To facilitate the organisation and management, the project is structured in “Work Packages” which together comprise the project. TACTICS consists of 10 Work Packages (WPs). Each WP is carried out by a varying number of involved parties. The WP leader supervises and adjusts the process flow and works closely with the project office. The activity of the WP will be overseen by the chair of the working group.

WP01: Animal models, neurochemistry & pharmacology (Leader: RUNMC-Pharm / J Glennon)

Given the clinical focus on three different compulsive paediatric populations (OCD, ASD and ADHD with high risk of substance abuse in WP3, 4, 5 & 6), WP1 will examine model-specific compulsive readouts, operant reversal learning and spontaneous alternation changes in the Y-maze in age-matched (3 to 6 weeks in rats and mice) juvenile male and female animals (n=8 per group) with analogous behaviors to each clinical population (8-12 years) in WP6.

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WP02: Animal imaging (Leader: UMCU / R Dijkhuizen)

To clarify the neural underpinnings of compulsive behavior, and to reveal potential targets for therapy, we will assess the development of functional and structural brain connectivity in the fronto-striatal circuit by means of multiparametric MRI in appropriate rodent models, in combination with specific treatment strategies.

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WP03: Human neurochemistry (Leader: KCL / D Murphy, S Williams)

The overall objective of WP3 is to investigate (i) the role of glutamate in compulsivity, and impulsive behaviors across different clinical phenotypes in a longitudinal observational design to identify disease-modifying factors (OCD, ASD); and (ii) the modulatory effect of treatment.

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WP04: Human imaging (Leader: RUNMC-Neuro, UMCU / J Buitelaar, S Durston)

The aim of WP4 is to identify neural, neurocognitive, genetic, and biomarker mechanisms underlying compulsive behaviors in high-risk subjects and controls using an existing dataset (the NeuroIMAGE cohort) of 1000 subjects. Examining developmental links between compulsivity, impulsivity and addiction at the clinical, cognitive and neural level by reassessing 600 subjects of the NeuroIMAGE cohort 4 years later also is part of WP4. Furthermore, a new cohort of children with ASD, OCD and controls (N=180) shall be collected to replicate common neural, neurocognitive and genetic mechanisms underlying compulsive behaviors across different clinical phenotypes in a longitudinal design, to identify disease-modifying factors (OCD, ASD) of these neural, neurocognitive and genetic mechanisms, to replicate high-risk profiles and/or biomarkers for the compulsivity trait, and develop clinical risks assessment tools. WP4 also examines effects of medication interventions (together with WP6) on fronto-striatal MRI measures in patients with OCD, ASD, and/or high-risk substance use (ADHD).

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WP05: Genotyping, phenotyping and proteomics (Leader: RUNMC-Gen / B Franke)

Identification of new candidate genes for compulsive behavior from the results of genome-wide association studies (GWAS) from (a) 1000 cases of the NeuroIMAGE sample using clinical compulsivity phenotypes, relevant cognitive and neuroimaging intermediate phenotypes of compulsivity and (b) 1700 samples of the Brain Imaging Genetics (BIG) sample using cortical thickness measures and regional brain volumes of compulsivity-related brain regions is part of WP5. Subsequently follows the integration of the findings from these studies with data available from the GWAS of the Obsessive Compulsive Foundation Genetics Collaborative (>2000 OCD cases) and the Psychiatric GWAS Consortium (PGC) to pick the most interesting candidate for animal studies (WP1) and for the selection of medications for proof-of-concept randomized controlled trials for compulsivity in WP6. WP5 also aims to characterize the samples - pre- and postmedication- from patients with OCD, ASD and healthy controls analysed in WP4 and treated in WP6 using deep sequencing and proteomics analysis of candidate genes/biological pathways (in collaboration with UCAM) to select those responsive to treatment.

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WP06: Pilot clinical pharmacological studies (Leader: CIMH / T Banaschewski, R Dittmann)

In WP6 the performance of open-label pilot studies and proof-of-concept randomized clinical trials in clinical populations of children and adolescents with compulsivity disorders will take place in order to document efficacy and safety of glutamatergic medications. Also the exploration of the effects of moderating and mediating factors on the response to these glutamatergic medications shall be examined in WP6, as well as the effects of these medications on biomarkers and neural mechanisms underlying compulsivity. These pilot data shall be made available to be used for future Paediatric Use Marketing Authorisation directed trial applications.

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WP07: Machine learning and data management (Leader: RUNMC-ICIS / T Heskes)

Many different sources of information related to the prediction of compulsivity will be gathered throughout the project. The objective of this work package is then to apply machine learning techniques to combine all this information and to establish predictive neural, genetic and molecular markers of compulsivity in paediatric populations.

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WP08: Business development and dissemination (Leader: RUNMC-Pharm / J Glennon)

WP8 will increase the visibility of TACTICS by reaching out to the scientific community, industry, patient organisations and other interested or potential stakeholders. A communication plan will be implemented.

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WP09: Ethics and training (Leader: UMCU, TAU / S Durston, D

Joel)

WP9 will focus on ensuring that the highest standards for the scientific and medical ethical aspects of the proposed studies are set and met. The studies will be conducted in compliance with European Directive 86/609/EEC, the Recommendation 2007/526/65/EC, ICH Good Clinical Practice (GCP) and the legal regulations of the European Union, national legislations and local animal use and medical ethical committees. The Declaration of Helsinki in its latest accepted version will be adhered to. Study protocols and substantial amendments will be approved by the responsible ethics committees and competent authorities before the studies commence. An Independent International Advisory Committee will be appointed to advise on any scientific and ethical issues. Dr. Ulrike Schulze (University of Ulm, Germany) will act as a consultant on ethical issues. The second key objective of this WP is to monitor the adherence of sites involved in data collection to standard operating protocols (SOPs), quality standards and implement relevant training strategies regarding inter-laboratory and inter-rater reliability, assessment measures, instruments and procedures including their precise application, evaluation, documentation and transfer of results. An ethical review / monitoring process and training programme will be implemented.

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WP10: Project Management (Leader: concentris / A Schwalber)

Effective project management is a central element of successful research. This is because large research projects entail a lot of administrative work. The management WP makes sure that the project achieves its objectives and delivers in time, budget and quality its milestones and deliverables. It is furthermore concerned with communication, reporting, meeting organisation, financial management and intellectual property rights. The responsibility for project management lies primarily with the coordinator who is supported by concentris.

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