University of Zurich[UZH]

Department of Economics – Neuroeconomics Seminar

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Pharmacological, Neuroimaging and Genetic Studies of the Human Dopamine Transporter

In this talk, I will present recent data from studies investigating the role of the dopamine transporter (DAT) in brain function, cognition and the clinical symptoms of attention deficit hyperactivity disorder (ADHD). Experimental studies using methylphenidate, a DAT blocker, indicate that temporal aspects of eye movement control is improved by this compound. Using functional magnetic resonance imaging (fMRI), we observed that methylphenidate has anatomically specific effects in the putamen, in agreement with the known pattern of DAT expression. We also observed that the 40-bp VNTR in the 3' UTR of the DAT gene (SLC6A3) predicts methylphenidate effects in a thalamo-cortical network during response inhibition, with 9R-carriers showing an increase in BOLD signal but 10R homozygotes showing a decrease. These findings are consistent with previous evidence of enhanced sensitivity to pro-dopaminergic interventions in 9R carriers and can be reconciled with our meta-analysis of pharmacogenetic studies of ADHD patients, where 10R homozygotes show less clinical response to methylphenidate treatment in naturalistic trials than other genotypes. Finally, a recent meta-analysis failed to show any association between the SLC6A3 VNTR and various domains of cognitive function in healthy adults. It is concluded that (1) DAT blockade through methylphenidate improves striatal functions underlying oculomotor control, (2) methylphenidate effects on brain function and ADHD symptoms depend in part on SLC6A3 genotype and (3) in the absence of pharmacological challenges the SLC6A3 VNTR has effects that are penetrant at the level of striatal DAT availability and brain function but not observable cognition. The pharmacogenetic findings are suggestive of lower tonic dopamine levels but stronger phasic dopamine response in 9R carriers.