A Meta-Analysis of the Effects of Chronic Stress on the Prefrontal Transcriptome in Animal Models and Convergence with Existing Human Data

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Competing Interests

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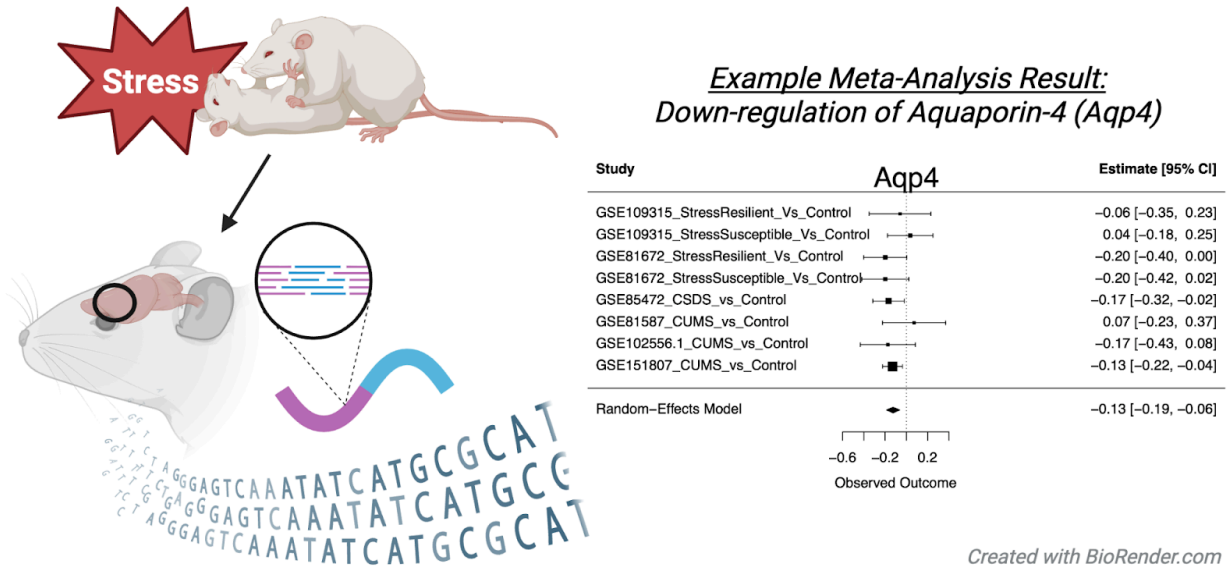
CRediT Statement

JX: Conceptualization, Methodology, Software, Formal analysis, Investigation, Data Curation, Writing - Original Draft, Writing - Review & Editing, Visualization
MHH: Conceptualization, Methodology, Software, Formal analysis, Writing - Original Draft, Writing - Review & Editing, Validation, Visualization, Supervision, Project administration
CAR: Methodology, Writing - Review & Editing
NRC: Writing - Review & Editing
EIF: Methodology, Writing - Review & Editing
EH: Methodology, Writing - Review & Editing
DMN: Methodology, Writing - Review & Editing
AS: Methodology, Writing - Review & Editing
TQD: Writing - Review & Editing
SJW: Writing - Review & Editing, Funding acquisition
HA: Writing - Review & Editing, Supervision, Funding acquisition

Data Availability Statement
All datasets used in this publication are publicly available In the National Center for Biotechnology Information (NCBI) Repository Gene Expression Omnibus (GEO, https://www.ncbi.nlm.nih.gov/geo/) under the accession numbers GSE84572, GSE109315, GSE81672, GSE81587, GSE102556, and GSE151807.

Graphical Abstract



Key Points

- Chronic stress is linked to many human psychiatric disorders involving the prefrontal cortex (PFC).
- Meta-analysis showed that stressed mice had less gene expression for glia and neural activity in the PFC.
- PFC gene expression in chronically stressed mice mirrors patterns seen in psychiatric patients.

