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FEATURED ARTICLES

Debride and groom

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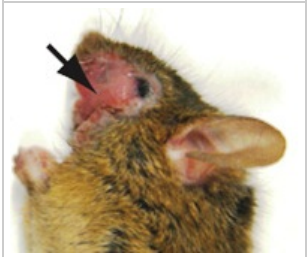
Mice lacking a postsynaptic density protein compulsively groom themselves past the point of injury and may offer a model of obsessive-compulsive disorder.



Sapap3 knockout mice develop facial lesions by 6 months of age. Image reprinted from *Nature*.

Did you remember to lock the door? For people with obsessive-compulsive disorder, intrusive thoughts (obsessions) like this one and the anxiety they produce can interfere with daily tasks. Many people with OCD develop ritualized behaviors (compulsions), like repeatedly checking the door, to deal with the anxiety. Currently, there are no genetic factors associated with OCD and no animal models in which to study it. Now Welch *et al*. report compulsive behavior and anxiety in mice lacking a postsynaptic density (PSD) protein in a recent article in *Nature*.

Neuroimaging studies show abnormalities in the circuit that links the cortex with the striatum in people with OCD. The striatum receives input from glutamatergic neurons in the cortex about a behavior's context. In turn, the striatum sends information back to the cortex (through the thalamus) to guide future behaviors. In people with OCD, the disruption of this circuit may lead to compulsive behaviors.

SAPAP family proteins localize to the PSD of excitatory synapses. Of the four *Sapap* genes, only *Sapap3* is highly expressed in the striatum. The authors generated mice lacking *Sapap3*. All *Sapap3* knockout mice developed lesions on their heads and necks by 6 months of age. Histological analysis showed no difference between *Sapap3* knockout and wild-type skin, and wild-type mice housed with *Sapap3* knockout mice did not develop lesions, suggesting that the lesions in *Sapap3* knockout mice were self-inflicted. At all times of the day and night, *Sapap3* knockout mice showed more self-grooming behaviors than wild-type mice. The increased grooming behavior persisted even after *Sapap3* knockout mice formed lesions, suggesting that *Sapap3* knockout mice compulsively groomed themselves past the point of discomfort, consistent with OCD in humans.

Sapap3 knockout mice showed increased anxiety-like behavior. Mice are fearful of bright open spaces and heights. Relative to wild-type mice, *Sapap3* knockout mice spent less time in the center of an open space, in a brightly lit chamber, and in the open arms of an elevated platform.

Approximately 50% of people with OCD benefit from selective serotonin reuptake inhibitors (SSRI). The SSRI fluoxetine blocked increased grooming behavior and reduced the latency to enter a bright chamber in *Sapap3* knockout mice. *Sapap3* knockout mice treated with fluoxetine behaved similarly to vehicle-treated wild-type mice. Targeted expression of *Sapap3* in the striatum of *Sapap3* knockout mice also rescued grooming and anxiety-related

behaviors, suggesting that these OCD-like behaviors are regulated in the striatum.

How does *Sapap3* deficiency affect striatal function? Relative to wild-type mice, striatal recording in *Sapap3* knockout mice showed increased AMPA and NMDA receptor-dependent field potentials, suggesting that *Sapap3* is important in glutamatergic transmission in the cortico-striatal circuit. The electron-dense layer of the PSD, which contains NMDA receptors, was thicker in the striatum of *Sapap3* knockout relative to wild-type mice, suggesting that *Sapap3* is important in the composition and structure of the PSD in the striatum.

Therefore, although it is unclear whether *Sapap3* knockout mice experience obsessive thoughts, the hallmark of OCD, *Sapap3* knockout mice may offer insight into the mechanism of OCD and other 'OC-spectrum disorders', including Tourette's syndrome and body dysmorphic disorder.

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1. Welch, J. M. *et al.* Cortico-spinal synaptic defects and OCD-like behaviours in *Sapap3*-mutant mice. *Nature* **448**, 894–900 (2007). | Article | PubMed | ChemPort |