IN BRIEF

CEREBRAL CORTEX

Expanding knowledge

A number of evolutionary mechanisms are proposed to have contributed to the rapid increase in cortical size and complexity in the human lineage. These include gene duplication events and the resulting emergence of novel human-specific gene paralogues. Two recent papers now provide evidence that the appearance of human-specific paralogues of *NOTCH2* had a role in human cortical expansion. The findings of Fiddes et al. and Suzuki et al. together reveal that members of a group of human-specific *NOTCH2* N-terminal-like (*NOTCH2NL*) genes are expressed in human cortical progenitors, including the radial glial cells that are thought to have a crucial role in cortical expansion, and demonstrate that NOTCH2NL proteins can activate Notch signalling pathways. They show that expression of *NOTCH2NL* genes in human and mouse cortical progenitors delays their exit from the cell cycle, prolonging neurogenesis, and may thereby have contributed to the growth in brain size in humans.

ORIGINAL ARTICLES Fiddes, I. T. et al. Human-specific *NOTCH2NL* genes affect Notch signalling and cortical neurogenesis. *Cell* **173**, 1356–1369 (2018) | Suzuki, I. J. et al. Human-specific *NOTCH2NL* genes expand cortical neurogenesis through Delta/Notch regulation. *Cell* **173**, 1370–1384 (2018)

SENSORY SYSTEMS

A matter of taste

To facilitate the selection of appropriate foods, the taste system must be able to determine both the identity and the hedonic value (or valence) of taste cues; however, the circuits that encode these features of taste cues and drive downstream behaviours are unclear. Wang et al. traced the projections of primary gustatory cortex neurons in mice and found that those originating in sweet- and bitter-responsive fields project to the basolateral amygdala (BLA) and central amygdala (CEA), respectively. Optogenetic stimulation of these amygdala subfields showed that they can confer valence to a neutral taste stimulus or transform the hedonic responses to otherwise appetitive or aversive taste stimuli. Silencing amygdala neurons disrupted valence coding without affecting the animals' ability to identify and discriminate between tastants. Thus, the cortex and amygdala function independently to represent taste identity and valence.

ORIGINAL ARTICLE Wang, L. et al. The coding of valence and identity in the mammalian taste system. *Nature* **558**, 127–131 (2018)

GLIA

Influencing identity

The ontogeny and transcriptional 'signature' of microglia are unique among tissue macrophages. However, reports of microglial plasticity have caused researchers to question the extent to which microglial identity is dictated by their yolk sac (YS) origins versus the environment that they experience within the CNS. Bennett et al. transplanted microglia isolated at different developmental stages, cultured microglia or macrophages derived from several other tissues into the brains of mice lacking endogenous microglia. All transplanted cell types rapidly engrafted in the parenchyma and exhibited microglial characteristics, suggesting that the CNS parenchymal environment provides signals that promote microglial identity; however, only those with YS origins fully recapitulated the microglial transcriptional signature, highlighting the importance of ontogeny for microglial identity.

ORIGINAL ARTICLE Bennett, F. C. et al. A combination of ontogeny and CNS environment establishes microglial identity. *Neuron* https://doi.org/10.1016/j.neuron.2018.05.014 (2018)

Credit: Juniors Bildarchiv GmbH/Alamy Stock Photo

SLEEP

Sleep it off

Sleep deprivation leads to an increase in 'sleep need' — a homeostatic drive to sleep — but the molecular substrates of sleep need are not known. Wang et al. now show in two different mouse models that increased sleep need is associated with the hyperphosphorylation of a set of 80 proteins in the brain, most of which are synaptic proteins.

To dissect the effects of increased sleep need from time spent awake, the authors used sleep-deprived mice and 'sleepy' mice, which carry a mutation in the gene encoding salt-inducible kinase 3 (SIK3), an AMP-activated protein kinase (AMPK) family member. These $Sik3^{Slp/+}$ mice spend less time awake than do wild-type mice, reflecting a consistently high sleep need.

The authors analysed proteomic and phosphoproteomic data from whole-brain lysates and used these to make three group comparisons: $Sik3^{Slp/+}$ mice versus wild-type mice; mice that had been sleep-deprived for 6 hours versus mice that slept for 6 hours; and sleep-deprived mice versus mice that were sleep-deprived for 6 hours and then had 3 hours of recovery sleep. Whereas the levels of most proteins did not seem to be altered with sleep need, there were considerable changes in the levels of different phosphoproteins between the $Sik3^{Slp/+}$ mice and wild-type mice, and between the sleep-deprived and slept or recovery-slept mice. Changes in the levels of 329 phosphopeptides were common to all three comparisons, suggesting that increased sleep need may be accompanied by changes in phosphorylation in the brain.

Next, the authors investigated sleep-need-associated changes in the phosphorylation state of different proteins. Many more proteins showed increases than decreases in phosphorylation in $Sik3^{Slp/+}$ mice. Importantly, 80 proteins exhibited increases in phosphorylation state in the sleep-deprived mice and the $Sik3^{Slp/+}$ mice; the authors term these 'sleep-need-index phosphoproteins' (SNIPPs). Strikingly, 69 of these 80 SNIPPs are synaptic proteins, and many SNIPPs showed progressive increases in phosphorylation with time deprived of sleep.

Using immunoprecipitation and mass spectrometry of brain lysates from mice expressing labelled SIK3 variants, the authors found that the $SIK3^{Slp}$ variant interacts with synaptic proteins more than does wild-type SIK3. Moreover, $SIK3^{Slp}$ interacts more than wild-type SIK3 with 28 of the SNIPPs. Thus, $SIK3^{Slp}$ may more readily bind its substrates and thus enhance the phosphorylation of SNIPPs. In support of this, intracerebroventricular injection of $Sik3^{Slp/+}$ or sleep-deprived mice with a pan-SIK inhibitor reduced SNIPP phosphorylation, and also inhibited slow-wave activity during non-rapid eye movement (NREM) sleep. Thus, lowering SNIPP phosphorylation may decrease sleep need.

Together, these results suggest that SNIPP phosphorylation may represent a molecular substrate or promoter of sleep need.

Natasha Bray

ORIGINAL ARTICLE Wang, Z. et al. Quantitative phosphoproteomic analysis of the molecular substrates of sleep. *Nature* https://doi.org/10.1038/s41586-018-0218-8 (2018)