Plain Language Summary

Chronic stress has been shown to have lasting effects on the brain, contributing to cognitive impairments and the risk of psychiatric disorders such as anxiety, depression, and post-traumatic stress disorder. The prefrontal cortex, a brain region that is important for behavioral and attentional control, is sensitive to chronic stress. We combined information from six public mouse datasets to identify consistent effects of chronic stress on gene expression (mRNA) in the prefrontal cortex. In these studies, mice that had experienced chronic stress showed a decreased amount of mRNA related to a variety of non-neuronal support cells (glia) and blood vessels, and general neural activity. The mouse chronic stress signature overlapped with gene-activity patterns reported in human psychiatric conditions, suggesting a biological bridge between chronic stress and the onset of psychopathology.

Abstract

Background: Chronic stress is a major risk factor for psychiatric disorders, including anxiety, depression, and post-traumatic stress disorder. Chronic stress can cause structural alterations like grey matter atrophy in key emotion-related areas such as the prefrontal cortex (PFC). To identify biological pathways affected by chronic stress in the PFC, researchers have performed transcriptional profiling (RNA-sequencing, microarray) to measure gene expression in rodent models. However, transcriptional signatures in the PFC that are shared across different chronic stress paradigms and laboratories remain relatively unexplored.

Methods: We performed a meta-analysis of publicly available transcriptional profiling datasets within the *Gemma* database. We identified six datasets that characterized the effects of either chronic social defeat stress (CSDS) or chronic unpredictable mild stress (CUMS) on gene expression in the PFC or medial prefrontal cortex (mPFC) in mice (n=117). We fit a random effects meta-analysis model to the chronic stress effect sizes (log(2) fold changes) for each transcript (n=21,379) measured in most datasets. We then compared our results with two other published chronic stress meta-analyses, as well as transcriptional signatures associated with psychiatric disorders.

Results: We identified 133 genes that were consistently differentially expressed across chronic stress studies and paradigms (false discovery rate (FDR)<0.05). Fast Gene Set Enrichment Analysis (fGSEA) revealed 53 gene sets enriched with differential expression (FDR<0.05), dominated by glial and neurovascular markers (*e.g.,* oligodendrocyte, astrocyte, endothelial/vascular) and stress-related signatures (*e.g.,* major depressive disorder, hormonal responses). Immediate-early gene markers of neuronal activity (*Fos, Junb, Arc, Dusp1*) were consistently suppressed. Many of the identified effects resembled those seen in previous meta-analyses characterizing stress effects (CSDS, early life stress), despite minimal overlap in included samples. Moreover, some of the differential gene expression resembled previous observations from stress-related psychiatric disorders, including alcohol abuse disorder, major depressive disorder, bipolar disorder, and schizophrenia.

Conclusion: Our study demonstrates that chronic stress induces a robust, cross-paradigm PFC signature characterized by down-regulation of glia/myelin and vascular pathways and suppression of immediate-early gene activity, highlighting cellular processes linking chronic stress exposure, PFC dysfunction, and the onset of psychiatric disorders.

Keywords: prefrontal cortex, chronic stress, microarray, RNA-Seq, meta-analysis

Introduction

Stress is defined as the psychophysiological response triggered by an actual or perceived threat (Schneiderman et al., 2005). Acute stress usually does not pose a significant health risk, especially in young and healthy individuals. Indeed, some level of activation of the stress system is essential at the neurobiological and functional level (McEwen & Akil, 2020). Chronic stress, however, can exceed the system's capacity to return to homeostasis, resulting in high allostatic load coupled with structural alterations in key brain regions (Schneiderman et al., 2005; McEwen et al., 2016), impairment in cognitive functions, such as learning and memory (Lupien et al., 2009), and the development of psychiatric disorders, including major depressive disorder (MDD) and post-traumatic stress disorder (PTSD) (Musazzi et al., 2023; Westfall et al., 2021).

