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Nagoya City University led group identifies important brain regions in gene-deficient mice with behavioral disorders: Involvement of *Scn2a* gene in schizophrenia

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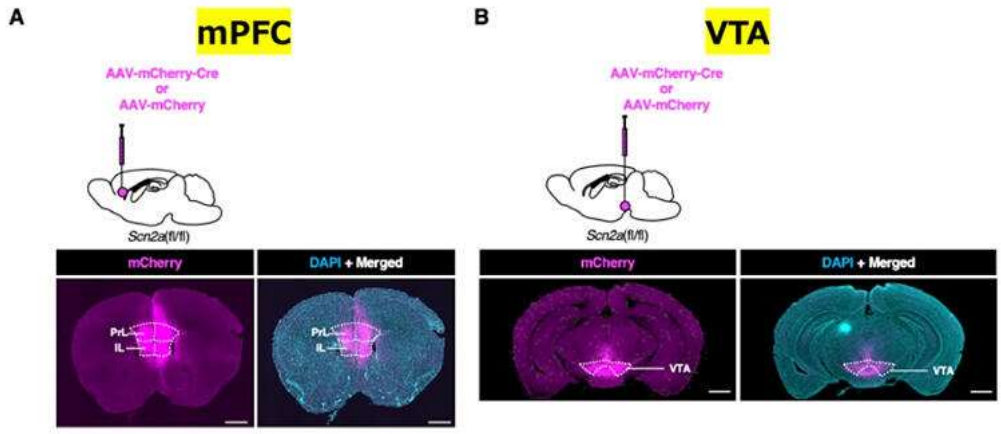
Lecturer Toshimitsu Suzuki and Professor Kazuhiro Yamakawa of the Institute of Brain Science (IBS) at the Graduate School of Medical Sciences of Nagoya City University, Professor Tsuyoshi Miyakawa of the Institute for Comprehensive Medical Science (ICMS) at Fujita Health University, and Professor Hiroaki Mizukami of the Center for Molecular Medicine at Jichi Medical University collaborated to create mice with a homozygous deletion of the *Scn2a* gene in the medial prefrontal cortex (mPFC) or ventral tegmental area (VTA) of the brain, which are regions associated with schizophrenia. Their subsequent detailed analysis revealed that *Scn2a* deficiency in the mPFC induced decreased locomotor activity, increased anxiety-like behavior, and reduced the prepulse inhibition (PPI) of the auditory startle response, whereas *Scn2a* deficiency in the VTA increased PPI. Other behavioral tests (number of approaches, amount of locomotor activity, and anxiety-like behavior in these mice) revealed no changes associated with *Scn2a* deficiency.

This achievement improves understanding of neural circuit disorders that cause schizophrenia and neurodevelopmental disorders associated with *Scn2a* gene mutations and leads to the development of treatments for such disorders. The results were published in the scientific journal *Molecular Neurobiology*.



AAVs were specifically injected into medial frontal cortex (mPFC) or ventral tegmental area (VTA). Expressions of mCherry were mainly observed in mPFC (A) or VTA (B).
Provided by Nagoya City University Hospital

Mutations in *Scn2a* gene, which encodes the voltage-gated sodium channel α2 subunit (Nav1.2), widely occur in epilepsy and neurodevelopmental disorders, including autism spectrum disorder, intellectual disability, and schizophrenia. However, the details pertaining to the brain regions and neural circuits responsible for the onset of the behavioral disorders associated with schizophrenia remain unclear. The research group used an adeno-

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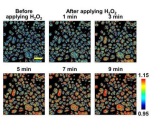
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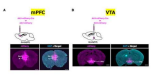
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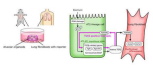
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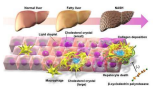
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The researchers subsequently conducted an open field test to observe the amount of spontaneous activity in the *Scn2a*-deficient mice. In this test, two mice were separately placed in new and unfamiliar rooms, and their behaviors were observed for 120 minutes. The experiment revealed that *Scn2a* deficiency in mPFC decreased locomotor activity and increased anxiety-like behavior, whereas *Scn2a* deficiency in VTA did not have these effects. These results contradict those previously observed in *Scn2a*-knockout mice, suggesting that brain regions other than the mPFC and VTA likely play a critical role in these behavioral defects.

The research team further conducted the PPI test, a psychophysiological indicator of schizophrenia. Listening to a soft sound before hearing a loud sound suppresses the startle response, inducing auditory startle-response PPI. The PPI test revealed that *Scn2a* deficiency in the mPFC lowered PPI, whereas deficiency in the VTA increased it.

These results demonstrated the opposite effects on PPI of *Scn2a* deficiency in the mPFC and VTA regions. Although it is widely established that *Scn2a* gene mutations cause schizophrenia, mice with systemic heterozygous *Scn2a* knockout did not show decreased PPI. However, although the results of the present study showed that decreased mPFC function due to *Scn2a* deficiency caused a decrease in PPI, this change is probably canceled out in systemic heterozygous *Scn2a* knockout-mice due to the opposite effects on PPI of VTA deficiency on other brain regions.

The research group combined these findings with those of previously research involving animal models of schizophrenia and proposed a PPI neural circuit model for mice lacking *Scn2a* in the mPFC or VTA. The results of the present study indicate that the mPFC is an important brain region in schizophrenia caused by *Scn2a* gene mutations and also reveal the counteracting effect of deficiency in the VTA on PPI.

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