SYNAPTIC PLASTICITY

Fatherhood changes the brain

Becoming a parent changes your life. Research has shown that it can also change your brain. Although this might not sound surprising to mothers, a new study reveals that fathers need not feel excluded.

Kozorovitskiy and colleagues investigated how fatherhood affects the brains of male marmosets. Marmoset babies are cared for by multiple members of the family, including the father. Marmoset males show parental behaviour: they spend most of the first month of fatherhood carrying their young on their backs, they clean and protect them and, after weaning, also feed them.

Comparing the brains of first-time and experienced marmoset fathers with those of non-fathers, all living with their mating partners, Kozorovitskiy *et al.* found that fatherhood was associated with changes in the prefrontal cortex (PFC). Interestingly, in humans parts of this area become activated when parents are shown images of their own children. The PFC contains receptors for neuropeptides that are known to mediate parental behaviour, such as vasopressin, oxytocin and prolactin.

Using Golgi staining and the lipophilic neuronal tracer DiI, the researchers showed that marmoset fathers had a higher density of dendritic spines on pyramidal cells in layers II/III of the PFC than non-fathers. The length of the dendrites was unchanged, indicating that an increase in the actual number of dendritic spines probably underlies the observed higher density. In addition, the PFC of marmoset fathers had elevated immunolabelling for the V1a vasopressin receptor and the proportion of dendritic spines that were labelled for this receptor had also increased. Levels of the V1b vasopressin receptor and receptors for oxytocin and prolactin were unaltered.

V1a receptor immunoreactivity in the PFC correlated negatively with offspring age. This suggests that the observed effects might not be permanent, and also that the amount of father–infant contact, which reduces as offspring get older, could drive the changes.

GLIA

Keeping neurons under wraps

Maintaining intact myelin sheaths is vital for PNS function, yet the molecular players involved in regulating this process are poorly understood. Now Charnay and colleagues show that the transcription factor KROX20, known to be involved in the onset of myelination, is also integral to its maintenance.

A role for KROX20 in preserving myelin integrity was suggested by its expression throughout adulthood in Schwann cells and by links between mutations in *KROX20* and congenital and late-onset human myelinopathies. However, previously generated *Krox20* mutant mice died at early perinatal stages (owing to the importance of *Krox20* in hindbrain development), and could not provide answers about later aspects of myelin development and maintenance. The researchers therefore developed two conditional mouse mutants that evade early lethality by delaying the onset of *Krox20* inactivation.

First, compound heterozygous mutants were generated, in which Cre recombinase was inserted into one allele of the *Krox20* locus. The second allele contained a *Krox20* exon flanked by *loxP* sites, marking it for excision by Cre recombinase. This resulted in the inactivation of *Krox20* by 4 days after birth, as Cre recombinase levels built up in *Krox20*-expressing cells. The complete absence of myelination in these animals, which survive for 6 weeks, indicated that continued *Krox20* expression is essential for the completion of myelination.

To investigate *Krox20*'s role in adult myelin maintenance, a second model was created using a Cre recombinase transgene that could be induced at a specific timepoint by tamoxifen treatment. Inactivation of *Krox20* at 3 months after birth resulted in a rapid breakdown of the myelin sheath, showing that continual expression of this gene is of key importance for myelin maintenance.

In response to *Krox20* inactivation, mature Schwann cells seemed to return to an immature state, indicated by the upregulation of markers of less differentiated Schwann cells, such as *Sox2*, and made abortive attempts to

The V1a receptor is activated by vasopression, so the authors next set out to establish where this ligand might be produced. As expected, they found vasopressin immunolabelling in the paraventricular and supraoptic nuclei of the hypothalamus. However, these nuclei do not project to the PFC. Interestingly, vasopressin immunoreactivity was also found in the very cells in the PFC that showed increased dendritic spine density in response to fatherhood. It is therefore possible that locally produced vasopression activates V1a receptors in the PFC, which then stimulate the formation of new dendritic spines.

This study shows that fatherhood modifies the brains of marmosets in regions associated with parental behaviour. The intriguing findings raise some interesting questions about the mechanisms that might underlie such plasticity, and whether the quality of paternal care influences these changes.

