Submitter name: Cecilia Flores
Submitted email: cecilia.flores@mcgill.ca

The *DCC* gene network in the prefrontal cortex and striatum as a predictor of cognitive control and psychopathology

Jose Maria Restrepo[1], Sachin Patel[2], Zihan Wang[2], Michael J. Meaney[2,3,4,5], Patricia P. Silveira[2,4], and Cecilia Flores[3,4]

[1]Integrated Program in Neuroscience, McGill University, [2]Ludmer Centre for Neuroinformatics and Mental Health, Douglas Mental Health University Institute, McGill University, [3]Department of Neurology and Neurosurgery, Faculty of Medicine, McGill University, Douglas Mental Health University Institute, [4]Department of Psychiatry, Faculty of Medicine, McGill University, [5]Singapore Institute for Clinical Sciences, Agency for Science, Technology and Research (A*STAR), Brenner Centre for Molecular Medicine

By the time humans reach adolescence, most neuroanatomical foundations are set in place. An exception is the establishment of medial prefrontal cortex (mPFC) dopamine connectivity, which reaches maturation in adulthood. Altered mPFC dopamine connectivity/function associates with cognitive control deficits in adulthood. Given the role of the guidance cue DCC signaling pathway in adolescent dopamine development, we investigated whether a polygenic score reflecting variation in the function of the *DCC* gene network in dopamine target regions (mPFC and striatum) is associated with measures of cognitive control in community samples of children and with psychopathology (addiction) in adults. We created a list of genes co-expressed with *DCC* in the mPFC and striatum, compiling SNPs from these genes in a score using the SNP-gene expression association betas described in GTeX. We created the polygenic score and investigated its ability to predict impulsive phenotypes in children, and likelihood and number of addictions in adults. A higher score was associated with higher measurements of impulsivity in 6-year old children, as measured with the Information Sampling Task (n=205) and the Stop Signal Reaction Time Task (n=398), and with a higher number of addiction comorbidities in adults (n=2719). Our novel biologically-informed genetic score, reflecting the function of the *Dcc* gene network in two key regions for developing dopamine neurons, can predict impulsivity and addiction severity in humans. These results translate observations made in rodent models, where variations in *Dcc* expression during development determine susceptibility to dopamine-related cognitive deficits and behavioral effects of drugs of abuse.