Nature Reviews Neuroscience | AOP, published online 26 June 2013; doi:10.1038/nrn3547

PSYCHIATRIC DISORDERS

Repetitive circuits

> these studies confirm the involvement of corticostriatal circuitry in compulsive behaviours

Compulsive behaviours, such as repeated hand-washing, blight the daily lives of individuals suffering from obsessive-compulsive disorder (OCD). Neuroimaging studies have correlated abnormal activity in corticostriatal circuits with OCD symptoms but have not established a causal link or determined the precise neural circuitry involved. Now, two papers published in *Science* explore the circuits underlying OCD-like repetitive behaviour in mice by using optogenetics.

Hyperactivity in the pathway that links the orbitofrontal cortex (OFC) with the ventromedial striatum (VMS) has been hypothesized to underlie OCD pathology. Ahmari *et al*. targeted the expression of the light-activated ion channel channelrhodopsin 2 (ChR2) to cortical glutamatergic neurons and then photostimulated OFC axon terminals in the VMS once a day for 5 days to mimic this hyperactivity. The repeated stimulation resulted in a progressive increase in grooming (a behaviour that has been likened to human OCD behaviours) that lasted for up to 2 weeks after the final episode of photostimulation.

Ahmari *et al*. showed that the increase in grooming corresponded to electrophysiological changes in VMS neurons: their rate of firing in response to light stimulation increased after the hyperstimulation protocol. Treatment with fluoxetine, a drug commonly used to treat OCD, both reversed the changes in grooming behaviour and normalized the light-evoked activity in VMS neurons.

In the second study, Burguière *et al*. trained SAP90/PSD95-associated protein 3 (*Sapap3*; also known as *Dlgap3*) mutant mice (which exhibit several OCD-related behaviours, including repetitive grooming) to associate an audible tone with the delivery of a water drop to the forehead. Both controls and mutant mice developed a conditioned response (facial grooming) to the tone; however, as training continued, the control mice eventually stopped responding to the tone and delayed grooming until after delivery of the water drop. *Sapap3* mutant mice, by contrast, continued to respond to the tone.

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This observation suggests that *Sapap3* mutant mice are deficient in their inhibition of conditioned responses, a function that has been linked to activity in the lateral OFC (lOFC) and striatum. Indeed, Burguière *et al*. observed increased firing of striatal medium spiny neurons (MSNs) in *Sapap3* mutant mice. Hypothesizing that this increased activity might result from impaired inhibition of MSNs by striatal interneurons, the authors aimed to restore normal MSN activity in the mutant mice by using optogenetics. To do so, they expressed ChR2 in cortical pyramidal neurons and then photostimulated the axon terminals of lOFC neurons in the striatum to drive feedforward inhibition of MSNs. This both normalized the activity of MSN neurons and reversed the deficits in inhibition of the conditioned response.

Together, these studies confirm the involvement of corticostriatal circuitry in compulsive behaviours and suggest a model in which sustained hyperactivity in striatal neurons, possibly resulting from altered inhibitory input, induces neuroplastic changes that lead to the behavioural symptoms of OCD.

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ORIGINAL RESEARCH PAPERS Ahmari, S. E. *et al*. Repeated cortico-striatal stimulation generates persistent OCD-like behavior. *Science* **340**, 1234–1239 (2013) | Burguière, E. *et al*. Optogenetic stimulation of lateral orbitofronto-striatal pathway suppresses compulsive behaviors. *Science* **340**, 1243–1246 (2013)
FURTHER READING Shepherd, G. M. G. Corticostriatal connectivity and its role in disease. *Nature Rev. Neurosci.* **14**, 278–291 (2013)