Uncovering the connections between autism, sensory hypersensitivity

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Supported by a grant, the Auerbach Lab at the Beckman Institute for Advanced Science and Technology will examine how different genes associated with autism spectrum disorders may similarly impact our brain's neurons, resulting in heightened sensitivity to sounds.

Autism spectrum disorders are genetically complex, and hundreds of genes are implicated in their development. As a result, some may

conclude that autism is a collection of disconnected disorders with comparable symptoms. However, much like how roads converge as they approach a destination, at some level of brain function there may be bottlenecks: points at which different genes lead to the same effects within the brain and ultimately result in similar symptoms.

"You have this really big constellation of clinical symptoms—of phenotypes—on one side, and tons of genes interacting on the other side," said lead investigator Benjamin Auerbach, an assistant professor of molecular and integrative physiology at the University of Illinois Urbana-Champaign.

"The question is: How do we get from point A to point B? In particular, how many different routes are there to possibly take?"

In previous research, Auerbach found that the two most common genetic mutations associated with ASD have opposite effects at the cellular level despite resulting in similar symptoms. The project will explore whether these similarities may instead be due to a shared mechanism at the level of neural circuits.

Auerbach and his team will focus on the auditory system, as sensory hypersensitivities are common in ASD and can strongly affect individuals' quality of life.

Someone who experiences auditory hypersensitivity has difficulty processing sound information. This is especially true in settings like shopping malls, schools, or public transportation, which are often busy, loud, and require individuals to filter out an overabundance of noise and other sensory input. Auditory hypersensitivity has been described as physically painful, impairs individuals' abilities to focus, and can make it difficult to interact with the environment and with other people.

Groups of neurons connect and communicate with each other by passing signals through synapses, which can be excitatory or inhibitory. Excitatory synapses amplify signals, while inhibitory synapses dampen them. Typically, a precise balance exists between the numbers of excitatory and inhibitory synapses within a neural circuit, and having an imbalance may lead to hyperexcitability—which in the case of auditory circuits could overamplify sound information.

This project will test whether the two most common ASD-related gene mutations lead to this kind of imbalance.

The project will focus on dysregulation of a specific type of inhibitory interneuron, parvalbumin-positive, or PV+, interneurons, as a potentially shared mechanism. PV+ interneurons are potent regulators of the sensitivity and activity of excitatory neurons. When their function isn't properly controlled, individuals may be more sensitive to sounds perceived by others at a normal volume.

The researchers will use rat models to explore how the brain reacts to sound stimuli, and how this may change with different ASD-related gene mutations. The team will use in-vivo electrophysiology to record the electrical activity from populations of auditory neurons in these rat models. This activity can be associated with behavioral changes in response to a stimulus such as playing sounds.

Additionally, the group will collaborate with Beckman researcher Howard Gritton, an assistant professor of comparative biosciences and bioengineering, to use optogenetics: a method to control cell activity with light. Neurons in a specific brain region can be engineered to activate in the presence of blue light. For example, researchers can target and activate PV+ neurons to test whether this alleviates auditory hypersensitivity symptoms in rats.

If activating PV+ neurons is shown to reduce auditory overload, the researchers hope to use that information to develop treatments. For example, the team aims to show that minocycline, a drug which manipulates PV+ interneurons, may be a potential treatment for sensory hypersensitivity.

Methods and results from this study may also help with identification and diagnosis of sensory issues. Methods used to gauge the response of rats to sound could be a basis for tools to quantitatively measure sensory hypersensitivity in humans, for use in clinical trials.

In addition, this research seeks to identify a biomarker for sensory hypersensitivity—in this case, a brain signal which could be measured through an EEG—which could be used as a clinical screening tool. Many past studies which identified potential treatments for sensory overload using animal models have not translated well to humans, and finding such a biomarker may assist with this.

"One reason for this is a lack of these behavioral and electrophysiological biomarkers that can translate between animals and humans in a very straightforward way," Auerbach said. "Sensory systems have the potential to be a really good tool to try and provide that bridge."

More information: Details about the project, titled "Identifying Convergent Circuit Disruptions Across Genetically-Distinct Models of Autism," is available online: reporter.nih.gov/search/UfecHu … ect-details/10638144

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