NEWS

Brain's prefrontal cortex conducts symphony of social players

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Many of the everyday activities that people with autism find challenging are extraordinarily complex. Social interactions, for instance, involve perceiving the behavior of others, interpreting its nuances and then carrying out an appropriate response. This sequence requires mental flexibility (the ability to switch tasks or strategies), short-term (or 'working') memory and impulse control.

These so-called 'executive functions' are important not only for social interactions but also for adapting to change, preventing emotional outbursts and for learning. Some evidence suggests that autistic **girls have more problems** with executive function than autistic boys do.

The root of these problems may lie in a part of the brain called the prefrontal cortex. This region orchestrates executive functions, like a maestro conducting a symphony.

Of course, a conductor needs an orchestra: The brain's striatum plucks the strings of motivation; the amygdala sounds the trumpets of emotion; and the thalamus integrates sensory input. These and other brain regions work effectively in many circumstances only under the prefrontal baton.

"Those regions aren't able to coordinate with each other as well, and they're not able to do their own jobs, without the orchestra conductor to keep them in line," says **Audrey Brumback**, assistant professor of neurology at the University of Texas at Austin.

An out-of-sync conductor may be partly to blame for some autism traits, including problems with social skills, tantrums and irritability. The prefrontal cortex has "been implicated in a huge variety of studies looking at the potential pathologies of autism," says **Declan Murphy**, professor of psychiatry at Kings College London.

The evidence comes from studies of brain structure and function, involves investigations of autistic people and animal models, and implicates both genetic and environmental risk factors. And

together, it gives scientists an anatomical target for treatments.

Expanding evidence:

In people with autism, the prefrontal cortex, located just behind the forehead, may show some structural anomalies. A postmortem analysis suggests that children with autism have **more neurons in the prefrontal cortex** than controls do. They may **also contain patches** of immature cells that do not show the layered organization characteristic of the cortex.

“You have an excess number of neurons, but they’re underdeveloped,” says **Eric Courchesne**, professor of neuroscience at the University of California, San Diego, who led these studies.

Imaging studies of autistic people also show **atypical functional connections** between the prefrontal cortex and other brain areas. For example, multiple studies have reported unusually **weak long-range connections**, and one study found that people with certain mutations in the **CNTNAP2** gene show **increased connectivity** within the region.

Other autism genes may also affect prefrontal cortex structure and function, as they are **expressed at high levels** there during mid-fetal development, a crucial time for autism risk. Mouse studies also support this idea. For example, researchers reported in September that mice lacking **SHANK3** have weak connectivity both **within the prefrontal cortex** and between the prefrontal cortex and other regions.

The prefrontal cortex also appears to be a hotspot for the immune system’s role in autism. **Mice lacking T cells** — a key component of the immune system — have social deficits reminiscent of autism. And mice that **lack interferon-gamma**, an immune molecule produced by T cells, show little interest in interacting with other mice. Both sets of mice show increased connectivity within the prefrontal cortex.

Light effects:

Another line of evidence implicates altered activity in the prefrontal cortex in some social difficulties that characterize autism.

For example, a 2017 study found that in mice lacking CNTNAP2 or **FMR1**, and in mice exposed prenatally to the **epilepsy** drug valproic acid, neurons that connect the prefrontal cortex to the thalamus **are less active** than in controls.

“This is really exciting because it’s one of the first studies where we’ve observed convergence between different animal models,” says Brumback, who did the work as a postdoctoral researcher in **Vikaas Sohal**’s lab at the University of California, San Francisco.

Brumback and others have used a technique called optogenetics to show that manipulating the activity of certain neurons within the prefrontal cortex affects social behavior in mice. Brumback and her colleagues found that boosting the activity of the sluggish prefrontal cortex neurons in valproic-acid-exposed mice further **diminishes social interest** in the mice, whereas turning off the cells improves their social behavior.

Similarly, a separate group of researchers reported in 2017 that in CNTNAP2 mice, **turning on inhibitory neurons** improves social behavior, as does turning off excitatory neurons. Yet another study last year revealed that **increasing the activity of inhibitory neurons** in the prefrontal cortex eases the social deficit in mice with mutations in **NLGN3**.

Together, these studies suggest that altering activity in the prefrontal cortex could benefit some people with autism. Researchers are testing drug therapies that might accomplish this. A small 2017 study showed that **a drug called riluzole** boosts the weak functional connectivity between the prefrontal cortex and other brain regions in autistic men, bringing it in line with that of controls.

Creating control:

Other researchers are looking to cognitive treatments to shape the activity of the prefrontal cortex. One group is exploring the use of **cognitive behavioral therapy** (CBT), a widely used form of psychotherapy, to ease aggression, irritability and anxiety in people with autism. The goal is to alleviate these traits by boosting emotional control, a function of the prefrontal cortex.

CBT involves reframing negative thoughts and changing how a person reacts to them. For example, a teenager who is anxious about talking to her teacher about an assignment might learn to approach the interaction by thinking her teacher wants to help her, not judge her.

A pilot study of CBT for anxiety in 10 autistic adolescents yielded promising results, according to lead investigator **Kevin Pelphrey**, professor of neurology at the University of Virginia in Charlottesville.

Adolescents with autism have poor connectivity between the prefrontal cortex and amygdala, an emotion hub in the brain, during tasks that require emotional control[1]. The therapy improves this connectivity and calms emotion-generating brain systems — much as a conductor might guide an orchestra into a diminuendo to quiet the music.

“It makes something that we knew was a pretty good therapy for a lot of people seem like it will be good for people with autism as well,” Pelphrey says.

His team is analyzing data from a trial of CBT for aggression and irritability in adolescents with neurodevelopmental conditions, including autism. They are also conducting a randomized controlled trial of CBT for anxiety in people with autism.

Ann Griswold contributed to this article.

REFERENCES:

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