To study chronic stress, researchers use diverse paradigms in laboratory rodent models including, but not limited to, social isolation, chronic mild stress, repeated restraint stress, chronic social defeat stress (CSDS), social instability stress, and chronic unpredictable/variable stress (CUMS) (Touchant & Labonté, 2022; Becker et al., 2021). Animals subjected to these different stress paradigms can manifest different responses but also show common behavioral phenotypes. For example, social isolation, early life stress, and chronic variable stress have all been shown to induce anxiety-like and depression-like behaviors (Touchant & Labonté, 2022). These models revealed that vulnerability and resilience to stress-related emotional disorders are likely affected by an interaction of genetic inborn differences, epigenetic programs, and environmental factors (Clinton et al., 2022).

A comprehensive understanding of stress responses requires focusing on effects within the brain. One key brain region in stress regulation is the prefrontal cortex (PFC). PFC is involved in emotional processing and cognition (Gray et al., 2002). Chronic stress has been shown to cause structural and functional changes in the PFC, including retraction in the dendrites and dendritic spines of pyramidal cells (Arnsten, 2009).

Analyzing stress-induced changes in gene expression within the PFC may improve our understanding of the etiology of stress-sensitive disorders. Transcriptional profiling, such as RNA sequencing (RNA-Seq) and microarray, can yield a large volume of information about the functional effects of stress-related interventions, yet there are also many challenges, including technical variation (Hicks et al., 2018) such as "batch effects" (Johnson et al., 2007) and sample heterogeneity (Hagenauer et al., 2018). These studies are often conducted with small sample sizes, which increases the likelihood of both false negative and false positive results due to low statistical power (Button et al., 2013).

To draw a more conclusive picture of stress-induced gene expression changes in the PFC, we conducted a meta-analysis of transcriptional profiling data from publicly available datasets investigating the effect of chronic stress on PFC gene expression in rodents. To minimize bias, we used standardized and systematic methods to identify, extract, and exclude datasets and run the meta-analysis. These methods enabled us to identify PFC transcriptional signatures related to chronic stress that are consistent across experiments and chronic stress paradigms. To strengthen the validity of our findings, we compared our results with recent related meta-analyses and systematic reviews that employed different methodological approaches. (Duan et al., 2025; Gururajan, 2022; Reshetnikov et al., 2022; Stankiewicz et al., 2022a). Additionally, we explored the relationship between chronic stress-induced transcriptional changes and those observed in stress-related psychiatric disorders by comparing our findings with large-scale meta-analyses of data from human cortical tissue (Gandal et al., 2018; Piras et al., 2022). These comparisons

allowed us to examine the translational relevance of our findings and identify convergent molecular signatures across different stress paradigms and stress-related psychiatric conditions.

Methods

Meta-Analysis Methods

General Overview: This meta-analysis was conducted as part of the *Brain Data Alchemy Project,* a collective effort to improve the reliability and generalizability of transcriptional profiling findings using meta-analyses of public datasets. This guided effort uses a standardized pipeline for dataset identification, inclusion/exclusion, and meta-analysis (protocol for 2022: (Hagenauer et al., 2024), example validation: (Rhoads et al., 2025), *not pre-registered*). It capitalizes on the data curation, preprocessing, and analysis efforts of the Gemma database (Lim et al., 2021; Zoubarev et al., 2012). Gemma currently houses >19,000 re-analyzed transcriptional profiling datasets, with preprocessing that includes up-to-date microarray probe alignment and RNA-Seq read mapping, sample and gene-level quality control, and identification of potential batch confounds. Within Gemma, differential expression analyses are performed using the *limma* (microarray) or *limma-voom* (RNA-Seq) pipeline, providing users with outputs from both the omnibus (full dataset) tests and individual contrasts. The R code (R v.4.2.0, R studio v.2022.02.4) for our analyses is released at: *https://github.com/Jinglin0320/Metaanalysis_GemmaOutput_CSDS_PFC_Jinglin*.

