Absence of familiarity triggers hallmarks of autism in mouse model through aberrant tail-of-striatum and prelimbic cortex signaling

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Autism spectrum disorder (ASD) involves genetic and environmental components. The underlying circuit mechanisms are unclear, but behaviorally, aversion toward unfamiliarity, a hallmark of autism, might be involved. Here, we show that in Shank3; ΔC/ΔC; ASD model mice, exposure to novel environments lacking familiar features produces long-lasting failure to engage and repetitive behaviors upon re-exposure. Inclusion of familiar features at first context exposure prevented enhanced dopamine transients in tail of striatum (TS) and restored context-specific control of engagement to wild-type levels in Shank3; ΔC/ΔC; mice. Engagement upon context re-exposure depended on the activity in prelimbic cortex (PreL)-to-TS projection neurons in wild-type mice and was restored in Shank3; ΔC/ΔC; mice by the chemogenetic activation of PreLprojection neurons. Environmental enrichment prevented ASD-like phenotypes by obviating the dependence on PreLactivity. Therefore, novel context experience has a key role in triggering ASD-like phenotypes in genetically predisposed mice, and behavioral therapies involving familiarity and enrichment might prevent the emergence of ASD phenotypes.
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