NAME OF PRESENTING AUTHOR: Giuseppe Fanelli

EMAIL ADDRESS OF PRESENTING AUTHOR: giuseppe.fanelli@radboudumc.nl

Insulinopathies of the brain? Genetic overlap between somatic insulin-related and neuropsychiatric disorders.

Giuseppe Fanelli [1,2], Barbara Franke [2,3], Ward De Witte [2], I. Hyun Ruisch [4], Jan Haavik [5], Veerle van Gils [6], Willemijn J. Jansen [6], Stephanie J. B. Vos [6], Lars Lind [7], Jan K. Buitelaar [8], Tobias Banaschewski [9], Søren Dalsgaard [10,11], Alessandro Serretti [1], Nina Roth Mota [2], Geert Poelmans [2], Janita Bralten [2]

[1] Department of Biomedical and Neuromotor Sciences, University of Bologna, Bologna, Italy

[2] Department of Human Genetics, Radboud University Medical Center, Donders Institute for Brain, Cognition and Behaviour, Nijmegen, The Netherlands

[3] Department of Psychiatry, Radboud University Medical Center, Donders Institute for Brain, Cognition and Behaviour, Nijmegen, The Netherlands

[4] Department of Child and Adolescent Psychiatry, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

[5] Department of Biomedicine, University of Bergen, Bergen, Norway

[6] Department of Psychiatry and Neuropsychology, School for Mental Health and Neuroscience, Maastricht University, Maastricht, The Netherlands

[7] Department of Medical Sciences, Uppsala University, Uppsala, Sweden

[8] Department of Cognitive Neuroscience, Donders Institute for Brain, Cognition and Behaviour, Radboud University Medical Center, Nijmegen, The Netherlands

[9] Department of Child and Adolescent Psychiatry and Psychotherapy, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany

[10] National Centre for Register-Based Research, Aarhus University, Aarhus, Denmark

[11] The Lundbeck Foundation Initiative for Integrative Psychiatric Research, PSYCH, Aarhus, Denmark

KEYWORDS: insulin; pleiotropy; Alzheimer's disease; obsessive-compulsive disorder; autism spectrum disorder.

ABSTRACT:

The prevalence of Alzheimer's disease (AD), autism spectrum disorder (ASD), and obsessive-compulsive disorder (OCD) is higher among patients with somatic insulinopathies, like metabolic syndrome (MetS), obesity, and type 2 diabetes mellitus (T2DM). Dysregulation of insulin signalling has been implicated in these neuropsychiatric disorders, and shared genetic factors might partly underlie these observed comorbidities. We investigated genetic overlap between AD, ASD, and OCD with MetS, obesity, and T2DM by estimating pairwise genetic correlations using the summary statistics of the largest available genome-wide association studies for these diseases. Stratified covariance analyses were performed to investigate the contribution of insulin-related gene-sets. Having tested these hypotheses, novel brain "insulinopathies" were explored by estimating the genetic relationship of six additional neuropsychiatric disorders with nine insulin-related diseases/traits. Significant genetic correlations were found between ASD and MetS (r_g=0.115, p=0.002), OCD and MetS (r_g=-0.315, p=3.9e-8), OCD and obesity (r_g=-0.379, p=3.4e-5), and OCD and T2DM (r_g=-0.172, p=3e-4). Stratified analyses showed negative genetic covariances between ASD and MetS/T2DM through gene-sets comprising insulin signalling and/or insulin processing genes, and between AD/OCD and MetS/T2DM through an insulin receptor recycling gene-set (p<6.17e-4). Significant genetic correlations with

insulin-related phenotypes were also found for anorexia nervosa, attention-deficit/hyperactivity disorder, major depression, and schizophrenia ($p<6.17e-4$). Our findings highlight genetic overlap of somatic insulin-related phenotypes with multiple neuropsychiatric disorders, pointing to a shared etiology. These results represent a starting point for a new research line on "insulinopathies" of the brain, which may support the development of more effective/tolerated treatment strategies for neuropsychiatric disorders.

GRANT SUPPORT: This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 847879 (PRIME, Prevention and Remediation of Insulin Multimorbidity in Europe).