Dataset Identification and Selection: Potential datasets were identified in the Gemma database (https://gemma.msl.ubc.ca/home.html) using pre-specified search terms related to chronic stress paradigms (*n*=174 datasets), and narrowed using standardized inclusion/exclusion criteria (**Figure 1**). Females were excluded because there was only a single available study in females (Deonaraine et al., 2020) and stress responses can differ greatly by sex (Takahashi, 2021). To keep the project manageable, we narrowed the datasets down further to CSDS and CUMS paradigms because these two models are well-established and widely used to model MDD (Gururajan et al., 2019; Nestler & Hyman, 2010). These two models have been shown to exhibit overlapping effects on the transcriptome, proteome, and metabolome in other brain areas (Gui et al., 2021; Li et al., 2023), potentially due to the highly unpredictable nature of the stressors. We excluded one study that used a non-standard CSDS protocol, exposing a single intruder to three resident mice for 2 h per day for 6 days. (Wang et al., 2019). Preprocessed gene expression data was confirmed to fall into a range typical for log(2) expression (RNA-seq: -5 to 12, microarray: 4 to 15). One dataset (GSE114224) was excluded because it had a highly restricted range, suggesting miscalculation.

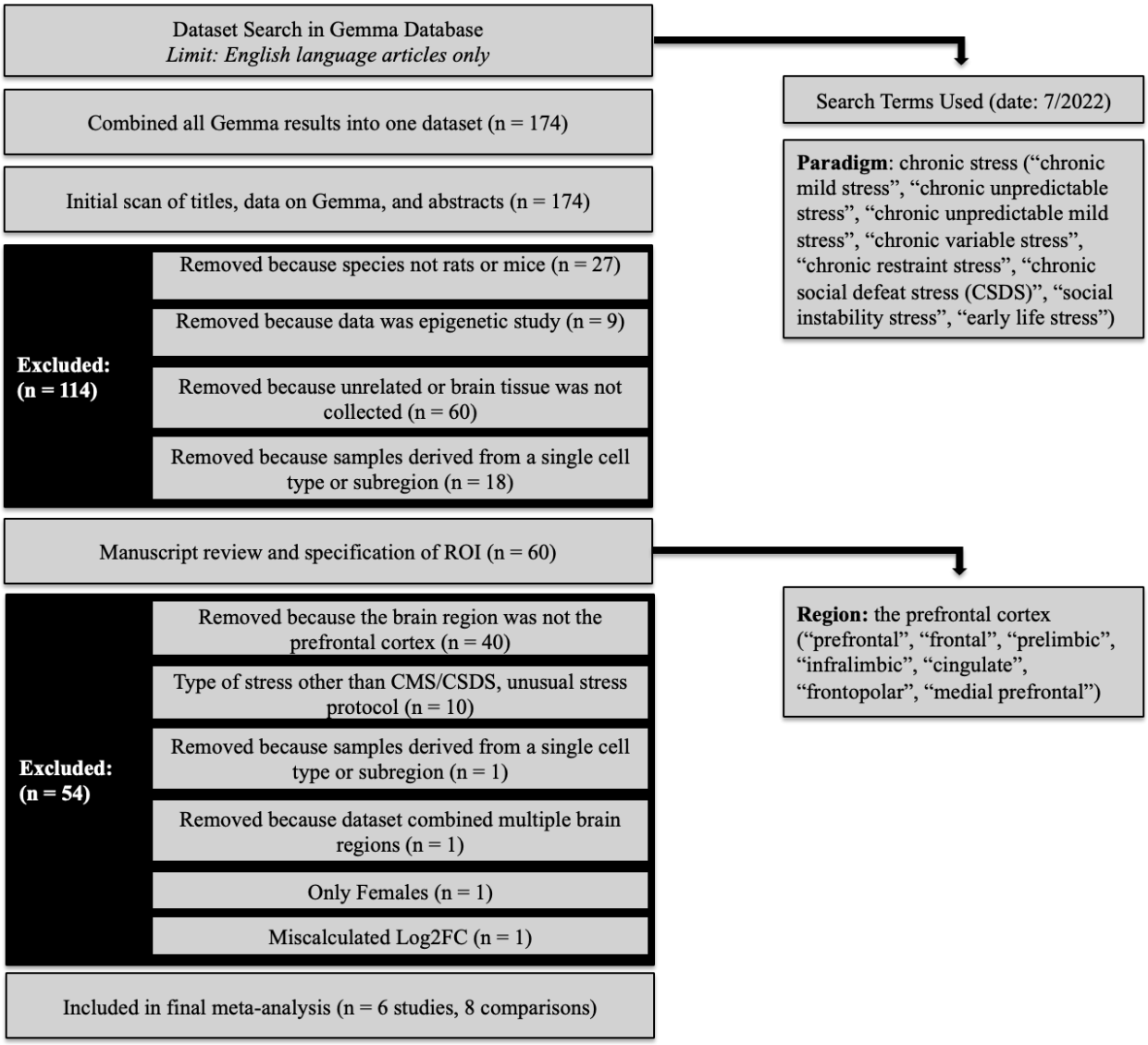


Figure 1. PRISMA diagram illustrating the dataset search terms and selection criteria used for the meta-analysis. Abbreviations: ROI=Region of Interest, Log2FC=Log(2)Fold Change, n= number of datasets.

Characteristics of the Selected Datasets: Six studies survived our criteria (*n*=8 stress vs. control contrasts, **Table 1**). Three studies employed the CSDS paradigm followed by a social interaction test to classify the mice into either a stress susceptible or stress resilient group. One of these studies administered CSDS for 14 days, with 5-minutes of daily contact with the aggressor (Lehmann et al., 2017). The other two studies applied CSDS for 10 days, with one study using 10-minutes of daily contact with the aggressor (Laine et al., 2018) and the other 5-minutes (Bagot et al., 2017). The other three studies utilized the CUMS paradigm. Animals were exposed to alternating stressors for either three weeks (Ma et al., 2016; Labonté et al., 2017) or four

