Glutamate and insulin signalling drive compulsive behaviour

Levels of glutamate and, surprisingly, insulin signalling in the brain hold the key to understanding the compulsive behaviour exhibited by people with disorders such as autism or obsessive-compulsive disorder, according to EU researchers.

Researchers from the EU project TACTICS have identified some of the underpinnings of compulsive disorders in children and adolescents. Their discovery that glutamate and insulin signalling can play a role in these behaviours holds the promise of better treatment options for people with autism spectrum disorder (ASD) and obsessive-compulsive disorder (OCD).

“TACTICS looks across different compulsive disorders such as autism, OCD and substance use in ADHD and asks — is there a common mechanism underlying compulsivity as a trait and are there shared biological underpinnings of that trait?’ says Jeffrey Glennon, deputy project co-ordinator and assistant professor in cognitive neuroscience at Radboud University Medical Center in the Netherlands.

The scientists believe that compulsive behaviour is caused by a dysfunction in the fronto-striatal circuits of the brain. ‘Our initial idea was that, with such people, fronto-striatal activity is overactive so the level of glutamate, the main excitatory chemical in your brain, is too high in these brain regions,’ says Dr Glennon.

Increased glutamate

The team first looked at glutamate tone in autism and OCD across childhood, adolescence and adulthood to see if it differed across the lifespan and found it did. They then began testing in humans if memantine, a drug that blocks glutamate action which is commonly used in the treatment of Alzheimer’s disease, could have anti-compulsive actions. The trial is still underway and due to finish in June 2018.

“We found glutamate was increased in the anterior cingulate cortex and striatum in juveniles with compulsive problems such as ASD and OCD. We also found there was a difference between children, adolescents and adults so the levels of glutamate were different at different life stages,’ says Dr Glennon.

Surprising result

But when the researchers came to look at the genetics, they were in for a surprise. ‘We took large genetic data sets on OCD...
and did an analysis and what popped up was not glutamate but insulin,’ says Dr Glennon, ‘we thought there is something happening with insulin signalling.’

Tests using animal models showed that manipulating the insulin-signalling system in the brain also has a marked effect on compulsive behaviour. ‘If you take the top gene from the insulin-signalling network and you knock it out, those animals show repetitive behaviour like in autism or checking behaviour like in OCD,’ says Dr Glennon, ‘they also show head tics analogous to Tourette’s Syndrome.’ This seems relevant as a high proportion of people with Tourette’s Syndrome also have OCD and it represents a compulsive phenotype involving involuntary movements.

The TACTICS team aim to explore the insulin-related signalling mechanisms further. ‘We feel it is such a strong lead,’ says Dr Glennon. A positive outcome from the memantine clinical trial could pave the way for bigger clinical trials possibly leading to fully licensed medications targeting glutamate in a few years’ time.

This would be welcome news for patients and their families. There is currently no treatment for the core symptoms of autism and the current options for OCD patients — cognitive behaviour therapy or prozac-type drugs — do not work for everyone. ‘Compulsive behaviours take up a lot of people’s time and energy, living with this stress and anxiety every day is horrible so if we could do something to reduce the compulsivity, that would really help,’ says Dr Glennon.