IN THE NEWS

Retail therapy

Many people use shopping as a way to cheer themselves up, but for compulsive shoppers it can cause profound misery, not to mention serious financial problems. However, thanks to a team at Stanford University in California, a solution might be at hand.

The researchers, led by Lorrin Koran, recruited 24 compulsive shoppers to their study. According to *BBC News Online* (18 July) "one had bought more than 2000 wrenches, another owned 55 cameras". The patients were treated with the antidepressant citalopram (Celexa) for seven weeks, followed by the drug or a placebo for a further nine weeks.

All of the patients who took citalopram for the entire course of the experiment reported that they had lost interest in shopping. Koran is reported as saying "Patients said to me: 'I go to the shopping mall with my friends and I don't buy anything. I can't believe it and they can't believe it'" (*BBC News Online*). By contrast, five of the eight patients in the placebo group relapsed after the drug was withdrawn. It is not yet known why citalopram is effective for treating compulsive shoppers, but Koran suggests that it might work by altering serotonin levels in the brain.

Although these initial findings are encouraging, the treatment has its drawbacks. As *NBC11 News* (16 July) reports, "Celexa does have some side effects, which include loss of sexual desire and sleepiness". Also, some experts have questioned the fundamental concept of using drugs to treat compulsive behaviour. Robert Lefever from the PROMIS Recovery Centre in Kent (UK) says "of course antidepressants help the disorder, in the same way they would help alcohol dependency. They are simply another addiction. It's the same relation as methadone to heroin" (*BBC News Online*).

Heather Wood

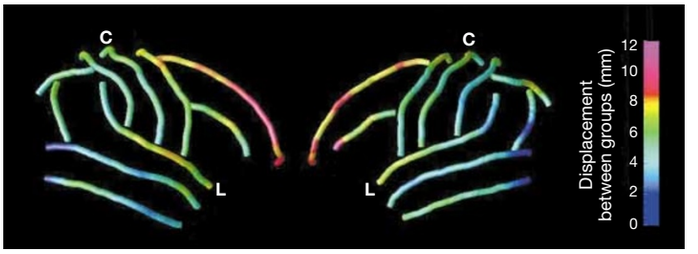
PSYCHIATRIC DISORDERS

Patterns of pathology

Neuroanatomical abnormalities that accompany autism include widespread deviations in cortical surface anatomy, a new study published in Cerebral Cortex indicates. Examining the differences between autistic and normal subjects in the pattern of cortical gyri and sulci could provide clues to the developmental pathology of the disorder.

Previous studies have described limbic and cerebellar pathology in autism, and evidence is accumulating for an involvement of neocortical regions. However, there is no clear consensus on the neural basis of this condition. In an attempt to home in on affected areas of the cortex, Levitt and co-workers carried out the first three-dimensional mapping of cortical sulcal patterns in autistic disorder.

Using MRI (magnetic resonance imaging) scans of the brains of autistic and normal children, Levitt *et al.* generated a high-resolution model of the cortex for each subject, and built average sulcal maps for the two groups. A comparison of these maps revealed displacements of several major sulci in patients with autism, primarily in frontal and temporal regions. For example, anterior and superior shifting of the superior frontal sulcus was detected bilaterally, and the left and right superior temporal sulci,



Three-dimensional variability in cortical sulci between the patient and control groups. C, central sulcus; L, lateral sulcus. Courtesy of Jennifer G. Levitt, University of California, Los Angeles.

SYNAPTIC PLASTICITY

Retro styling

It is easy to think of synaptic communication as one-way traffic, but in many cases, postsynaptic cells can also signal back to the presynaptic neuron to regulate synapse structure and function. The *Drosophila* neuromuscular junction (NMJ) illustrates how retrograde signalling contributes to synapse homeostasis, and two studies reported in *Neuron* identify new components of the signalling mechanism.

In the *Drosophila* embryo, motor neurons compensate for the growth of their target muscles by making extra synaptic boutons and by raising the number of neurotransmitter release sites at each synapse. These events rely on bone morphogenetic protein (BMP) signalling through the Wishful thinking (Wit) receptor on the presynaptic terminal. Until now, the Wit ligand that is released by the postsynaptic muscle cell was unknown. McCabe *et al.* knocked out the *glass bottom boat* (*gbb*) gene, which codes for a BMP homologue. This manipulation produced a phenocopy of the Wit-knockout phenotype, which is characterized by reductions in NMJ size and activity, and defects in synaptic ultrastructure. *In vitro* studies confirmed that Gbb acts as a ligand for Wit. These findings point towards a role for Gbb in controlling the growth of the NMJ.

In the second study, Haghighi *et al.* investigated the modulation of neurotransmission by retrograde signalling. They found that reducing Ca^{2+}/calmodulin-dependent kinase II (CaMKII) activity in the postsynaptic muscle cell led to an increase in neurotransmitter release from the presynaptic neuron. Conversely, activating CaMKII constitutively in the muscle cell reduced the level of synaptic transmission. The authors propose that CaMKII senses the level of synaptic activity by monitoring Ca^{2+} levels. Synaptic activity causes an influx of Ca^{2+} into the muscle. This activates CaMKII, which in turn triggers a retrograde signal that inhibits neurotransmitter release from the presynaptic terminal. Once again, a BMP signal seems to be responsible, but it is not yet known whether Gbb is involved.

A third study by Pratt *et al.*, which was also reported in *Neuron*, showed that postsynaptic CaMKII also mediates synapse remodelling in the mammalian brain. This indicates that at least some of the *Drosophila* retrograde signalling machinery has been conserved during evolution, and it seems likely that further examination of the *Drosophila* NMJ will bring to light more aspects of retrograde signalling that apply across the animal kingdom.

Heather Wood

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FURTHER READING Pratt, K. G. *et al.* Activity-dependent remodeling of presynaptic inputs by postsynaptic expression of activated CaMKII. *Neuron* **39**, 269–281 (2003)

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,
Senior Subeditor, Nature

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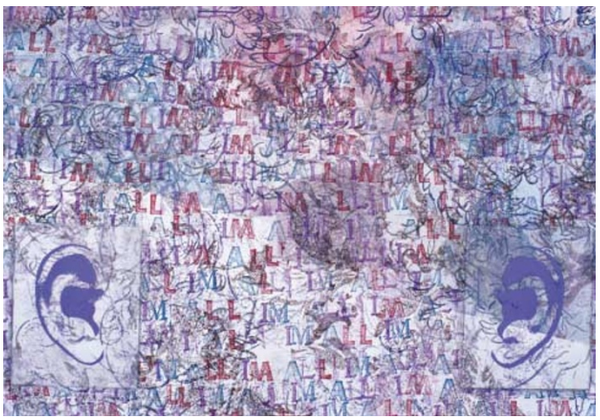
Encyclopedia of Life Sciences: http://www.els.net/autism



*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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