weeks (Yu et al., 2021). Altogether, there was a final sample size of *n*=117 subjects, which should be sufficiently powered (80% power at alpha=0.05) to detect medium effect sizes.

ID Number	n	Species	Authors	Year	Platform	Tissue	Type of Stress	Stress Duration	Comparisons of Interest
GSE84572	12	mouse	Lehmann et al.	2017	Microarray (Affymetrix)	mPFC	CSDS	14 days, 5 min/day	Susceptible vs. Control
GSE109315	32	mouse	Laine et al.	2018	RNA-seq	mPFC	CSDS	10 days, 10 min/day	Susceptible vs. Control, Resilient vs. Control
GSE81672	25	mouse	Bagot et al.	2017	RNA-seq	PFC	CSDS	10 days, 5 min/day	Susceptible vs. Control, Resilient vs. Control
GSE81587	4	mouse	Ma et al.	2016	RNA-seq	mPFC	CUMS	3 weeks	CUMS vs. Control
GSE102556.1	38	mouse	Labonté et al.	2017	RNA-seq	PFC	CUMS	3 weeks	CUMS vs. Control
GSE151807	6	mouse	Yu et al.	2021	Microarray (Affymetrix)	PFC	CUMS	4 weeks	CUMS vs. Control

Table 1. Overview of the datasets included in the meta-analysis. The table lists the Gene Expression Omnibus (GEO) ID for the dataset, sample size (n), authors and year of publication, and transcriptional profiling platform. Study details include the brain region examined, the type of chronic stress, the duration of stress, and the specific experimental groups included in the statistical comparisons (contrasts) extracted for inclusion in the meta-analysis. Abbreviations: mPFC (medial prefrontal cortex), PFC (prefrontal cortex), CSDS (chronic social defeat stress), CUMS (chronic unpredictable mild stress).

Result Extraction: The differential expression results for each of the relevant eight stress-related statistical contrasts (stress vs. control) were imported into R. Rows with probes or transcript sequences that mapped to multiple gene annotations (official gene symbol) were excluded, and gene-level average effect sizes (log(2) fold change or Log2FC), standard errors (SE), and sampling variances (SV) were calculated and aligned across datasets by gene symbol.

