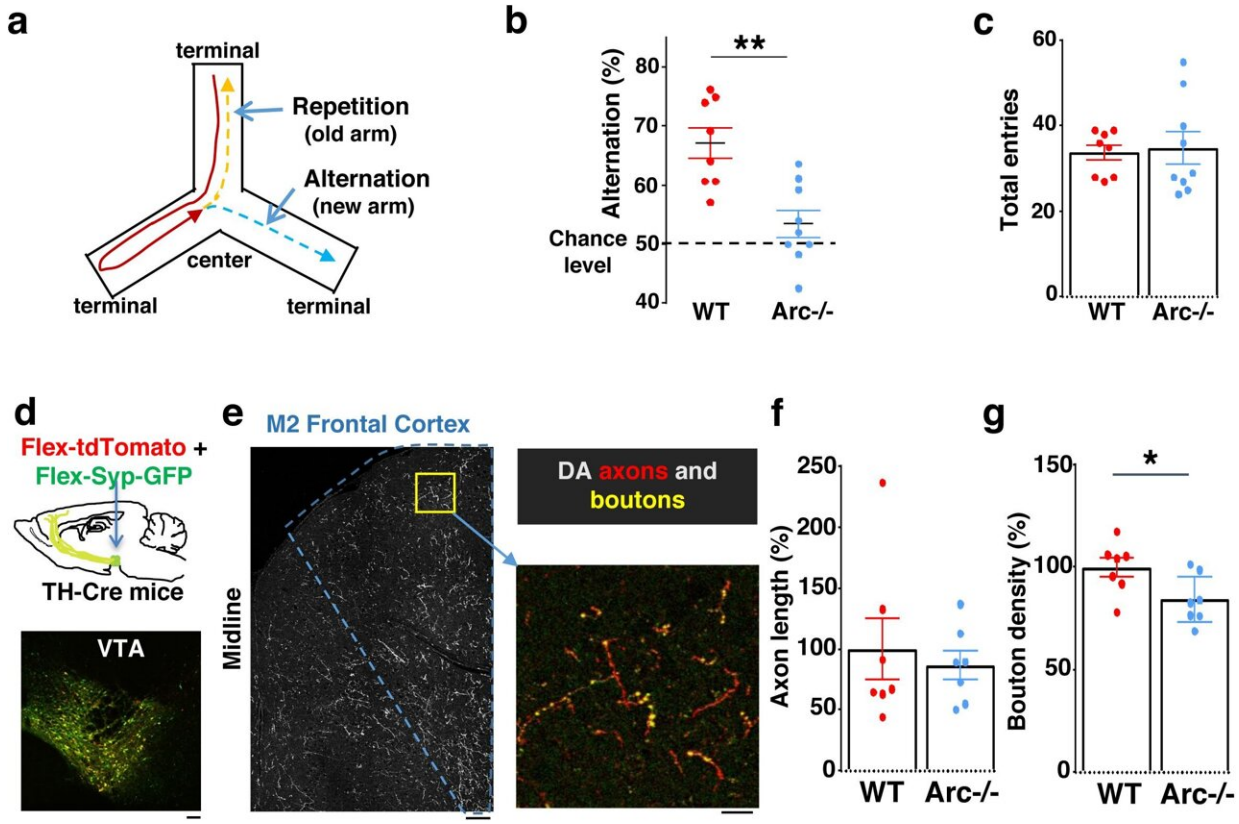
Researchers find possible target for treating neuropsychiatric disorders in teens

June 2 2023, by Kelsie Smith Hayduk



Characterization of cognitive and mesofrontal deficits in Arc mutant mice.(a) Diagram showing the navigation choices for mice in a Y-maze. At the center of the maze, a mouse has a choice to enter either a new arm (alternation) or a previously visited old arm. (b) Alternation percentage in the Y-maze task showing significant reduction in the Arc-/- animals compared to wildtype animals (**p=0.001, t-test, t(15)=3.975, WT N = 8, Arc-/- N = 9 mice, both groups passed Shapiro-Wilk normality test at alpha=0.05). (c) Total arm entries are comparable between Arc-/- and WT. (d) Top, schematic for AAV injection

in TH-Cre animals to label dopaminergic neurons. Bottom, confocal image showing tdTomato (red) and SypGFP (green) labeling in the VTA. Scale bar, 100 μm. (e) Left, confocal image showing labeled dopaminergic axons in the frontal cortex. The dotted line indicates the region-of-interest for M2. Scale bar, 100 μm. Right, zoomed-in region showing labeled axons (tdTomato, red) and boutons (tdTomato+SypGFP, yellow). Scale bar, 20 μm. (f, g) The normalized axon length (f) is not significantly different. The normalized bouton density (g) is significantly reduced in Arc-/- animals compared to WT (*p=0.034, t-test, t-test, t(12)=2.393, N=7 mice for each group). The axon length is normalized by the number of labeled cells in VTA, the bouton density is normalized by the axon length, and both are expressed as a percentage of the group average in WT mice. All the error bars indicate SEM. Credit: (2023). DOI: 10.7554/eLife.87414.1

The brain continuously changes during childhood and throughout adolescence. The onset of neuropsychiatric disorders like schizophrenia often begins during young adulthood. Dysfunction of the dopamine system—necessary for cognitive processing and decision-making—begins during this point in development.

Researchers at the Del Monte Institute for Neuroscience at the University of Rochester are coming closer to finding a possible target for treating neuropsychiatric disorders like schizophrenia and autism during this time of development that could affect the brain circuitry into adulthood.

"Brain development is a lengthy process, and many neuronal systems have critical windows—key times when brain areas are malleable and undergoing final maturation steps," said Rianne Stowell, Ph.D., a postdoctoral fellow in the Wang Lab at the University of Rochester Medical Center and co-first author on research out in the journal *eLife*. "By identifying these windows, we can target interventions to these time periods and possibly change the course of a disease by rescuing the

structural and behavioral deficits caused by these disorders."

Researchers targeted underperforming neurons in the dopamine system that connect to the frontal cortex in mice. This circuitry is essential in higher cognitive processing and decision-making. They found that stimulating the cells that provide dopamine to the frontal cortex strengthened this circuit and rescued structural deficiencies in the brain that cause long-term symptoms.

Previous research from the Wang Lab identified that this specific arm of the dopamine system was flexible in the adolescent brain but not in adults. This most recent research used this window for plasticity in the system as an opportunity for therapeutic intervention.

"These findings suggest that increasing the activity of the adolescent dopaminergic circuitry can rescue existing deficits in the circuit and that this effect can be long-lasting as these changes persist into adulthood," Stowell said. "If we can target the right windows in development and understand the signals at play, we can develop treatments that change the course of these brain disorders."

More information: Surjeet Mastwal et al, Adolescent neurostimulation of dopamine circuit reverses genetic deficits in frontal cortex function, *eLife* (2023). DOI: 10.7554/eLife.87414.1

Provided by University of Rochester Medical Center