# Gene-environment interaction in myelin plasticity after chronic psychosocial stress

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## Background

- Anxiety disorders have genetic predisposition, but mechanisms underlying the interaction of genetic and environmental risk factors are poorly understood.
- We used unbiased gene expression profiling in a mouse model to identify biological pathways underlying stress-induced anxiety.

## 1. Genetic background strongly modulates mouse behavioral response to chronic stress

- The chronic social defeat stress (CSDS) model involves brief confrontations of two male mice, repeated for 10 days. Consequently, some mice (susceptible) develop social avoidance, while others do not (resilient).
- We identified a strong genetic background effect in CSDS-induced social avoidance in four inbred mouse strains [C57BL/6NCrl (B6), BALB/cAnNCrl (BALB), 129S2/SvPasCrl (129), and DBA/2NCrl (D2), Fig. 1].

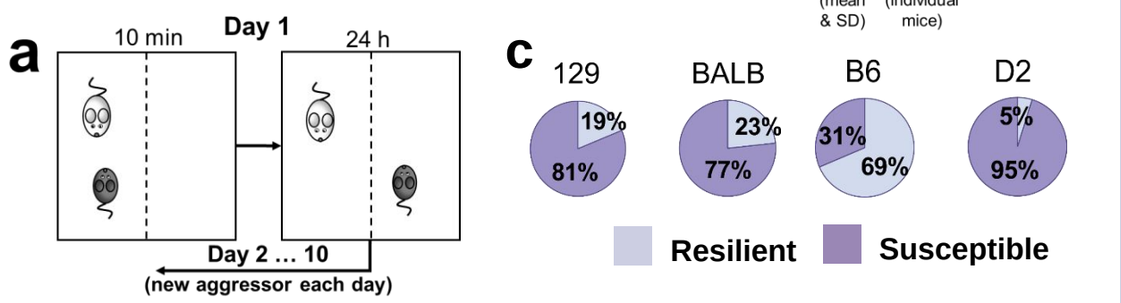



**Figure 1.** CSDS procedure (**a**), division of resilient (Res) and susceptible (Sus) mice after CSDS (**b**), distribution of phenotypes in 4 inbred strains (**c**).

## 2. Oligodendrocyte genes are over-represented among differentially expressed genes after CSDS

- We performed RNA-seq on medial prefrontal cortex (mPFC), bed nucleus of the stria terminalis (BNST) and ventral hippocampus (vHPC) after CSDS in stress susceptible, resilient and control B6 and D2 mice.
- RNA-seq: rRNA-depleted total RNA, cDNA libraries sequenced with Illumina NextSeq.
- Gene set enrichment analysis: GSEA Desktop v3.0. Differentially expressed genes were compared to a database of curated gene sets to determine enrichment of genes in specific sets.

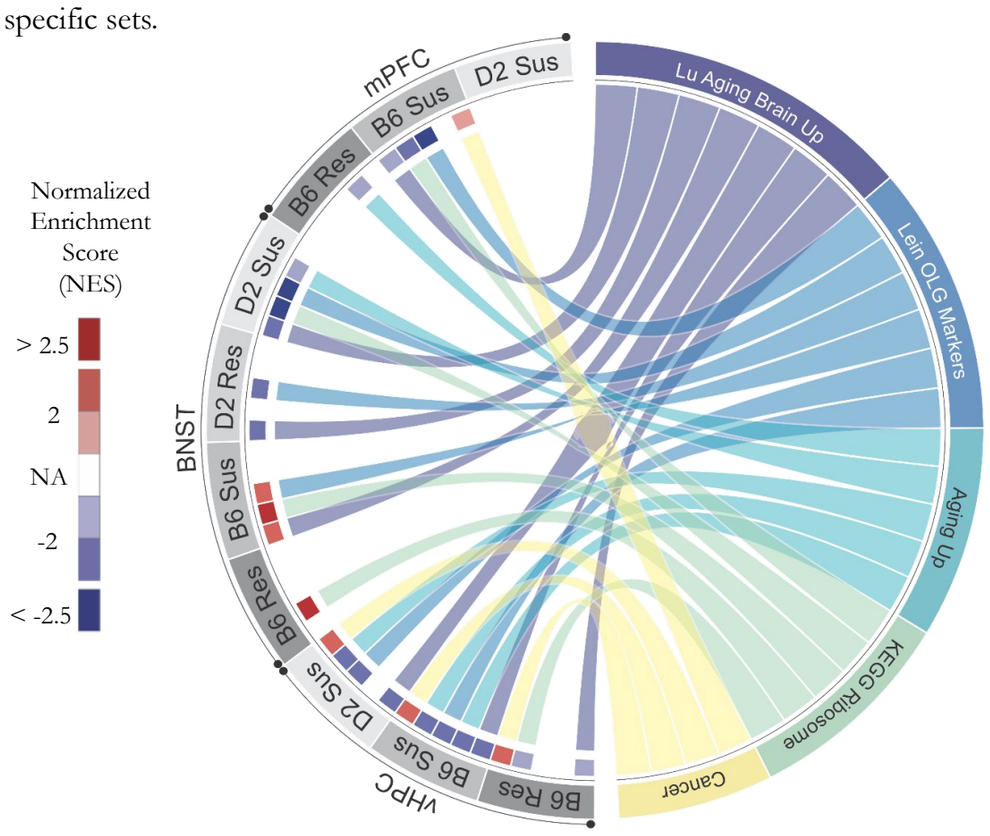
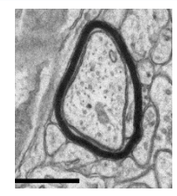



