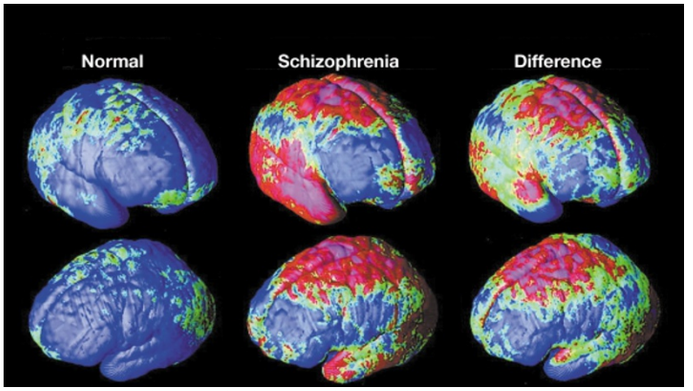

Grey matter loss in adolescents with schizophrenia. Warmer colours denote regions with the most significant losses. © 2001 National Academy of Sciences, USA.

PSYCHIATRIC DISORDERS

Mapping grey matter

Schizophrenia is perhaps the most intensively studied of the psychiatric disorders, and there is increasing evidence that its pathogenesis involves neurodevelopmental abnormalities. Patients seem to show loss of grey matter, but it is unclear whether this occurs early or late in neural development. Thompson *et al.* have followed patients with early-onset schizophrenia to study the dynamics of this reduction in volume.

The researchers used high-resolution magnetic resonance imaging to track structural changes in the brains of adolescents with early-onset schizophrenia over five years. The authors compared the scans across the time course of the experiment, and compared schizophrenic patients with control subjects and 'medication-matched' teenagers who had other psychiatric disorders. There was a greater loss of grey matter in patients with schizophrenia than in normal adolescents, and the loss followed a specific spatial pattern as time progressed.

The control subjects did show some loss of grey matter over the five-year span of the experiment, consistent with previous findings. But this reduction was fairly homogeneous across the brain. By contrast, patients with schizophrenia showed a specific, wave-like pattern of loss that began in the parietal cortices and progressed over the following years to affect frontal and temporal regions. Medication-matched non-schizophrenic patients also showed a greater loss of grey matter than did controls, but the loss was less marked than for the patients with schizophrenia and did not include the temporal cortex.

Previous work has shown that grey matter deficits in some areas of the brain in adult schizophrenic patients and their families are attributable to genetic factors, whereas in other areas they seem to be related to environmental factors. Intriguingly, the parietal cortices, where the dynamic loss in teenagers with schizophrenia begins, fall into the latter category, whereas loss in the frontal and temporal regions, which are affected later, seems to be genetically mediated. These findings are consistent with the idea that an environmental trigger contributes to the onset of schizophrenia.

Grey matter deficits in different brain areas also show interesting correlations with the clinical progression of the disease. Specifically, faster loss in the temporal cortices is associated with more severe positive symptoms (for example, hallucinations and delusions), whereas loss in the frontal cortices correlates with increased negative symptoms (such as lack of emotional responses and poverty of speech).

Although the causes of schizophrenia are still mysterious, a better understanding of the structural changes that occur during the progression of the disease in these adolescent patients could provide further insight into the mechanisms of the adult-onset form of the disease. And the tight correlations between the pattern of loss and specific symptoms could point towards the mechanisms that underlie these symptoms. However, these findings also indicate that treatments for schizophrenia will need to be aimed at slowing the loss of grey matter, raising another question — just what causes this progressive wave of tissue loss?

Rachel Jones

References and links

ORIGINAL RESEARCH PAPER Thompson, P. M. *et al.* Mapping adolescent brain change reveals dynamic wave of accelerated gray matter loss in very early-onset schizophrenia. *Proc. Natl Acad. Sci. USA* **98**, 11650–11655 (2001)

IN BRIEF

NEUROLOGICAL DISORDERS

Mutant protein in Huntington disease is resistant to proteolysis in affected brain.

Dyer, R. B. & McMurray, C. T. *Nature Genet.* **29**, 270–278 (2001)

Although the cause of Huntington's disease is unknown, one leading theory is that the expanded huntingtin protein is cleaved and that the amino-terminal fragments accumulate, causing cell death. However, Dyer and McMurray have now shown that the mutant huntingtin protein is relatively resistant to proteolysis. They propose instead that the full-length mutant protein causes toxicity by sequestering full-length and cleaved normal huntingtin.

OPIOID RECEPTORS

Prolonged morphine treatment targets δ-opioid receptors to neuronal plasma membranes and enhances δ-mediated antinociception.

Cahill, C. M. *et al. J. Neurosci.* **21**, 7598–7607 (2001)

Opioid receptor ligands can cause complex regulatory changes in the receptor, and it has been proposed that the three different subtypes of opioid receptor can interact. Cahill *et al.* found evidence in support of this idea by showing that prolonged treatment with morphine, a μ-receptor agonist, can cause a marked increase in the density of δ-opioid receptors at the cell surface, both *in vitro* and *in vivo*. The receptor density increase was accompanied by potentiation of the anti-nociceptive effect of a δ-receptor agonist.

NEUROTECHNIQUES

Delivery of the Cre recombinase by a self-deleting lentiviral vector: efficient gene targeting *in vivo.*

Pfeifer, A. *et al. Proc. Natl Acad. Sci. USA* **98**, 11450–11455 (2001)

In genetic engineering, crossbreeding of mice carrying genes flanked by *loxP* sites and those expressing the Cre recombinase is often used to generate region-specific knockout mice. Region-specific Cre expression can be achieved through viral transfection, but this can give rise to a strong immune response. Pfeifer *et al.* describe the use of lentiviral vectors to deliver Cre. To avoid toxicity, they designed a Cre transgene that is itself excised by Cre, so that the gene is expressed only for a short time before being deleted.

NEUROTECHNIQUES

A miniature head-mounted two-photon microscope: high-resolution brain imaging in freely moving animals.

Helmchen, F. *et al. Neuron* **31**, 903–912 (2001)

Helmchen *et al.* have developed a head-mounted two-photon microscopy system that allows *in vivo* imaging of the cortex in awake, freely moving rats. Two-photon microscopy allows the detection of fluorescence down to imaging depths of around 0.5 mm; in the head-mounted system, it could be used to obtain images of blood vessels filled with fluorescently labelled blood, or pyramidal neurons labelled with a calcium indicator. This should allow the measurement of blood flow or calcium transients in response to physiological stimuli.

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