Autism spectrum disorders

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Sensory perception deficits in ASD mouse models

Autism spectrum disorders (ASDs) are neurodevelopmental conditions characterized by social and communication difficulties, as well as the presence of repetitive behaviors. Beyond these traditional traits, individuals with ASD also tend to have sensory processing difficulties – a feature often overlooked in ASD research. By showing that different genetic mouse models of ASD share similar perceptual impairments, a study opens new avenues to better understand the origin of sensory differences in autism.

The investigators first tested a genetic mouse model of ASD affecting *Setd5*, a gene encoding a histone-associated protein. They subjected *Setd5*$^{+/-}$ mice and their wild-type (WT) siblings to a perceptual task, the innate looming escape response (LER) paradigm in which the mice automatically trigger a sequence of consecutive looms when entering a threat zone. In this paradigm, the visual stimulus is expected to trigger a defensive escape behavior in the mice. Here, while both WT and ASD mice escaped to the shelter upon stimulus presentation, *Setd5*$^{+/-}$ mice showed delayed LER compared to WT mice. In addition, while WT animals developed appropriate place avoidance to the threat zone after the first exposure to the looming stimulus, ASD mice showed no signs of sensitization. When testing two additional ASD mutations, *Cul3* and *Ptchd1*, the team obtained similar behaviors to that of *Setd5*$^{+/-}$ mice in the LER paradigm, indicating convergent perceptual and memory deficits across mouse models.

Next, the investigators combined in vivo optogenetic stimulation and in vitro and in vivo electrophysiology to uncover the underlying causes of these sensory deficits. The results revealed that the perceptual impairments in *Setd5*$^{+/-}$ mice were caused by a K^+ channel (Kv1)-mediated hypoexcitability in the dorsal periaqueductal grey (dPAG), a subcortical node essential for the escape response. However, dPAG neurons in *Cul3* and *Ptchd1* mice showed different intrinsic properties compared to *Setd5*$^{+/-}$ neurons, suggesting that different molecular perturbations caused by different genetic mutations can still lead to similar LER deficits across ASD models.

Altogether these findings shed a new light on sensory symptoms in ASD, providing important insight for future studies designed to uncover the causal relationships between sensorimotor deficits, such as LER, and traditional ASD symptoms, such as social and communication difficulties.

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