Name: Bonnie Alberry, PhD
Email: bonnie.alberry@mail.mcgill.ca
PI Name: Patricia Pelufo Silveira MD, PhD
PI email: patricia.silveira@mcgill.ca
Presentation preference: Oral Presentation

Sex-specific prefrontal cortex gene networks moderate the effect of early adversity on childhood behavior and adult substance abuse

Bonnie Alberry[1], Barbara Barth[2], Aashita Batra[2], Marcio Bonesso Alves[1], Danusa Mar Arcego[1], Nicholas O'Toole[3], Sachin Patel[3], Irina Pokhvisneva[3], Michael J. Meaney[1,3,4], Patricia Pelufo Silveira[1,3]

[1]Department of Psychiatry, McGill University; [2]Integrated Program in Neuroscience, McGill University; [3]Ludmer Centre for Neuroinformatics and Mental Health, Douglas Mental Health University Institute, McGill University; [4]Singapore Institute for Clinical Sciences, Agency for Science, Technology and Research

Early adversity influences physiological and psychological outcomes, including substance abuse behavior. Using an intrauterine growth restriction model of adversity in rats, we defined sex-specific networks of coexpressed genes at birth in the prefrontal cortex using RNA sequencing and weighted gene co-expression network analysis (WGCNA). SNPs from genes represented in each network were combined into an expression-based polygenic score (ePRS) for males and females in children (MAVAN) and adults (SAGE). In girls, the female ePRS moderates the effect of birth weight on emotional reactivity at ages four (N=143,β=9.590,*p*=0.001) and five (N=122,β=8.216,*p*=0.02), with high ePRS associated with more reactivity in response to adversity. In women, it moderates the effect of adversity on DSM4 dependence on alcohol (N=2180,β=0.242,$p=3.84\times10^{-4}$), marijuana (N=2177,β=0.332,$p=1.96\times10^{-4}$), and cocaine (N=2179,β=0.348,$p=1.13\times10^{-4}$). Higher ePRS associates with greater incidence of alcohol dependence for females with greater adversity (β=0.420,*p*=0.002), while lower ePRS associates with fewer incidences of marijuana (β=-0.659,*p*=0.006) or cocaine (β=-0.702, *p*=0.002) dependence with more adversity. In males, the male ePRS moderates the effect of birth weight on emotional reactivity at age five (N=142,β=7.205,*p*=0.02) and impulsivity at age six (N=109,β=2.333,*p*=0.03). In adults, it moderates the effect of adversity on DSM4 dependence on marijuana (N=1847,β=0.263,*p*=0.002), opiates (N=1844,β=0.265,*p*=0.02), and other drugs (N=1844,β=0.251,*p*=0.008). Higher ePRS associates with greater incidence of marijuana dependence with greater adversity (β=0.350,*p*=0.02), lower ePRS associates with fewer incidences of opiate (β=-0.536,*p*=0.04) or other dependence (β=-0.503,*p*=0.01) facing adversity. These data suggest the sex-specific networks of genes in prefrontal cortex moderate the early environment effect on child and adult behavior including substance abuse.