Researchers identify key brain systems affected by fragile X syndrome

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(Medical Xpress)—Researchers at the Stanford University School of Medicine have identified several large-scale neural systems in the brain that appear to be impaired by fragile X syndrome, the most common form of inherited intellectual disability.

The findings could help scientists devise treatments for the disorder, which is caused by a gene mutation on the X chromosome.

People with fragile X syndrome display strikingly similar behavior to that of people with autism, including pronounced social awkwardness, repetitive actions, language impairment and a restricted range of interests. But while autism is diagnosed solely by assessing behavior, fragile X has a distinct physical cause that stems from blocked production of a particular protein needed for proper brain development. The syndrome typically becomes apparent in children by age 2 as they show delayed development of language abilities.

The neural systems the researchers identified include the language, visuospatial and salience networks. (The salience network is thought to be involved in evaluating emotional stimuli and generating appropriate responses.) These networks correspond to the cognitive and behavioral deficits commonly observed in individuals with fragile X syndrome, who experience difficulties communicating, switching between tasks and regulating their stress levels. The neural network exhibiting the greatest impairment was the salience network, the researchers say.

"Given that the salience network is involved in regulating physiological responses to emotional stimulation, this finding could explain why individuals with fragile X syndrome often become extremely stressed when they encounter new situations," said Scott Hall, PhD, an assistant professor of psychiatry and behavioral sciences at the School of Medicine and a member of the Child Health Research Institute at Lucile Packard Children's Hospital.

Hall is lead author of a study describing the research. The study was published online Sept. 25 in *JAMA Psychiatry*.

The National Institutes of Health estimates that fragile X syndrome occurs in one in 4,000 males and one in 8,000 females in the United States.

The findings could aid in developing different kinds of treatment for fragile X, both by helping researchers understand where the processing problems or deficits lie in the brain and also in potentially giving them a way to assess the effectiveness of a particular treatment, either by comparing brain scans from before and after a behavioral therapy session or observing scans during a course of medication, Hall said.

The researchers conducted magnetic resonance imaging scans of 17 males and females, ages 10 to 23, all diagnosed with fragile X syndrome. They were compared with a control group of 16 males and females of similar ages, who all exhibited comparable cognitive and behavioral symptoms to those of the fragile X subjects but who did not have the syndrome.

Participants underwent an MRI scan to elucidate their brain structures by measuring gray-matter density. Then they had a functional MRI scan that recorded activity in their brains' "resting-state networks" while they did their best to lie still and keep their eyes closed.

"There are about 15 different networks we can assess with resting-state fMRI. Each network supports a specific cognitive, motor or sensory function like memory, language or vision," said Michael Greicius, MD, assistant professor of neurology and neurological sciences, and senior author of the study. "They are called resting-state networks because even at rest, when not actively carrying out their specific functions, they still exhibit a low level of activity. This allows us to identify the networks and gauge the strength of connections between different brain regions within them."

The scans were analyzed using a recently developed method of quantifying brain activity. The fragile X subjects showed significantly less functional connectivity in several networks in their brains compared with the control group. The amount of functional connectivity is a reflection of the strength of neural connections. The most pronounced difference was in the salience network, which was markedly under-connected, Hall said.

Because many of the participants were significantly cognitively impaired and had difficulty remaining still, the researchers had them practice lying still in a mockup of an MRI while listening to a recording of the sounds they would hear when they were later scanned in the real MRI.

Specific regions of the brain that are structurally altered by the absence of the protein needed for proper brain development had already been identified, but until this study researchers didn't know how the neural systems that span the brain might be affected.

"Being able to measure therapy-related changes by imaging resting state networks could really help researchers ascertain the effectiveness of the therapies," Hall said. "In the future, it may be possible to use this technique to help define subgroups of autistic children, which could aid in developing successful therapies for people with autism."

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