the left inferior frontal gyrus and the right lateral sulcus were found to be shifted anteriorly in the patient group.

In view of developmental data that point to a posterior shifting with age of the inferior frontal gyrus, Levitt *et al.* speculate that anterior displacements in autism could reflect delayed or incomplete maturation, at least in the frontal lobe. Further studies will be required to identify the root of sulcal displacements in autism, and to establish whether such changes represent causes or consequences of the disorder.

Rebecca Craven,
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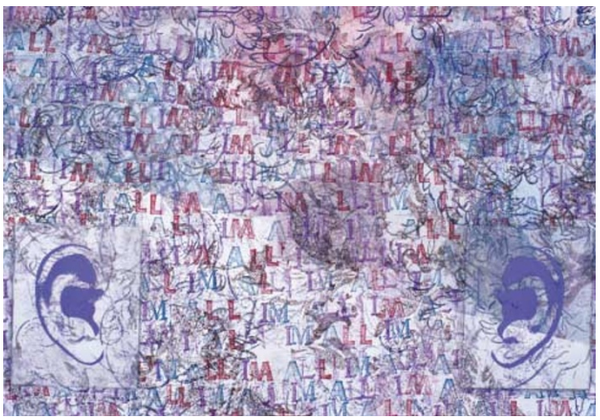

*Six*th sense

The mammalian auditory system is comprised of the outer, middle and inner ears, and is responsible for both hearing and balance. Homeobox *Six* genes are expressed in many tissues throughout mammalian organogenesis, but their role in auditory system development is not well understood. Zheng *et al.*, reporting in *Development*, have investigated the expression of *Six1* during mammalian inner ear development and the role of this gene in auditory system development.

Inner ear development begins with the invagination of the otic placode to form the otic vesicle and subsequent structures of the inner ear. In normal mice, *Six1* is expressed in all the sensory regions of the inner ear. Heterozygous *Six1*$^{+/-}$ mice showed some hearing loss, with internal examination of the auditory system revealing abnormalities in the middle ear. Homozygous *Six1*$^{-/-}$ mice lacked all sensory organ formation in the outer, middle and inner ears.

***Six1* regulates cell proliferation during early otic development, as revealed from examination of the otic vesicles in *Six1*$^{-/-}$ mice. Despite the absence of apparent morphological differences in *Six1*$^{-/-}$ and wild-type mice, closer examination revealed numerous apoptotic cells in the wall of the *Six1*$^{-/-}$ otic vesicle. It therefore seems likely that *Six1* regulates cell number during early otic development.**

Zheng *et al.* went on to examine the interactions between *Six1* and other signalling factors that have previously been established in early otic development. They found that the expression of *Eya1*, *Pax2* and *Pax8* were unaffected in *Six1*$^{-/-}$ otic vesicles. However, *Six1* was required for *Fgf3* expression and the maintenance of *Fgf10*, *Bmp4*, *Nkx5.1* and *Gata3* in the otic vesicle. So, *Six1* is not required for the initiation of inner ear development, but is crucial for the regulation of signalling factors that are involved in cell-fate specification in the inner ear.

Further studies are needed to establish the complete molecular picture of how *Six1* regulates the patterning of the inner ear.

Emma Green

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Mighty mouse

Murine models that exhibit one of the pathological lesions that characterize Alzheimer's disease have been available for some time. Now, the first triple transgenic mouse to develop both amyloid-β (Aβ) plaques and tangles of hyperphosphorylated tau protein in AD-relevant brain regions has been unveiled in the 31 July issue of *Neuron*.

Frank LaFerla's team used microinjection of single-cell embryos — rather than standard cross-breeding techniques — to create mice harbouring transgenes that encode mutant forms of human amyloid precursor protein (APP), tau and presenilin-1. Immunohistochemistry revealed that the hippocampus and cerebral cortex of the triple-transgenics contained high steady-state levels of both human tau and APP, which was processed to form Aβ in an age-dependent manner. Deposition of extracellular Aβ preceded the formation of tau tangles, lending weight to the amyloid cascade hypothesis, which predicts that Aβ is the initiating trigger for the formation of tangles and the onset of Alzheimer's disease.

As synaptic dysfuntion is correlated with the cognitive decline that characterizes Alzheimer's disease, the authors electrophysiologically probed synaptic plasticity. Long-term potentiation (LTP) — which is thought to contribute to learning and memory — was severely impaired in the CA1 hippocampal region of the transgenics. Control mice lacking the APP transgene showed no LTP deficits, leading the authors to propose that intraneuronal accumulation of Aβ underlies synaptic dysfunction in Alzheimer's disease.

Suzanne Farley

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