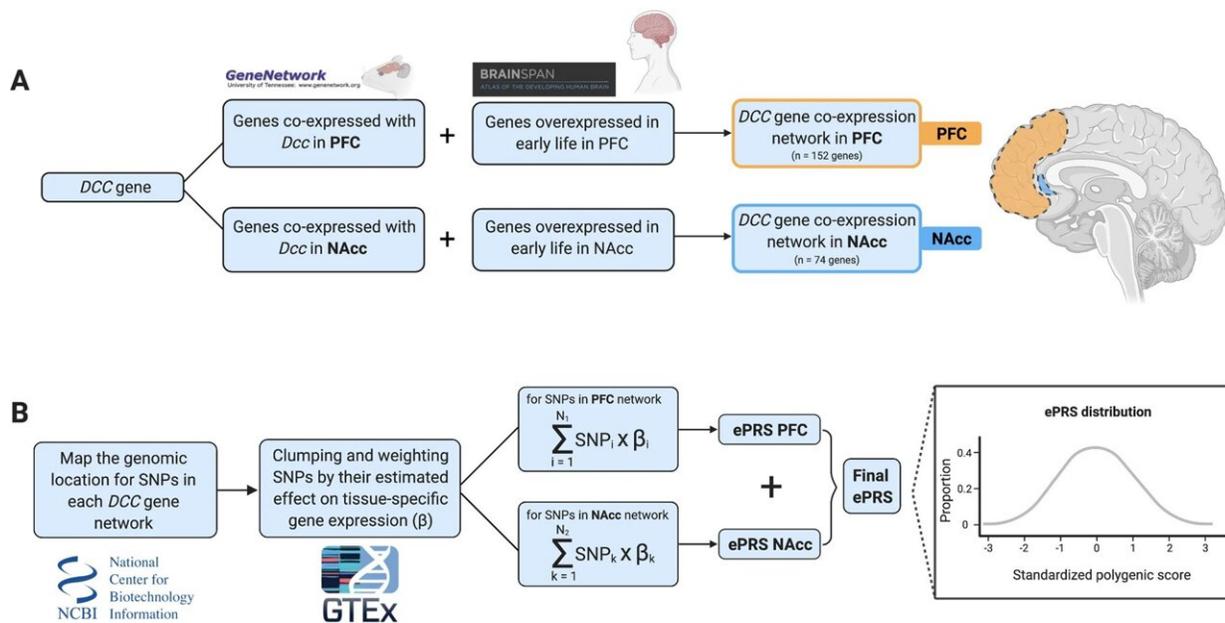


A new understanding of the neurobiology of impulsivity

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Flowchart depicting the steps involved in the creation of the corticolimbic DCC-ePRS score. A The GeneNetwork database was used to generate a *Dcc* gene co-expression matrix in the PFC and NAcc in mice. Genes with a correlation of co-expression $\geq |0.5|$ were retained. Brainspan was used to identify human homologous transcripts and to filter each gene list by selecting the transcripts enriched during the first 18 months of life, as compared to adulthood, defined by a differential expression ≥ 1.5 , within the same brain area. Each resulting gene list comprised the DCC co-expression network for their respective brain area. B Based on their annotation in the NCBI library, using GRCh37.p13 assembly, common SNPs within each co-expression network, GTEx data base, and genotyping cohort were subjected to linkage disequilibrium clumping to remove highly correlated SNPs ($r^2 \geq 0.2$). Using data from the GTEx project, alleles at

a given cis-SNP were weighted by the estimated brain-region-specific effect of the genotype on gene expression. The sum of these estimated effects resulted in ePRS scores for the DCC co-expression networks in the PFC and NAcc, which we aggregated into a single global ePRS score. Credit: *Molecular Psychiatry* (2022). DOI: 10.1038/s41380-022-01533-7

While not all impulsive behavior speaks of mental illness, a wide range of mental health disorders which often emerge in adolescence, including depression and substance abuse, have been linked to impulsivity. So, finding a way to identify and treat those who may be particularly vulnerable to impulsivity early in life is especially important.

A group of researchers, led by scholars at McGill University, have developed a genetically based [score](#) which could help identify, with a high degree of accuracy (greater than that of any impulsivity scores currently in use), the [young children](#) who are most at risk of impulsive behavior.

Their findings are especially compelling because the score they have developed was able to detect those at a higher risk of impulsivity within three ethnically diverse community samples of children, from a cohort of close to 6,000 children.

This discovery of a novel score for impulsivity in [early life](#) can inform prevention strategies and programs for children and adolescents who are at risk for psychiatric disorders. In addition, by describing the function of the gene networks comprising the score, the study can stimulate the development of new therapies in the future.

A shift in perspective leads to new findings

The impulsivity risk score was developed by looking at the co-expression of a number of [genes](#) in the [prefrontal cortex](#) and the striatum, areas of the brain that play a role in decision-making and emotional regulation, among other things.

"Typically, [genetic approaches](#) to identifying the neurobiological signature for impulsivity (or any other condition or disease) tend to focus on identifying the variation in a few [genetic markers](#) that might be responsible for the problem," said Patricia Pelufo Silveira, an Associate Professor in the Department of Psychiatry and Researcher at the Douglas Research Center and one of the two senior authors on the recent paper in *Molecular Psychiatry*.

"We came at the problem from the opposite direction, by focusing on a gene known to be associated with the maturation of the brain in these two key areas and then looking for a network of other genes that were most closely associated with it."

It took a lot of hunting

This approach was based on earlier work in mice models, led by Cecilia Flores, a co-senior author on the paper and a Full Professor, in the Department of Psychiatry which had identified the importance of a specific gene (known as DCC), which acts as a "guidance cue" that determines when and precisely where brain dopamine cells form connections in the prefrontal cortex and striatum. This coordinated development is essential for the maturation of impulse control.

But to create the new [impulsivity](#) score, it took a lot of hunting to narrow down the genes most closely associated with DCC.

"Our approach exploits the fact that genes operate within [complex networks](#) that, ultimately, perform very precise biological functions.

These so-called gene networks have the property of being highly tissue-specific, so we began with an unbiased look at groups of genes that are co-expressed with DCC in brain regions known to play an important role supporting inhibitory control," says co-author Jose Maria Restrepo, a Ph.D. student in the Integrated Program in Neuroscience at McGill University.

"The results underline the importance of data sharing and open science", adds Flores. "Imagine if we had had to collect this information in all these countries over all these years. Our discovery was only possible because we had access to all these data."

More information: Jose M. Restrepo-Lozano et al, Corticolimbic DCC gene co-expression networks as predictors of impulsivity in children, *Molecular Psychiatry* (2022). [DOI: 10.1038/s41380-022-01533-7](https://doi.org/10.1038/s41380-022-01533-7)

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