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Sex-Specific Developmental Gene Networks Linking Risk-Taking Behaviors in Rodents and Humans

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Early adversity is a risk factor for future psychopathology, including addictive-like behaviors, with emerging evidence of sex-specific effects. However, the mechanisms underlying these differences remain unclear. This study investigated reward-seeking and reward-risk-taking behaviors in rats exposed to prenatal adversity and identified sex-specific gene networks in the medial prefrontal cortex (mPFC) associated with these behaviors, which may serve as biomarkers in humans. Sprague Dawley dams were assigned to either a control (ad libitum diet) or food restriction (FR) group starting on gestational day 10. Offspring were tested at postnatal day 90 for lever-pressing behavior under a fixed-ratio 1 (FR1) schedule of reinforcement and in the novelty-suppressed feeding (NSF) test. Bulk RNA sequencing at P0, P21, and P90 (n=12/group) was analyzed using Weighted Gene Co-expression Network Analysis (WGCNA) and TimeNexus to identify active gene subnetworks responsive to the FR model across development. Sex-specific expression-based polygenic scores (ePRS) were derived from SNPs within these networks and tested for predictive validity in adults from the UK Biobank. FR offspring, regardless of sex, exhibited increased lever pressing for food reward ($p=0.035$, two-way ANOVA, n=11-12/group). However, only FR females demonstrated faster initiation of eating the food reward placed at the center of the aversive arena in the NSF ($p<0.05$, Log-rank Mantel–Cox, n=16-19/group). In women, the female ePRS predicted risk-taking behavior ($p=0.003$, B=-0.03, n=208,995), whereas the male ePRS had no significant effect in men ($p>0.05$, n=179,591). This study demonstrates a novel approach for identifying brain-specific gene networks as biomarkers of susceptibility to risk-taking behaviours in humans.