**Figure 2.** Circos diagram showing top enriched gene sets. Genes in the "Lein OLG markers" (blue) set were significantly enriched in 6/10 comparisons (susceptible (Sus) / resilient (Res) vs. same-strain control). A positive normalized enrichment score (NES) indicates enrichment of upregulated genes, and a negative NES shows enrichment of downregulated genes.

## 3. Region and strain-specific differences in myelin thickness after chronic stress in mice

- We quantified myelin thickness after CSDS using transmission electron microscopy (Fig. 3). We divided the axons into three groups based on diameter without the myelin sheath (small, medium or large).



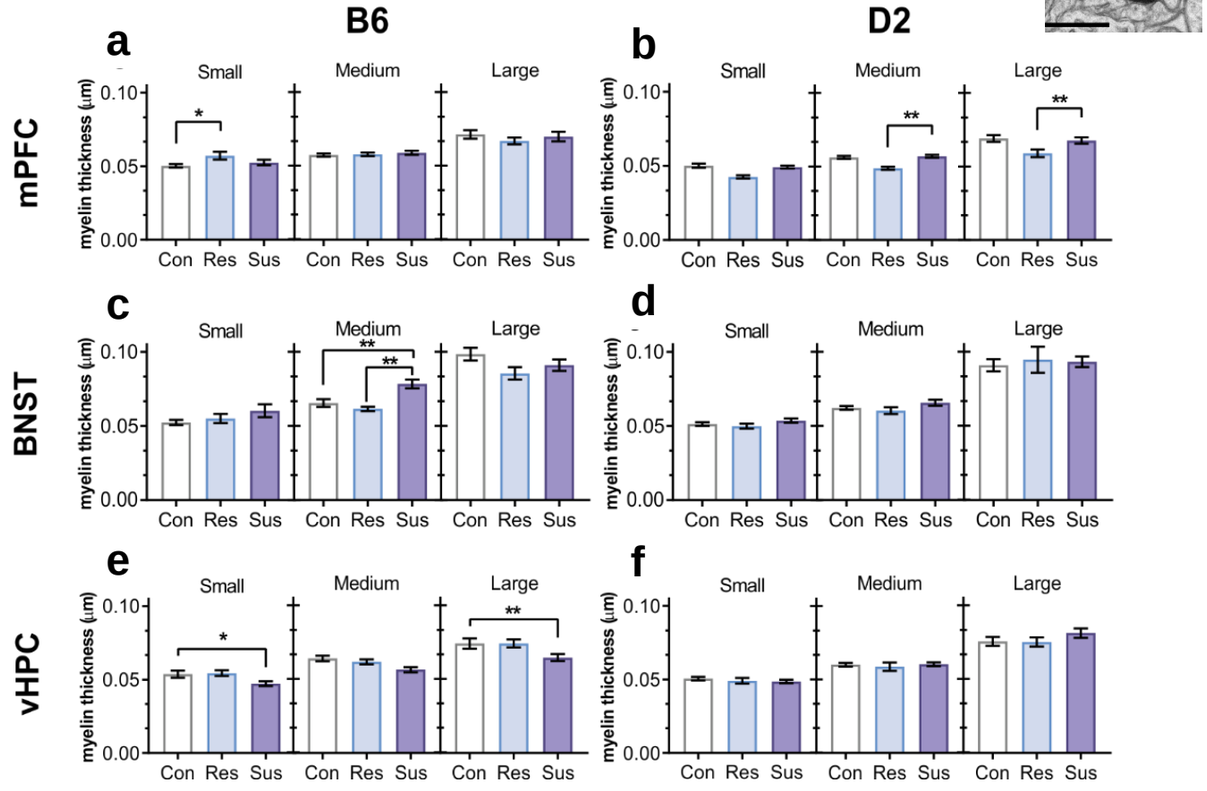



**Figure 3.** Myelin thickness in resilient (Res), susceptible (Sus) and control (Con) B6 and D2 mice.

## 4. Myelin plasticity is specific to stress-associated brain regions

- We measured the thickness of the corpus callosum after stress in sections stained with a myelin-binding anti-CNPase antibody (Fig. 4).
- We quantified the expression levels of myelin-related genes (*Opalin, Ermn, Mobp, Plp1* and *Mbp)* in the dorsal hippocampus, hypothalamus and cortex by q-RT-PCR. Only *Opalin* was expressed on a lower level in the hypothalamus of D2 susceptible mice compared to controls ($p = 0.006$).

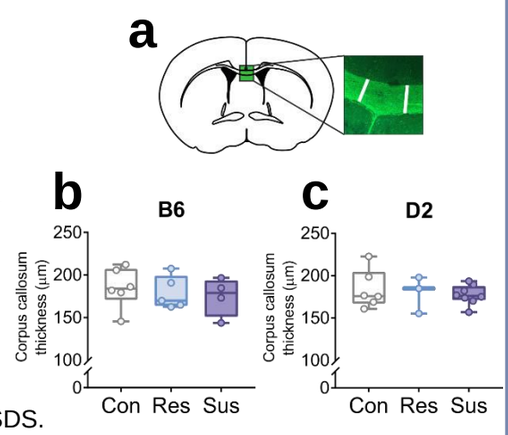



