task; importantly, this reduction was blocked by administration of a NOPR antagonist. Chemogenetic stimulation of pnVTA^{Pnoc} neurons also reduced reward-seeking behaviour in the PR task.

The authors further confirmed the involvement of nociceptin–NOPR in constraining reward seeking by modulating NOPR activity. Administration of a selective NOPR agonist reduced the number of nose-pokes and rewards in the PR task in wild-type mice but not in *Nopr*$^{-/-}$ mice. Conditional deletion of *Nopr* in DA neurons in the VTA resulted in an increased number of nose-pokes and rewards received in the PR task. Selective re-expression of *Nopr* in VTA DA neurons of *Nopr*$^{-/-}$ mice and administration of a NOPR agonist resulted in a reduced number of nose-pokes and rewards received in the PR task. In conclusion, the results of this study confirm that nociceptin and NOPR activity in DA neurons constrain motivation to seek rewards.

Grant Otto

ORIGINAL ARTICLE Parker, K. E. et al. A paranigral VTA nociceptin circuit that constrains motivation for reward. *Cell* **3**, 653–671 (2019)

DRG pioneer axons use actin-based protrusions to enter the spinal cord. TeNT^{+} DRG pioneer axons, pioneer axons treated with GM6001 or *mmp14a* knockdown pioneer axons formed invadopodia-like structures at the DREZ, indicating that vesicle release is not required for the formation of these structures. Instead, inhibiting the formation of invadopodia-like structures reduced the number of DRG pioneer axons that accumulated vesicles upon contact with the DREZ (28.6 %) compared with controls (100%). These data suggest that actin reorganization drives the accumulation of synaptic-like vesicles at the DREZ and that the release of components (including Mmp14a) from these vesicles is required for DRG pioneer axons to enter the spinal cord.

This study positions synaptic vesicles in a neuronal invasion pathway ahead of synaptogenesis in zebrafish.

Katharine H. Wrighton

ORIGINAL ARTICLE Nichols, E. L. & Smith, C. J. Synaptic-like vesicles facilitate pioneer axon invasion. *Curr. Biol.* https://doi.org/10.1016/j.cub.2019.06.078 (2019)

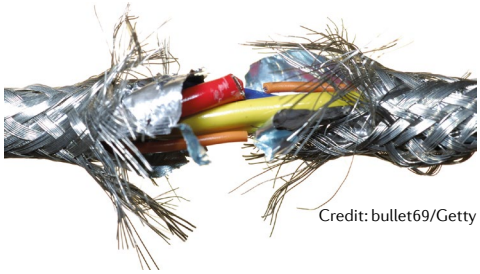
NEUROGENETICS

Damaged wires

People carrying a heterozygous deletion of the 15q11.2 locus between break point 1 (BP1) and BP2 have a 2–4-fold increase in likelihood of developing brain disorders such as autism spectrum disorder (ASD), schizophrenia and epilepsy. These individuals also show functional connectivity defects and white matter changes in areas such as the corpus callosum — a key axonal commissure required for bilateral functional connectivity. In addition, >40% of individuals with 15q11.2 BP1–BP2 haploinsufficiency show delayed development of motor skills, and motor coordination and balance deficits have been described in people with ASD. Of the four genes contained in the 15q11.2 BP1–BP2 region, cytoplasmic FMRP-interacting protein 1 (CYFIP1) is likely to be the main mediator in particular because of its involvement in actin cytoskeleton dynamics (the process of myelination involves actin remodelling) and regulating protein synthesis. The mechanisms underlying white matter changes in people with 15q11.2 BP1–BP2 haploinsufficiency are poorly understood, but two recent papers show that CYFIP1 plays a crucial role.

Silva et al. used CRISPR–Cas9 technology to develop a rat model containing a heterozygous deletion of *Cyfip1* (*Cyfip1*$^{+/-}$ rats). Whole-brain analysis of white matter structure in these rats using diffusion tensor imaging (DTI) revealed extensive differences in white matter microstructure compared with wild-type controls. Fractional anisotropy (a proxy for white matter integrity) was reduced in most brain areas including the corpus callosum. Ultrastructural analysis of the corpus callosum of *Cyfip1*$^{+/-}$ rats using transmission electron microscopy showed reduced myelin thickness but no effect on axon density or calibre. Moreover, the corpus callosum of *Cyfip1*$^{+/-}$ rats contained fewer oligodendrocyte lineage cells and mature oligodendrocytes (which produce myelin) than that of wild-type animals.

Next, the authors looked at expression of the mature oligodendrocyte marker myelin basic protein (MBP). *Cyfip1*$^{+/-}$ rats had lower MBP expression in the corpus callosum than did wild-type rats. Cultured oligodendrocytes taken from *Cyfip1*$^{+/-}$ rats showed MBP staining localized in the soma region. By contrast, MBP distribution in wild-type oligodendrocytes showed widespread distribution through the cell, including in cell processes, a pattern that precedes myelination. These findings suggest that translocation of MBP within oligodendrocytes from *Cyfip1*$^{+/-}$ rats is compromised and this could underlie the myelin thinning observed in these rats.



Credit: bullet69/Getty

Finally, to investigate effects on behavioural flexibility, the authors used an appetitive reversal learning task in which rats learned to associate one of two stimuli with a reward, which were later switched. *Cyfip1*$^{+/-}$ rats learned the first stimulus–reward association as well as wild-type animals, but showed deficits in their ability to relearn after the association had been switched to the other stimulus.

Domínguez-Iturza et al., using resting-state functional MRI in *Cyfip1*$^{+/-}$ mice, revealed functional connectivity deficits compared with controls. Specifically, *Cyfip1*$^{+/-}$ mice showed a general decrease in functional connectivity, particularly in bilateral connections between hemispheres (that is, corpus callosum-dependent) in areas such as somatosensory cortex.

The authors next analysed myelin structure in the corpus callosum using DTI and electron microscopy. Consistent with Silva et al., who used a rat model for *CYFIP1* haploinsufficiency, Domínguez-Iturza et al. found in the *Cyfip1*$^{+/-}$ mouse model a reduced fractional anisotropy and reduced myelin thickness compared with wild-type animals.

Callosal myelination is required for efficient axonal transmission. The authors found that following stimulation of callosal axons that project to layer 2/3 cortex, synaptic plasticity was different in *Cyfip1*$^{+/-}$ mice compared with controls, indicating altered transmission through the corpus callosum in *Cyfip1*$^{+/-}$ mice.

Finally, the authors found that *Cyfip1*$^{+/-}$ mice showed impaired performance on the rotarod and ladder rung walking tests (indicative of impaired motor co-ordination). *Cyfip1*$^{+/-}$ mice scored worse in the texture novel object recognition test, which is thought to represent one of the ASD-like behaviours, and showed reduce pre-pulse inhibition, indicating reduced sensory–motor gating, defects of which are found in people with schizophrenia.

Together, these studies suggest that haploinsufficiency in *Cyfip1* in rodents results in reduced myelin thickness in the corpus callosum, altered neurotransmission and behavioural deficits that have parallels to those observed in ASD and schizophrenia.

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ORIGINAL ARTICLES Silva, A. I. et al. *Cyfip1* haploinsufficient rats show white matter changes, myelin thinning, abnormal oligodendrocytes and behavioural inflexibility. *Nat. Commun.* **10**, 3455 (2019) | Domínguez-Iturza, N. et al. The autism- and schizophrenia-associated protein CYFIP1 regulates bilateral brain connectivity and behaviour. *Nat. Commun.* **10**, 3454 (2019)