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PSYCHIATRIC DISORDERS

Modelling compulsive behaviour

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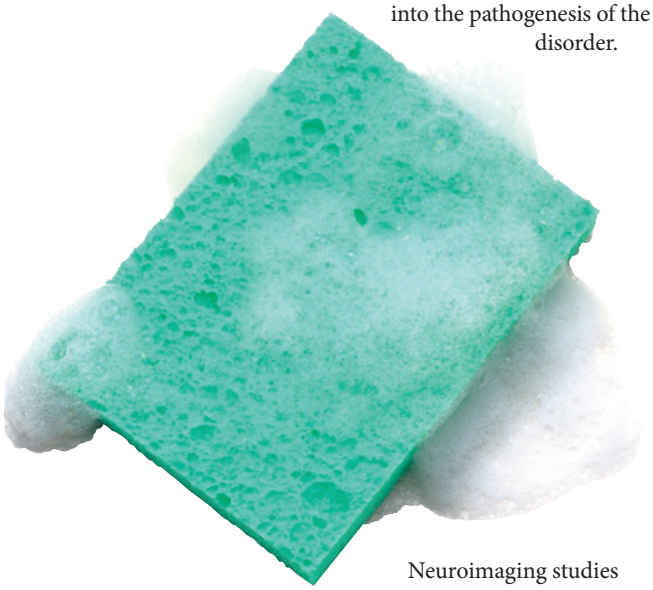
Obsessive-compulsive disorder (OCD) is characterized by anxiety, obsessions (persistent intrusive thoughts) and compulsions (repetitive activity), and severely impairs the lives of those affected; however, little is known about the underlying neurological deficits. A transgenic mouse that replicates some of the features of OCD could provide new insights into the pathogenesis of the disorder.



Neuroimaging studies have linked OCD to dysfunction in the circuits that connect the cortex, the striatum and the thalamus, but the nature of the dysfunction is not clear. Feng and colleagues generated transgenic mice in which a component of the excitatory postsynaptic density (PSD), SAP90/PSD95-associated protein 3 (SAPAP3), is absent, and found that these mice displayed OCD-like behaviour.

At 4–6 months of age, *Sapap3*-null mice (*Sapap3*$^{-/-}$ mice) developed skin lesions as a result of excessive grooming — behaviour that is reminiscent of the ritualistic behaviours (such as hand-washing) that are observed in OCD. The authors tested the anxiety levels of the mice using several behavioural paradigms and found that they also exhibited heightened anxiety-like behaviour.

Patients with OCD are often treated with drugs that modulate serotonergic signalling, although is it unclear how these alleviate the symptoms of OCD. When the authors treated *Sapap3*$^{-/-}$ mice with a selective serotonin-reuptake inhibitor for 6 days, they saw a reduction in the excessive grooming and anxiety-like behaviour. Normal behaviour was also restored when a lentivirus expressing *Sapap3* was injected into the striatum, confirming the importance of the loss of striatal SAPAP3 for the behavioural phenotype.

To determine the site of action of SAPAP3, the authors examined cortico-striatal synapses in brain slices from *Sapap3*$^{-/-}$ mice. α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA)- and *N*-methyl-D-aspartate-receptor-mediated synaptic transmission were abnormal, and biochemical examination of striatal PSD proteins revealed alterations in the levels of different NMDA-receptor subunits. Furthermore, the thickness of the dense layer of the PSD, which contains neurotransmitter receptors, was reduced.

It is unknown whether loss of SAPAP3 contributes to OCD in humans, but this study provides further evidence of a link between cortico-striatal dysfunction and OCD-like behaviour. Although an animal model will probably never replicate every symptom of OCD, the *Sapap3*$^{-/-}$ mouse might provide insights into the mechanisms that underlie key aspects of the disorder, and it could aid the development of improved therapeutics.

Katherine Whalley

ORIGINAL RESEARCH PAPERS
Welch, J. M. *et al.* Cortico-striatal synaptic defects and OCD-like behaviours in *Sapap3*-mutant mice. *Nature* **448**, 894–900 (2007)