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Genetic differences in estrous cycle effects on the rat brain transcriptome

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Males and females often differ on propensity for a substance use disorder (SUD), etiology and clinical manifestation of SUD, and response to SUD treatment strategies. The fluctuation of sex-related hormones in the brain and/or circulation may contribute to some of these differences. Others have shown that stage of the estrous cycle influences RNA transcription levels and splicing in particular brain regions. In this study, we examined whether these cycle-induced effects on RNA expression differ based on genetic background. We used female rats from the two progenitor strains of the HXB/BXH recombinant inbred panel (BN-Lx/Cub and SHR/OlaIpcv). Females were assessed for estrous cycle stage immediately prior to sacrifice and were placed in one of three categories: proestrus, diestrus, or estrus. Aged-matched male rats of the same strains were included in the transcriptome studies. RNA-Seq was used to measure expression levels of RNA transcripts (>200 bp long) in whole brain. More than 300 genes displayed differences in expression level related to stage of the estrous cycle, and of these transcripts, approximately 73% showed strain-specific differences in expression. Furthermore, over 100 genes were differentially expressed between male and female rats when ignoring estrous cycle and only 31% of these sex differences were influenced by strain. These results indicate that not only does the stage of the estrous cycle influence RNA transcription levels in the brain, but these estrous cycle effects may differ due to genetics to a greater degree than general sex effects.