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Meta-analysis of transcriptomic changes in prefrontal cortex after chronic social defeat stress

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Motivation and Aim: Chronic social defeat stress (CSDS) is a valid classic model of depression in rodents. The use of animal models of depression opens new horizons in research of molecular brain changes.

Methods and Algorithms: Here we report a meta-analysis of transcriptomic changes in prefrontal cortex (PFC) of C57BL/6 male mice. We searched for all case-control studies on CSDS with 10 or 30 days duration that reported RNA sequencing measurements on PFC in C57BL/6 male mice and integrated it with our own transcriptomic data.

We analyzed stress effects after 10 days of CSDS (5 datasets), 30 days of CSDS (2 datasets) and compared resilient and susceptible to stress animals that were identified in 2 studies after 10 days of CSDS. RNA-seq data were subjected to standard pipeline: preprocessed with fastp v0.20.1, mapped to GRCm38 using HISAT2 aligner v2.2.1 and quantified with featureCounts v2.0. Differential gene expression analysis was performed via the DESeq2 R-package. Genes with p-adj < 0.05 were designated as differentially expressed genes (DEGs). GSEA was conducted using gseGO function from ClusterProfiler (v4.0.5) R package.

Results: We found 17 DEGs (11 upregulated and 6 downregulated) in CSDS10 group compared to control. 10 days of CSDS lead to upregulation of genes involved in neuroinflammation (*Vwf, Il1r1, Il6ra*), oxidoreductase activity (*Hbb-bt, Hbb-bs*) and melanocortin receptor 4 gene (*Mc4r*) involved in energy homeostasis. Change in expression of glucocorticoid responsive genes wasn't unidirectional (*Fkbp5* upregulated, *Hsd11b1* downregulated). GSEA showed that 10 days of CSDS resulted in activation of gene expression related to social behavior, regulation of T cell cytokine production and neural tube patterning.

When comparing resilient and susceptible to stress mice we identified 92 DEGs (23 upregulated and 69 downregulated). Most downregulated genes in susceptible compared to resilient mice were oligodendrocyte-specific. Susceptible mice were shown to have lowered expression of myelin-related genes – structural (*Mbp, Mal, Mobp, Plp1*), enzymes (*Ugt8a*), transcription factor – *Olig2* etc.

The biggest changes we saw were in CSDS30 group with 580 DEGs (303 upregulated and 277 downregulated). Upregulated genes are involved in the following processes – transcription (*Polr2k, Polr2g, Rbbp4*), translation (*Eif1, Eif2s2*), alternative splicing (*Snrpa1, Snrpd1, Snrpd2, Snrpe, Snrpg*) and ATP synthesis (*Atp5g3, Atp5e, Atp5j, Atp5k, Atp5l, Atp5o*). While downregulated genes are involved in NMDA receptor signaling (*Grin1, Grin2c, Camk2g*), neuronal trafficking (*Htt, Disc1*) and steroid receptor modulators (*Ncor2, Ncoa3, Bcor*).

Conclusion: Collectively, our results on PFC gene expression changes suggest that (1) the most persistent expression changes induced by 10 days of CSDS are associated with glucocorticoid signaling, neuroinflammation, and oxidoreductase activity; (2) susceptibility to 10 days of CSDS is strongly associated with a decrease in the expression of key genes associated with myelination processes: 3) 30 days of CSDS lead to changes in energy-consuming processes such as transcription and translation, the activation of these processes is probably required for adaptation at the cellular level under conditions of prolonged chronic stress.

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