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On the Alignment of Gene Expression with Delay Discounting (DD) in Heterogeneous Stock (HS) Rats

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Only a handful of studies have focused on how gene expression aligns with delay discounting (DD). Establishing this connection will be essential to understanding the role of DD in the genetics of substance abuse. 200 HS/NIH rats were phenotyped for DD using an adjusting amount procedure. Two phenotypic features were extracted: lnk (hyperbolic discounting function) and the traditional area under the curve (AUC). AUC and lnk were only moderately correlated (r = -0.33). Bulk RNA-Seq data (25 million paired end reads) were obtained from 3 brain regions: basolateral amygdala (BLA), nucleus accumbens core (NAcC) and the prelimbic cortex (PL). Across all three brain regions, genes negatively correlated ($p < 0.05$) with lnk were enriched in genes (FDR < 0.01) associated with the translation of mitochondrial genes. In the BLA, genes positively associated with DD, were enriched in ontologies associated with the regulation of neuronal development and signal transduction. Key genes included *Grin2a, Grin2b* and *Grm5.* In the PL, genes with the same ontology were detected but here the genes were positively associated with the AUC i.e. the apparent functionality was the opposite of the BLA related genes. The PL glutamate related genes included *Grin2c, Grin2d* and *Grik5*. Of interest, in the BLA the genes positively associated with the AUC are highly enriched (FDR < 10^{-5}) in ontologies associated with the primary cilium. In conclusion and to our knowledge, these are the first data to examine from a multi-region and genome-wide perspective, gene expression and DD. Supported by DD 046077.