Leonie Welberg

ORIGINAL RESEARCH PAPER Kozorovitskiy, Y. *et al.* Fatherhood affects dendritic spines and vasopressin V1a receptors in the primate prefrontal cortex. *Nature Neurosci.* **9**, 1094–1095 (2006)

initiate re-myelination. KROX20 has previously been suggested to suppress *Sox2*, indicating that, in addition to its established role in activating myelination, KROX20 might maintain myelin by repressing Schwann cell dedifferentiation.

This study shows that KROX20 is crucial for myelin maintenance, and introduces two models of delayed *Krox20* inactivation that might aid investigations into human myelinopathies. In particular, the inducible mutant replicates many features of late-onset myelinopathies such as Charcot-Marie-Tooth disease. Moving forward, it will be important to understand the mechanisms by which *Krox20* governs Schwann cell fate and to investigate the relationship to similar processes in the CNS.

Katherine Whalley

ORIGINAL RESEARCH PAPER Decker, L. *et al.* Peripheral myelin maintenance is a dynamic process requiring constant *Krox20* expression. *J. Neurosci.* **26**, 9771–9779 (2006)

PSYCHIATRIC DISORDERS

Depression gene in action

It is well established that interactions between genes and the environment contribute to psychiatric disorders. However, the way in which this is translated into changes in the brain has long been elusive. Now, a multimodal imaging study led by Turhan Canli, in collaboration with Klaus-Peter Lesch, shows that the variants of the serotonin transporter gene (*5-HTT*), which is involved in depression, have different effects on brain function depending on the level of stress that individuals have in their lives.

People carrying a short allele of *5-HTT* tend to have increased anxiety-related temperaments and are more vulnerable to depression compared with people who have two long alleles of the gene. Canli and colleagues set out to test whether this is due to heightened responses of the amygdala and hippocampus to negative emotional stimuli, as suggested by the phasic activation model. If this theory is correct, short-variant carriers with higher levels of stress in life should show more brain activity in response to stimuli such as fearful or sad faces. By contrast, the tonic activation model posits that the presence of the short allele and higher levels of stress increases the resting activity of the amygdala and hippocampus, rather than elevating brain reactivity to emotional stimuli or stress.

In support of the tonic activation model, the researchers found that in participants with a short allele of *5-HTT* there was a negative correlation between the reactivity of the amygdala and hippocampus — as measured by functional MRI — and the level of stress, regardless of the emotional nature of the stimuli. By contrast, a positive correlation was identified in people with two long alleles of the gene.

To further investigate the significance of these findings, Canli *et al.* used the perfusion scanning technique to measure the absolute cerebral blood flow — an indicator of the level of resting activity — in those brain regions. The resting activity of the amygdala and hippocampus was higher in subjects with a short *5-HTT* allele than in those with two long alleles. Interestingly, the more stress short-variant carriers have in their lives, the higher the resting activity. The opposite was observed in people with two long alleles.

The researchers also uncovered similar correlations between self-reported levels of rumination — a form of dysfunctional cognitive reappraisal of negative life events — and stress. So, short-allele carriers with high levels of stress tended to ruminate a lot, which might increase their risk for depression and anxiety disorders.

These intriguing findings lend support to the tonic activation model, and further suggest that short-variant carriers might be in a chronic state of vigilance, threat or rumination, which makes them more vulnerable to mental illnesses.

Jane Qiu

ORIGINAL RESEARCH PAPER Canli, T. *et al.* Neural correlates of epigenesis. *Proc. Natl Acad. Sci. USA.* 9 October 2006 (doi:10.1073/pnas.0601674103)
FURTHER READING Meyer-Lindenberg, A. & Weinberger, D. R. Intermediate phenotypes and genetic mechanisms of psychiatric disorders. *Nature Rev. Neurosci.* **7**, 818–827 (2006) | Caspi, A. & Moffitt, E. T. Gene–environment interactions in psychiatry: joining forces with neuroscience. *Nature Rev. Neurosci.* **7**, 583–590 (2006)