Background

Compulsivity is characterized by a repetitive, irresistible urge to perform a behavior, the experience of loss of voluntary control over this intense urge, the diminished ability to delay or inhibit thoughts or behaviors, and the tendency to perform repetitive acts in a habitual or stereotyped manner. Compulsivity is a cross-disorder trait underlying phenotypically distinct psychiatric disorders that emerge in childhood (autism spectrum disorder, ASD; obsessive-compulsive disorder, OCD) or adolescence (substance abuse). Our approach integrates clinical data sets for ‘addictive’ (ADHD high risk for substance use), ‘anxious’ (OCD) and ‘stereotypical’ (ASD) compulsive behaviors with highly predictive animal models for new pharmacotherapy.

Objectives

In a series of ‘proof-of-concept’ studies, the cohesion of structural neuroimaging studies (MRI/DTI), neurochemistry (MRS/microdialysis), behavior, genetics (GWAS), proteomics and (Bayesian) machine learning tools in both male and female paediatric clinical populations and behavioral animal models will seek to better understand underlying mechanisms related to glutamate dysfunction in frontostriatal circuits and its remediation/prevention by early intervention studies with glutamate-based (riluzole and memantine) clinically used drugs. The leading drug-based interventions will be tested in pilot Phase IIb-like studies for ‘proof-of-principle’ efficacy in paediatric OCD and ASD populations.

This approach will

1. establish predictive neural, genetic and molecular markers of compulsivity in pediatric populations;
2. provide evidence of disorder modifying pharmacologic strategies as a therapeutic approach;
3. develop a novel animal model for pharmaceutical screening and proof of concept studies;
4. build and valorize a translational biomarker compulsivity database and
5. provide pilot efficacy and safety data in paediatric clinical populations to support future large scale clinical trials according to these strategies.

Results

TACTICS is a multidisciplinary project that includes preclinical and clinical research and involves experts from academia andsmall and medium-sized enterprises (SMEs) that has been developed to identify the neural, genetic and molecular factors involved in the pathogenesis of compulsivity. Compulsivity is defined as the repetitive, irresistible urge to performa behaviour, the experience of loss of voluntary control over this intense urge, the diminished ability to delay or inhibit thoughts or behaviours, and the tendency to perform repetitive acts in a habitual or stereotyped manner. Compulsivity is a cross-disorder trait underlying phenotypically distinct psychiatric disorders that emerge at early age (autism spectrum disorder, ASD), in late childhood (obsessive-compulsive disorder, OCD) or during adolescence (substance use

disorders, SUD, and behavioural addictions such as gambling, gaming and internet addiction). Compulsivity is closely linked to two other concepts, namely impulsivity and addictive behaviour. In particular Attention-deficit Hyperactivity Disorder (ADHD) is a disorder characterized by high impulsivity and known for an increased risk for later SUD.

The preclinical studies provide no evidence for changes in frontostriatal glutamate tone in animal models of compulsive behaviour. Both the NMDA antagonist memantine and the glutamate release inhibitor riluzole do not have effects on compulsive behaviour. The absence of treatment effects of memantine may be at least partly be explained by interactions between the dopaminergic (quinpirole) and the glutamatergic (memantine) systems. Our results further suggest that anti-glutamatergic drugs may not be effective inindividuals with altered dopaminergic neurotransmission.

In the human MRI studieslow grey matter volumes of the (pre)frontal, central and cerebellar rather than from the striatal regions were related to persistence versus remission of ADHD. Polygenic risk scores for ADHD did not differentiate between persistence and remission. ASD, OCD and ADHD share common alterations of the subcortical structures, but also each have unique alterations of particular cortical areas. Exposure to stress influences ADHD severity,but only in individuals with an s-allele of the serotonin transporter gene. Stimulant treatment may lower the risk for later SUD, and affect white matter infrastructure and brain regions involved in cortical control.

MR spectroscopy learned that levels of glutamate were higher in the anterior cingulate cortex (ACC)of children with compulsivity disorders compared with controls. There were no differences in glutamate levels between ASD and OCD. This increase in glutamate in the ACC is consistent with several prior studies.

Genetics work in TACTICS identified and confirmed brain-based insulin signalling as an important biological process disturbed by OCD and compulsivity. This led to the generation of a new animal modelthatwas highly compulsiveand providedleadsfor future studies to develop novel therapeutic for OCD and the compulsivitytrait. TACTICS further confirmed an important additional concept that there is genetic continuity between psychiatric disorders (ASD, ADHD, as well as OCD) and related population behavioural traits.

The planned randomized, double-blind, placebo-controlled add-on treatmentstudywith a glutamatergic compound (memantine) in ASD and OCD faced several severe challenges and recruitment problems. As a consequence, few participants have been enrolledand only descriptive reporting will be done.

TACTICS has built a multi-task and multi-source learning tool for causal discovery that extends previously existing algorithms by relaxing several assumptions these methods typically rely on, namely data obeys a Gaussian distribution or is discrete, and data has no missing values. This algorithm and software has beenvalorisedby formation of the spinout company Machine2Learn.

By now, TACTICS has published more than 80peer-reviewed publications, more than 10 of which are in high-impact journals.

Read the final summary report of its key results & impact!