a rapid increase in the size of cortical microglial arbors. Thus, reducing NA signalling may increase microglial process surveillance.

Microglia have previously been shown to express β_2-adrenergic receptors (β_2-ARs). Both of the current studies found that blocking β_2-ARs in awake mice increased microglial process surveillance and ramification, mimicking the effects of anaesthesia. Consistent with this, Stowell et al. showed that in anaesthetized mice, β_2-AR agonism caused retraction of microglial processes and reduced the movement of microglia towards laser-injury sites. Therefore, activation of microglial β_2-ARs reduces microglial process surveillance.

Liu et al. found that microglial processes in anaesthetized mice made longer-lasting contacts with neuronal dendrites than did microglia in awake mice, suggesting that changing microglial dynamics could affect plasticity. Indeed, previous work has demonstrated that interfering with microglial signalling can impair ocular dominance plasticity (ODP) — a form of cortical plasticity caused by monocular deprivation. Stowell et al. found that chronically treating monocularly deprived mice with a β_2-AR agonist impaired ODP and reduced microglial contacts with neuronal dendrites. Moreover, deletion of β_2-ARs selectively from microglia protected against the ODP-disrupting effect of the β_2-AR agonist. Thus, aberrant activation of microglial β_2-ARs may disrupt microglial–neuronal interactions and affect plasticity.

Together, these studies provide evidence that microglia behave differently under anaesthesia versus during wakefulness. Moreover, microglial functions — including surveillance of the parenchyma, response to injury and interactions with neurons — are modulated by the stimulation of microglial β_2-ARs.

Natasha Bray

ORIGINAL ARTICLES Liu, Y. U. et al. Neuronal network activity controls microglial process surveillance in awake mice via norepinephrine signaling. *Nat. Neurosci.* **22**, 1771–1781 (2019) | Stowell, R. D. et al. Noradrenergic signaling in the wakeful state inhibits microglial surveillance and synaptic plasticity in the mouse visual cortex. *Nat. Neurosci.* **22**, 1782–1792 (2019)

In combination, the findings point to a role for RHOA in restraining axon extension.

Next, the authors probed the mechanisms that mediate the effects of RHOA on axon growth. Biochemical analyses of cultured RHOA KO neurons revealed a reduction in the activity of myosin II, an actin-binding protein that is activated by one of the key downstream effectors of RHOA signalling. Treating cultured wild-type neurons with the myosin II inhibitor blebbistatin resulted in faster axon growth, whereas overexpression of a constitutively active form of the myosin II regulatory subunit MLC2 reduced axonal growth in RHOA KO neurons. This pointed to myosin II as a key mediator of the effects of RHOA on axon extension.

Myosin II is known to be involved in actin-cytoskeleton remodelling. Actin-filament staining in fixed neuronal cultures, followed by super-resolution microscopy, revealed some important differences between the growth-cone cytoskeletons of RHOA KO neurons or blebbistatin-treated neurons and control neurons. Dense, arc-shaped bundles of actin fibres (known as 'actin arcs') that are thought to prevent the forward protrusion of microtubules were present in the growth cones of most wild-type neurons, but in very few RHOA KO neurons or blebbistatin-treated neurons. The loss of actin arcs in these neurons was accompanied by an increased speed of microtubule advance at the leading edge of the growth cone. Microtubule destabilization via treatment with nocodazole restored axon growth in RHOA KO neurons to wild-type levels.

This study shows that, in mice, RHOA regulates axon extension by promoting myosin II-driven changes in the actin cytoskeleton that restrict microtubule protrusion. As well as enhancing our understanding of a key developmental process, these findings could help us to discover ways to enhance axon regeneration after injury.

Katherine Whalley

ORIGINAL ARTICLE Dupraz, S. et al. RhoA controls axon extension independent of specification in the developing brain. *Curr. Biol.* **29**, 3874–3886 (2019)

IN BRIEF

AUDITORY SYSTEM

Musical pleasure lies in surprise

The basis of musical pleasure in the brain is not clear. Here, participants' ratings of chord pleasantness were found to be predicted by an interaction between uncertainty (lack of prior anticipation) and surprise (deviation from expectation), as quantified using a machine-learning model trained with 80,000 chord progressions. Chords were rated as more pleasant if uncertainty was low and surprise was high, or vice versa. Functional MRI revealed that this interaction modulated responses in the auditory cortex, amygdala and hippocampus.

ORIGINAL ARTICLE Cheung, V. K. M. et al. Uncertainty and surprise jointly predict musical pleasure and amygdala, hippocampus, and auditory cortex activity. *Curr. Biol.* https://doi.org/10.1016/j.cub.2019.09.067 (2019)

GENES AND DISEASE

A protective mutation

Carriers of the *PSEN1*^{E280A} mutation overproduce amyloid-β (Aβ) and develop autosomal dominant Alzheimer disease (ADAD) in their forties. However, this study reports that one woman with *PSEN1*^{E280A} did not show cognitive impairment until her seventies, despite a high burden of Aβ pathology. The woman had two copies of a rare *APOE3* allele with a R136S mutation that reduces APOE3's affinity for heparan sulfate proteoglycans, which have been suggested to promote neuronal uptake of tau. Thus, *APOE3*^{R136S} might delay ADAD by limiting tau pathology.

ORIGINAL ARTICLE Arboleda-Velasquez, J. F. et al. Resistance to autosomal dominant Alzheimer's disease in an *APOE3* Christchurch homozygote: a case report. *Nat. Med.* **25**, 1680–1683 (2019)

BEHAVIOURAL NEUROSCIENCE

A measure of mouse traits

Our understanding of consistent individual differences in behaviour — or 'traits' — in non-human species is limited. Forkosh et al. placed 168 mice in groups of 4 in 'social boxes' and used automatic location tracking to record each animal's behaviour over 4 days. They used a linear discriminant analysis of 60 behavioural dimensions to identify four 'identity domains' (IDs) with high between-individual discriminative ability and high within-individual stability over time, even when mice were placed in different groups. ID scores correlated with scores on multiple behavioural assays and with transcriptomic variance in certain brain regions.

ORIGINAL ARTICLE Forkosh, O. et al. Identity domains capture individual differences from across the behavioral repertoire. *Nat. Neurosci.* https://doi.org/10.1038/s41593-019-0516-y (2019)

NEUROLOGICAL DISORDERS

Hunting out mutant huntingtin

Huntington disease (HD) is caused by the accumulation of mutant huntingtin (mHTT) that contains an expanded polyglutamine (polyQ) tract. Through screening, Li et al. identified four compounds that tether mHTT, but not wild-type HTT, to the autophagy-related protein LC3. The compounds drove autophagy-dependent reductions of mHTT in neurons from a mouse model of HD. Intraperitoneal delivery of two of the compounds reduced cortical mHTT levels in HD mice and improved behavioural deficits in fly and mouse models of HD. Allele-specific linker compounds might have potential in treating HD and other polyQ disorders.

ORIGINAL ARTICLE Li, Z. et al. Allele-selective lowering of mutant HTT protein by HTT–LC3 linker compounds. *Nature* **575**, 203–209 (2019)