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Genetic liability for internalizing versus externalizing behavior manifests in the adult hippocampus: A comparison of the results of transcriptional profiling studies performed in eight bred rat models

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Background: For over 17 years, we have selectively-bred rats for either high or low levels of exploratory activity within a novel environment. These “bred High Responder” (bHR) and “bred Low Responder” (bLR) rats model temperamental extremes, exhibiting large differences in internalizing and externalizing behaviors relevant to mood and substance use disorders.

Methods: We previously characterized persistent differences in gene expression related to bHR/bLR phenotype in the adult hippocampus, a region critical for emotional regulation, by meta-analyzing five transcriptional profiling datasets (microarray, RNA-Seq) spanning 43 generations of selective breeding ($n=46$). We compared our results to published results or re-analyzed data from nine publications profiling hippocampal expression in other bred/genetic rat models targeting behavioral traits that we considered extremes on the internalizing/externalizing spectrum: Flinders Sensitive (vs. Flinders Resistant or Sprague-Dawley), Wistar Kyoto (vs. Fischer 344), Wistar More Immobile (vs. Wistar Less Immobile), Congenitally Learned Helpless (vs. No Learned Helpless), Roman Low Avoidance (vs. High Avoidance), Syracuse Low Avoidance (vs. High Avoidance), and High Anxiety within the NIH Heterogeneous Stock (vs. Low Anxiety).

Results: Within our meta-analysis, the effect of bHR/bLR phenotype on gene expression was significant for 74 genes ($FDR < 0.05$, out of 16,269). One third (25/74) had been previously identified as differentially expressed in the hippocampus of other bred rat models related to internalizing/externalizing behaviors and 10% (8/74) had been identified by more than one study.

Conclusion: By cross-referencing hippocampal transcriptional profiling results across eight bred/genetic rat models we pinpoint strong candidates for mediating the influence of selective breeding on internalizing/externalizing behavior.