**Figure 4.** No differences in corpus callosum thickness after CSDS.

## 5. Subclinical anxiety in humans associates with higher mean diffusivity at the forceps minor

- To investigate if white matter structure is altered in human anxiety, we carried out diffusion tensor imaging in young adults with or without anxiety symptoms (Fig. 5).

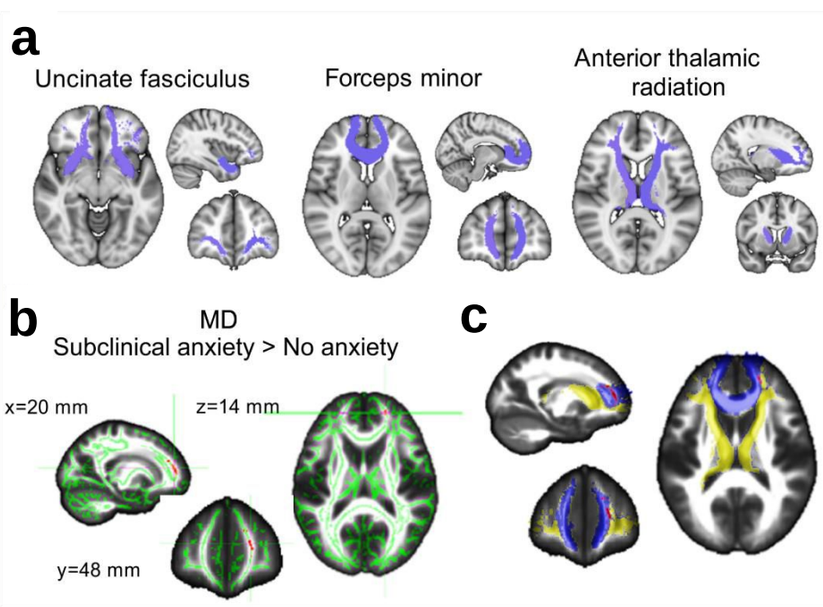



**Figure 5. Diffusion tensor imaging in young adults.** (**a**) ROIs selected for tract-based analysis. (**b-c**) Regions of higher mean diffusivity (red) in participants with subclinical anxiety (score ≥ 2 on the Brief Psychological Rating Scale) vs participants with no anxiety ($p_{FWER} < 0.01$).

## Conclusions

- Genetic background influences behavioral and transcriptomic responses to chronic psychosocial stress.
- Myelin plasticity was one of the major responses to chronic psychosocial stress.
- Myelin thickness differences varied between stress-associated brain regions, suggesting that stress resilience involves active changes to myelin thickness, potentially influencing axonal conduction and spatial synchronization.
- Identification of genetic regulators of the myelin stress response will provide mechanistic insight into the molecular basis of anxiety, a critical step in developing targeted therapy.

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