UNveiling the MEchanism(s) underlying the switch to mania during antidepressant treatment: The role of glutamate (UNMET)

Project Coordinator: Dr. Judith Homberg, Cognitive Neuroscience, Stichting Katholieke Universiteit, Nijmegen, The Netherlands
Project Partners:
Prof. Dr. Laurence Ris, Neurosciences Department, University of Mons, Mons, Belgium
Prof. Dr. Peter Gass, Department of Psychiatry and Psychotherapy, Central Institute of Mental Health Mannheim, Mannheim, Germany
Dr. Paolo Brambilla, Dipartimento di Neuroscienze e Salute Mentale, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano, Italy
Prof. Daniela Jezova, Biomedical Research Center, Institute of Experimental Endocrinology, Bratislava, Slovakia

Bipolar Disorder (BD) is a severe psychiatric disorder characterized by the alternation of mania, hypomania, depression as well as mixed affective states. The lifetime prevalence of BD type I is 0.6% of the general population. The treatment of BD is difficult because of the opposite nature of its symptoms (i.e. depression and mania). Furthermore, the available treatments, all symptomatic, can cause severe side effects.
A critical feature of BD is the switch to mania during antidepressant treatment. The mechanisms underlying such transitions are still elusive and represent an unmet need of pharmacopsychiatry. Accordingly, our project will address in both animal and humans the neurobiological mechanisms underlying antidepressant-induced mania, focusing on the role played by glutamatergic transmission in the prefrontal cortex-striatum-lateral habenula pathway, taking advantage of the availability of two animal models, the serotonin transporter knockout (KO) and the dopamine transporter KO rats. We hypothesize that serotonin and dopamine modulate the glutamate system thus altering the top-down control exerted by prefrontal cortex over the striatum and lateral habenula contributing to mania. UNMET will, by integrating molecular, electrophysiological and neurochemical approaches in rats together with neuroimaging techniques in rats and humans, provide a proof-of-principle of the glutamatergic mechanisms underlying mania and test an antidepressant adjunctive preventing mania.