

Supplementary figure legends

Supplementary figure 1. Experimental timeline and methods utilized in the study. Mice were exposed to chronic social defeat stress (CSDS) on 20 consecutive days and were then subjected to the social interaction (SI) test to evaluate social avoidance, tail suspension test (TST) to evaluate despair-like behavior, and the sucrose preference test (SPT) to evaluate anhedonia. Mice with single depressive-like phenotypes, along with stress-resilient and stress-naïve controls, were selected for single-cell RNA-sequencing (scRNA-Seq) of the habenular complex.

Supplementary figure 2. Receiver operating characteristic (ROC) curves of behavioural assays and phenotypic comparisons of behavioural measures. (A,C,E) ROC curves representing the true positive rate (TPR) and false positive rate (FPR) of a binary classifier for different threshold values on the social interaction test (A), sucrose preference test (C), and tail suspension test (E). The dashed line represents the performance of a random classifier, and the red lines highlight the optimal TPR-FPR pairs used to select threshold values for the behavioural measures. (B,D,F) Behavioural measure comparisons between single behavioural phenotypes and stress-resilient and stress-naïve controls for the social interaction test (B), sucrose preference test (D), and tail suspension test (F). Note: * <0.05 , ** <0.01 , *** <0.001

Supplementary figure 3: Cell type composition across behavioural phenotypes. Stacked bar plots showing the relative proportions of major cell types within each behavioural phenotype (control, resilient, SI, SPT, susceptible, and TST). This analysis confirmed that transcriptional differences between phenotypes were not confounded by unequal representation of specific cell types.

Supplementary figure 4: This image displays six Venn diagrams, each representing the DE genes in specific cell types when comparing a Phenotype group against the Control group. The cell types examined are Astrocytes, Microglia, Endothelial cells, Fibroblasts, and Macrophages. Each Venn diagram illustrates the overlap and unique sets of DE genes across four categories: Resilient, SI, SPT, Susceptible, and TST. The numbers within the overlapping regions and unique segments represent the count of DE genes shared or specific to those categories.

Supplementary figure 5. The UpSet plots display intersections of differentially expressed genes across the five phenotypes (SPT, SI, TST, Resilient, Susceptible). Blue color represents downregulated genes, and red color represents upregulated genes. For each plot, bar heights indicate the size of each gene intersection, while the filled and connected dots show which phenotypes contribute to each intersection set.

Supplementary figure 6. Cross-species conservation of human habenula marker signatures across recovered mouse habenular subregions and phenotype-associated transcriptional overlap. (A) Heatmap showing conservation of mapped human habenula marker modules across recovered mouse lateral habenula (LHb) and medial habenula (MHb) subregions. Values indicate the mean z-scored module score for each human marker population across mouse regions. (B) Summary table showing the top calibrated human match for each recovered mouse habenula subtype across three complementary metrics: marker-gene overlap, module-score conservation, and rank-correlation-based matching. (C&D). Heatmaps showing Fisher's exact test enrichment of phenotype-associated differentially expressed gene lists across recovered LHb (C) and MHb (D) subregions. Columns indicate mouse phenotype-associated DE lists, and rows indicate

recovered mouse subregions. Numbers denote overlapping genes, and color intensity represents $-\log_{10}$ false discovery rate (FDR).