Meta-Analysis: To perform the meta-analysis, we used the *metafor* package (v.3.4.0, (Viechtbauer, 2010)) to fit a random effects model to the effect sizes of chronic stress (Log2FC values) and accompanying SV for each gene represented in at least five stress vs. control statistical contrasts (*n*=21,379 genes). A minimum of five stress vs. control contrasts was chosen to ensure that a minimum of at least three studies were represented in the meta-analysis, to increase the power and generalizability of the results. Random effects modelling was chosen to account for the heterogeneous methods and sample characteristics across the included studies that might introduce variability amongst their true effects. To fit the random effects model, we used the function *rma()* from the metafor package, which treats this heterogeneity as purely random (normally distributed), estimated using restricted maximum-likelihood estimation (REML). The function uses the inverse-variance method, which treats the precision of each study's estimated effect as inversely related to the study's SV. Due to limited dataset availability, we used a simple, intercept-only model as our main outcome. The resulting p-values were

corrected for false discovery rate (FDR) using the Benjamini-Hochberg method (*multtest* package: v.2.8.0, (Pollard et al., 2005)).

Functional Ontology: To identify functional patterns, fast Gene Set Enrichment Analysis (fGSEA: (Sergushichev, 2016)) was performed on the meta-analysis results, ranked by estimated Log2FC, using Brain.GMT (Hagenauer et al., 2024) and associated example code (https://github.com/hagenaue/Brain_GMT). Brain.GMT is a curated database of gene sets related to nervous system function, tissue, and cell types, packaged with traditional gene ontology gene sets (MSigDB "C5": 14,996 gene sets).

Comparison of Meta-Analysis Results to Related Studies:

Other Meta-Analyses Examining Chronic Stress Effects on the Rodent PFC: While conducting our study, several meta-analyses were published addressing the effects of chronic stress on the PFC. These included a meta-analysis of the effects of either 10 days or 30 days of CSDS (Reshetnikov et al., 2022), and a meta-analysis of the effects of chronic stress, broadly defined (CSDS, CUMS, or chronic restraint) (Gururajan, 2022). Although both of these meta-analyses used public RNA-Seq data, due to differing inclusion/exclusion criteria they showed either only small partial overlap with our own sample (*10 days CSDS*: n=56, overlap 15%: n=18 of our 117; *Chronic Stress:* n=101, overlap 32%: 37 of our 117) or no overlap (*30 days CSDS:* n=20), and therefore could provide some independent insight into our findings. Results from the CSDS meta-analyses were extracted from *Table STS3A* (*10 Days CSDS*) and *Table STS3B* (*30 Days CSDS*) (Reshetnikov et al., 2022), which only contained results for genes surviving a nominal $p<0.05$ threshold (*10 Days CSDS*: 1968 genes; *30 Days CSDS*: 3132 genes). Results from the chronic stress meta-analysis were extracted from *Suppl Table 1G* (*"Combined Analysis"*) (Gururajan, 2022), which only contained results for genes surviving an FDR<0.05 threshold (160 genes).

Other Large Studies Characterizing Stress Effects on the Rodent Brain: We also compared our results to other studies examining stress effects on the brain using large sample sizes. These included a meta-analysis of the effects of early life stress on the prefrontal transcriptome ((Duan et al., 2025): *n*=89, full results for all genes extracted from *Table S1*) and a large study examining the effects of chronic daily corticosterone on the hippocampal transcriptome ((Juszczak et al., 2025): *n*=48, full results for all genes extracted from *Suppl Data 2 ("All")).* The supplement for (Juszczak et al., 2025) also provided a comprehensive database including results from large *"vote-counting"*-style literature reviews characterizing the direction of effect (up, down, mixed effects) for genes showing reported effects of acute and chronic stress in brain transcriptomic studies (Stankiewicz et al., 2022): mice (58 studies), rats (20 studies), squirrel monkeys (1 study)). Finally, we ran comparisons with the effects of acute stress and corticosterone treatment (Jaszczyk et al., 2023; Juszczak et al., 2025; Stankiewicz et al., 2022a) and acute sleep deprivation (Diessler et al., 2018; Rhoads et al., 2025), which are more tangential and relegated to the supplement.

