Cause of obsessive-compulsive disorder discovered

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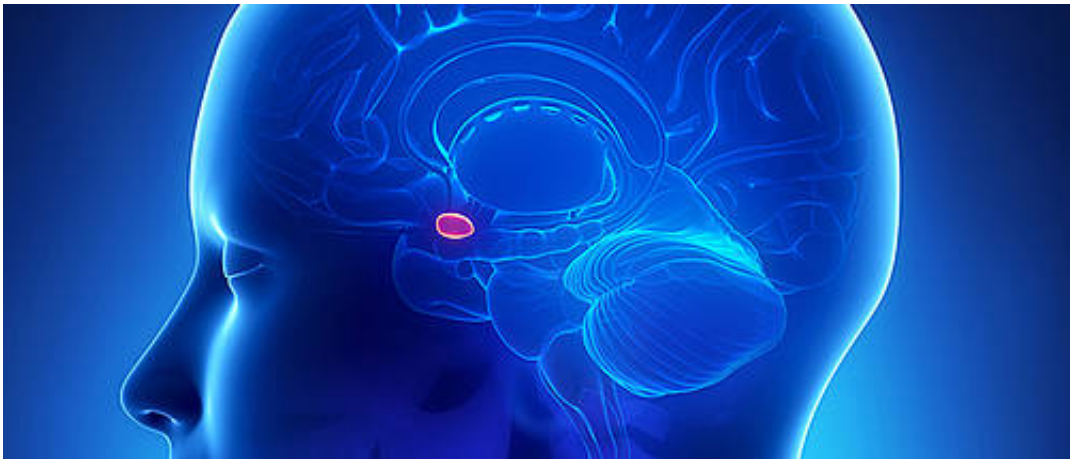

Credit: Julius-Maximilians-Universität Würzburg, JMU

An overactive molecular signal pathway in the brain region of the amygdala can lead to obsessive-compulsive disorder (OCD). A research team from Würzburg has established this connection.

Some people have an extreme fear of dirt or bacteria. As a result, they may develop a habit of compulsive washing and repeatedly cleaning their hands or body. They are trapped in a vicious circle, as the fear of new contamination returns quickly after washing. Sufferers see no way out. They are even incapable of changing their behaviour when the excessive washing has led to skin irritation or damage.

Around two percent of the general population suffer from some kind of obsessive-compulsive disorder (OCD) at least once in their life. The disorder is characterised by persistent intrusive thoughts which the sufferers try to compensate for by repetitive ritualized behaviour.

Like depression, eating disorders and other mental diseases, OCD is treated with antidepressants. However, the drugs are non-specific, that is they are not tailored to the respective disease. Therefore, scientists have been looking for new and better targeted therapies that have fewer side effects.

Missing protein triggers urge to wash

Professor Kai Schuh from the Institute of Physiology at the Julius-Maximilians-Universität (JMU) Würzburg (Germany) and his team explore the underlying causes of obsessive-compulsive disorder in collaboration with the JMU's Departments of Psychiatry and Neurology.

"We were able to show in mouse models that the absence of the protein SPRED2 alone can trigger an excessive grooming behaviour," Schuh says. He believes that this finding is crucial as no clear trigger for this type of disorder has been identified until now. Previous research pointed to multiple factors being responsible for developing OCD.

Occurring in all cells of the body, the protein SPRED2 is found in particularly high concentrations in regions of the brain, namely in the basal ganglia and the amygdala. Normally, the protein inhibits an important signal pathway of the cell, the so-called Ras/ERK-MAP kinase cascade. When it is missing, this signal pathway is more active than usual.

Hyperactive signal cascade in the brain

"It is primarily the brain-specific initiator of the signal pathway, the receptor tyrosine kinase TrkB, that is excessively active and causes the overshooting reaction of the downstream components", biologist Dr. Melanie Ullrich explains.

Administering an inhibitor to attenuate the overactive signal cascade in the animal model improves the obsessive-compulsive symptoms. Moreover, the JMU research team was able to treat the OCD with an antidepressant, similarly to standard therapy in humans. Their detailed results have been published in the journal *Molecular Psychiatry*.

New targets for therapies pinpointed

"Our study delivers a valuable new model that allows the disease mechanisms to be investigated and new therapy options for obsessive-compulsive disorders to be tested," Professor Schuh says.

The recently discovered link between OCDs and the Ras/ERK-MAP kinase cascade also opens up new targets for therapy. Drugs that inhibit this cascade are already available and some of them are approved for human treatment.

According to Melanie Ullrich, these are cancer drugs, as overactivation of the Ras/ERK-MAP kinase cascade is also a frequent trigger of cancer: "So we are wondering whether such drugs could also be effective in the treatment of obsessive-compulsive disorders and whether they are beneficial in terms of side effects."

More information: M Ullrich et al. OCD-like behavior is caused by dysfunction of thalamo-amygdala circuits and upregulated TrkB/ERK-MAPK signaling as a result of SPRED2 deficiency, *Molecular Psychiatry* (2017). DOI: 10.1038/mp.2016.232

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