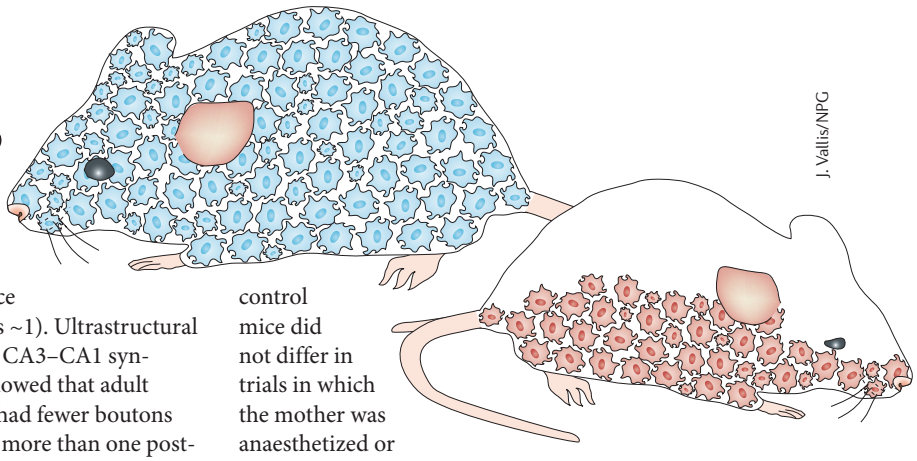
GLIA

A critical mass of microglia?



J. Vallis/NPG

Microglia have various functions beyond their role as the brain's resident immune cells — for example, the phagocytosis of weak synapses during brain development. Gross and colleagues now show that mice with a reduced density of microglia during postnatal development have, as adults, weaker synaptic transmission, altered brain connectivity and behavioural changes that resemble some aspects of autism.

Fractalkine (also known as CX3CL1) is produced by neurons and binds to a receptor that is exclusively expressed by microglia. Previous studies showed that mice lacking the fractalkine receptor (*Cx3cr1*$^{-/-}$ mice) have a temporary reduction in microglia density and more immature, weak synapses than control mice in the second and third postnatal week. The authors set out to investigate the possible long-term consequences of this transient reduction in microglia.

They first assessed synaptic transmission at CA3–CA1 synapses in brain slices of adult *Cx3cr1*$^{-/-}$ mice and their wild-type littermates. Specifically, they measured spontaneous excitatory postsynaptic currents (sEPSCs), which reflect both induced and spontaneous vesicle release, and miniature EPSCs (mEPSCs), which reflect only spontaneous vesicle release. The sEPSC/mEPSC amplitude ratio is a measure of synapse maturation known as 'synaptic multiplicity' — the extent to which axons sprout to make multiple connections onto the same target neuron. This ratio was higher in wild-type mice than in *Cx3cr1*$^{-/-}$ mice (in which it was ~1). Ultrastructural examination of CA3–CA1 synapses indeed showed that adult *Cx3cr1*$^{-/-}$ mice had fewer boutons synapsing with more than one postsynaptic spine on the same dendrite. Together, these findings point to reduced CA3–CA1 connection strength in *Cx3cr1*$^{-/-}$ mice.

Next, the authors compared long-range connectivity in the two groups of mice. They found reduced local field potential (LFP) coherence between the prefrontal cortex and hippocampus in awake *Cx3cr1*$^{-/-}$ mice compared with wild-type mice. Similarly, functional MRI showed decreased synchronization between the prefrontal cortex and hippocampus in anaesthetized *Cx3cr1*$^{-/-}$ mice. These findings suggest that a transient decrease in microglia density during development reduces functional long-range connectivity in adulthood.

Altered connectivity has been found in individuals with autism, and with this in mind, the authors examined the effects of fractalkine receptor knockout on social and repetitive behaviours. Juvenile wild-type mice showed a preference for a tube containing their mother over an empty tube, whereas juvenile *Cx3cr1*$^{-/-}$ mice had no preference for either tube. Similarly, in adulthood, *Cx3cr1*$^{-/-}$ mice showed reduced interest in a conspecific animal in a social interaction test compared with wild-type mice. These effects seemed to require some form of interaction with the target animal, as 'social interest' levels in *Cx3cr1*$^{-/-}$ and control mice did not differ in trials in which the mother was anaesthetized or the conspecific animal was replaced by soiled bedding from this animal. Interestingly, LFP recordings during a social exploration test revealed increased theta-band coherence between the prefrontal cortex and hippocampus in wild-type mice but not in *Cx3cr1*$^{-/-}$ mice, suggesting that connectivity changes may underlie the altered social behaviour in *Cx3cr1*$^{-/-}$ mice. Adult *Cx3cr1*$^{-/-}$ mice also spent more time grooming than wild-type mice, which is suggestive of increased repetitive behaviour.

This study points to a possible 'critical period' in development during which a sufficient number of microglia must be present to ensure normal long-range connectivity and social behaviour. The findings complement results of an earlier study that showed deficits in hippocampus-dependent memory and synaptic plasticity in *Cx3cr1*$^{-/-}$ mice, suggesting that a developmental reduction in microglia numbers may have a role in the aetiology of a range of conditions with a developmental origin.

Leonie Welberg

> "adult *Cx3cr1*$^{-/-}$ mice had fewer boutons synapsing with more than one postsynaptic spine on the same dendrite"

ORIGINAL RESEARCH PAPER Zhan, Y. *et al.* Deficient neuron-microglia signaling results in impaired functional brain connectivity and social behavior. *Nature Neurosci.* http://dx.doi.org/10.1038/nn.3641 (2014)
FURTHER READING Rogers, J. T. *et al.* CX3CR1 deficiency leads to impairment of hippocampal cognitive function and synaptic plasticity. *J. Neurosci.* **31**, 16241–16250 (2011)