condition is not normally present in rats, but we can subject rats to many of the factors that increase the chance of developing characteristics of autism.

These include environmental risks, such as poor prenatal health and maternal exposure to toxins, drugs and stress, as well as genetic risks, such as mutations in the autism-linked genes **FMR1**, **NLGN**, **NRXN1**, **CNTNAP2** and **SHANK1**. Rodents with analogous mutations or disruptions of those genes often have fewer social interactions than do other rats[10,11].

What had largely been missing from the rodent studies were signs of some of the classic social problems of people with autism, particularly difficulty interpreting social cues and producing the appropriate responses. But some research from 2011 sparked our interest. This study found that rodents with a mutation in SHANK1 have trouble interpreting a variety of social signals, including vocalizations and scent markings of other rodents[12].

Over the past few years, we have been studying social transmission of fear in rats that lack a segment of the NRXN1 gene, replicating a **mutation associated with autism**. Our preliminary data show that rats missing NRXN1 do indeed lack the ability to recognize social cues during social fear learning.

But is this social impairment related to a problem in the social brain network?

Studies in our lab are beginning to link activity in the social brain network to social learning in several ways. We are testing whether nodes of the social brain network show abnormal activity in rats with the NRXN1 mutation. We are also investigating whether similar social impairments result when we dampen or boost the activity of these nodes using **optogenetics**, a molecular technique that makes neurons sensitive to beams of light.

We are using this approach to look at the role of the amygdala in social transmission. By activating and deactivating various areas in the structure in rats, we have been able to show that certain parts of it are necessary for social fear learning. These areas turn out to overlap with regions that are abnormal in NRXN1 rats.

We believe this research can have important implications for people, particularly those who have autism, by telling us what parts of the brain are needed for, and not just activated during, social transmission. The studies should also tell us whether these same regions are abnormal in rodents that have a mutation similar to one associated with autism.

Eventually, our research may show whether altering the activity of these regions in rodents can alleviate some of the social symptoms of autism induced through genetic mutation and point the way to treatment of people with autism. We are particularly interested in an emerging class of brain treatments that work by stimulating physical changes in specific areas of the brain.

These include deep brain stimulation, involving surgical implantation of a device that can deliver electrical pulses to discrete areas much as a cardiac pacemaker does. A noninvasive approach is **transcranial magnetic stimulation**, in which one or more small magnetic fields induce electrical currents in the brain. Both have been shown to reduce symptoms of Parkinson's disease, migraine, depression and **epilepsy** and to aid recovery from stroke and brain injury.

Our hope is to pave the way for clinical studies that target specific nodes of the social brain network, using these approaches to alleviate symptoms of autism. But that’s still a few cups of coffee away.

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