AUTISM

Pinpointing common deficits

> with training, the motor routines of *Nlgn3*-KO animals in the rotarod task became less variable than those of wild-type mice

Two mutations in the gene encoding neuroligin 3 (NLGN3) — a post-synaptic adhesion molecule — have been associated with autism spectrum disorders (ASDs). How these mutations elicit behavioural changes remains unknown, not least because it has been difficult to ascribe common behavioural and synaptic deficits to these mutations in mice. Now, Rothwell, Fuccillo *et al*. reveal that both mutations impair striatal circuits in mice and that these impairments may promote repetitive behaviours, a feature of ASDs.

The two mutations linked to ASDs are the deletion of *NLGN3* and the R451C point mutation, which reduces NLGN3 levels. *Nlgn3*-knockout (*Nlgn3*-KO) mice and mice harbouring the point mutation (*Nlgn3*-R451C mice) exhibit social interaction deficits, typically found in ASDs, but these deficits differ between the two lines. Thus, to search for an ASD-relevant behavioural change that was common to both lines, the authors examined another ASD symptom domain, namely repetitive behaviours.

The authors tested *Nlgn3*-KO and *Nlgn3*-R451C mice in the accelerating rotarod task, which requires mice to develop and maintain repetitive motor activity: the mutant mice learnt the task more quickly than wild-type animals and managed to complete trials involving greater 'terminal' speeds of rod rotation. Moreover, with training, the motor routines of *Nlgn3*-KO animals in the rotarod task became less variable than those of wild-type mice. Together, these data suggest that the *Nlgn3* mutations promote the development of repetitive behaviours.

To examine which brain areas are involved in generating the repetitive behaviours, the authors created mice in which *Nlgn3* could be conditionally knocked out (*Nlgn3*-cKO mice) with Cre recombinase expression and crossed these animals with mice expressing Cre in specific neuronal subpopulations. One brain area that was targeted using this approach was the striatum, which is known to influence the acquisition of repetitive and stereotyped behaviours. Indeed, knocking out *Nlgn3* expression in striatal medium spiny projection neurons (MSNs) that express D1 dopamine receptors (D1-MSNs), but not in D2-MSNs, recapitulated the motor phenotypes of the *Nlgn3*-KO and *Nlgn3*-R451C mice, suggesting that the *Nlgn3* mutations target D1-MSN function.

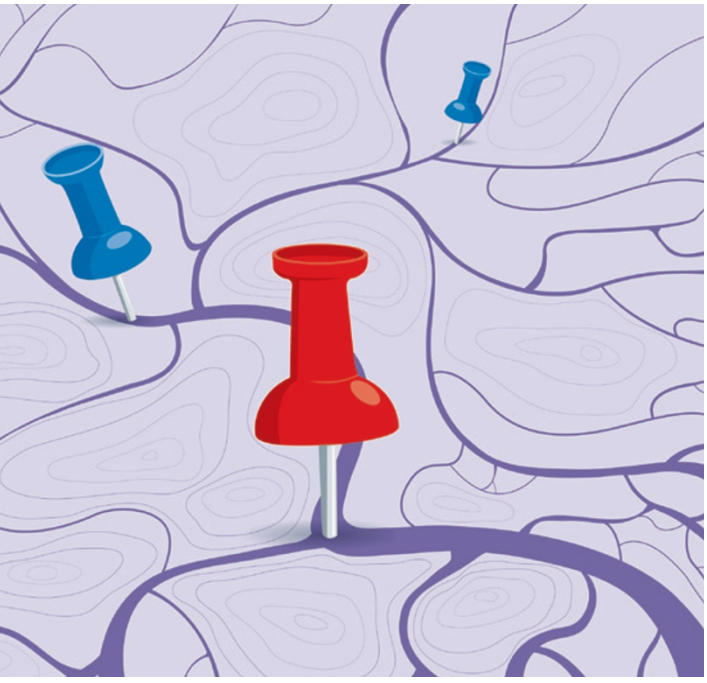
Quantitative RT-PCR showed that *Nlgn3* mRNA was expressed at high levels in D1-MSNs compared with D2-MSNs in the nucleus accumbens (NAc) but was expressed in low levels in both cell types in the dorsal striatum. Furthermore, the injection of an adeno-associated virus expressing Cre into striatal subcompartments in *Nlgn3*-cKO mice revealed that deletion of *Nlgn3* specifically in the NAc enhanced performances on the rotarod task. This suggests that D1-MSNs in the NAc — which is typically associated with reward-related behaviours rather than motor function — have an important role in the observed repetitive behaviour.

Finally, the authors examined the effect of NLGN3 on synaptic function in the NAc. They could not detect any changes in spontaneous miniature excitatory postsynaptic currents in D1-MSNs or D2-MSNs in *Nlgn3*-KO mice; however, they found that the frequency of spontaneous miniature inhibitory postsynaptic currents in NAc D1-MSNs was decreased in *Nlgn3*-KO and *Nlgn3*-R451C mice. Moreover, the ratio of the peak GABA receptor-mediated current to the peak AMPA receptor-mediated current was reduced in D1-MSNs in *Nlgn3*-KO mice. Thus, the loss of NLGN3 seems to be associated with an alteration in the balance between synaptic excitation and inhibition in this cell type.

This study reveals that ASD-associated *NLGN3* mutations promote repetitive behaviour in mice and pinpoints a specific synaptic deficit in the striatal circuitry that underlies this phenotype.

Darran Yates

Jennie Vallis/NPG



ORIGINAL RESEARCH PAPER Rothwell, P. E. *et al.* Autism-associated neuroligin-3 mutations commonly impair striatal circuits to boost repetitive behaviors. *Cell* **158**, 198–212 (2014)