Large Studies Characterizing the Effects of Stress-Related Psychiatric Disorders on the Human Cortex: We compared our results to the effects of stress-related psychiatric disorders on cortex. These included several large meta-analyses examining the effects of suicide in different regions of the frontal cortex ((Piras et al., 2022) : *n*=380). Results were extracted from *Table S1*, which contained results for genes surviving an FDR<0.05 threshold in any of the four

meta-analyses. We also referenced large microarray meta-analyses characterizing the effects of multiple psychiatric disorders on the cortical transcriptome (MDD (*n*=176), Bipolar Disorder (*n*=197), and Schizophrenia (*n*=314)), and a re-analysis of the effects of Alcohol Abuse Disorder on the superior frontal cortical transcriptome (n=32) (*Table S1* in (Gandal et al., 2018): results for all genes), as well as two large validation meta-analyses of RNA-Seq data characterizing the effects of Bipolar Disorder (*n*=171) and Schizophrenia (*n*=384) in the frontal cortex (*Table S2* in (Gandal et al., 2018): results for all genes). It is important to note that the results of these psychiatric meta-analyses can only be considered partially independent: the Bipolar Disorder and Schizophrenia microarray meta-analyses share an overlapping set of comparison control subjects, which also partially overlap the MDD microarray meta-analysis. Likewise, the Bipolar Disorder and Schizophrenia RNA-Seq meta-analyses share an overlapping set of control subjects. In contrast, there was no overlap between the samples included in the large meta-analyses of (Gandal et al., 2018) and (Piras et al., 2022). We also compared our meta-analysis results to a review of reported PTSD effects on the PFC transcriptome ((Stankiewicz et al., 2022): *n*=121), summarized in terms of categorical direction of effect in *Suppl Data 2* of (Juszczak et al., 2025).

To compare our results with human findings, we extracted information about human and mouse gene orthology from "HCOP: Orthology Predictions Search" (https://www.genenames.org/tools/hcop/, bulk download: 8-21-2025). This information was filtered down to 1) one-to-one mouse-to-human mapped orthologs, 2) orthologs with matching gene symbols, and 3) orthologs with multiple-to-one mouse-to-human mappings that had the most databases supporting the orthology (*column: "support"*, ties broken by row index).

Statistical Methods for Result Comparisons: To conduct these comparisons, we extracted all available results for our 133 differentially expressed genes ("DEGs" FDR<0.05). If there were Log2FC values available, we examined the correlation with the Log2FC estimated from our chronic stress meta-analysis using both parametric (regression, Pearson's correlation) and non-parametric (Spearman's correlation) methods (functions: *summary.lm, cor.test*).

Results

Meta-Analysis

Overview: Of the 21,379 genes included in the meta-analysis, 21,296 produced stable meta-analysis estimates (full results: **Table S1**). Our meta-analysis revealed 133 DEGs (FDR<0.05), 97 of which were downregulated and 36 upregulated. A hierarchically-clustered heatmap of the top DEGs did not reveal a clear pattern related to stress paradigm or stress susceptibility, but potentially some clustering by platform (**Figure 2**).

Example DEGs are illustrated with forest plots, showing the consistency of differential expression across studies and paradigms (**Figures 3&4).** Chronic stress broadly downregulated gene expression important for glial development and function (**Figure 3**) in the PFC, including Aquaporin 4 (*Aqp4*; **Figure 3A**), S100 calcium-binding protein B (*S100b*; **Figure 3B)**, Fatty Acid 2-Hydroxylase (*Fa2h*; **Figure 3C),** P2X purinoceptor 7 (*P2rx7*; **Figure 3D**), ELOVL fatty acid elongase 5 (*Elovl5*; **Figure 3E**), and Hepatocyte cell adhesion molecule (*Hepacam*; **Figure 3F**). Chronic stress also suppressed immediate early gene (IEG) responses linked to neuronal

activity and plasticity in the PFC (**Figure 4**), including Fos proto-oncogene, AP-1 transcription factor subunit (*Fos*, **Figure 4A**), JunB proto-oncogene, AP-1 transcription factor subunit (*Junb*, **Figure 4B**), Activity-regulated cytoskeleton-associated protein (*Arc,* **Figure 4C**), and Dual specificity phosphatase 1 (*Dusp1*, **Figure 4D**).

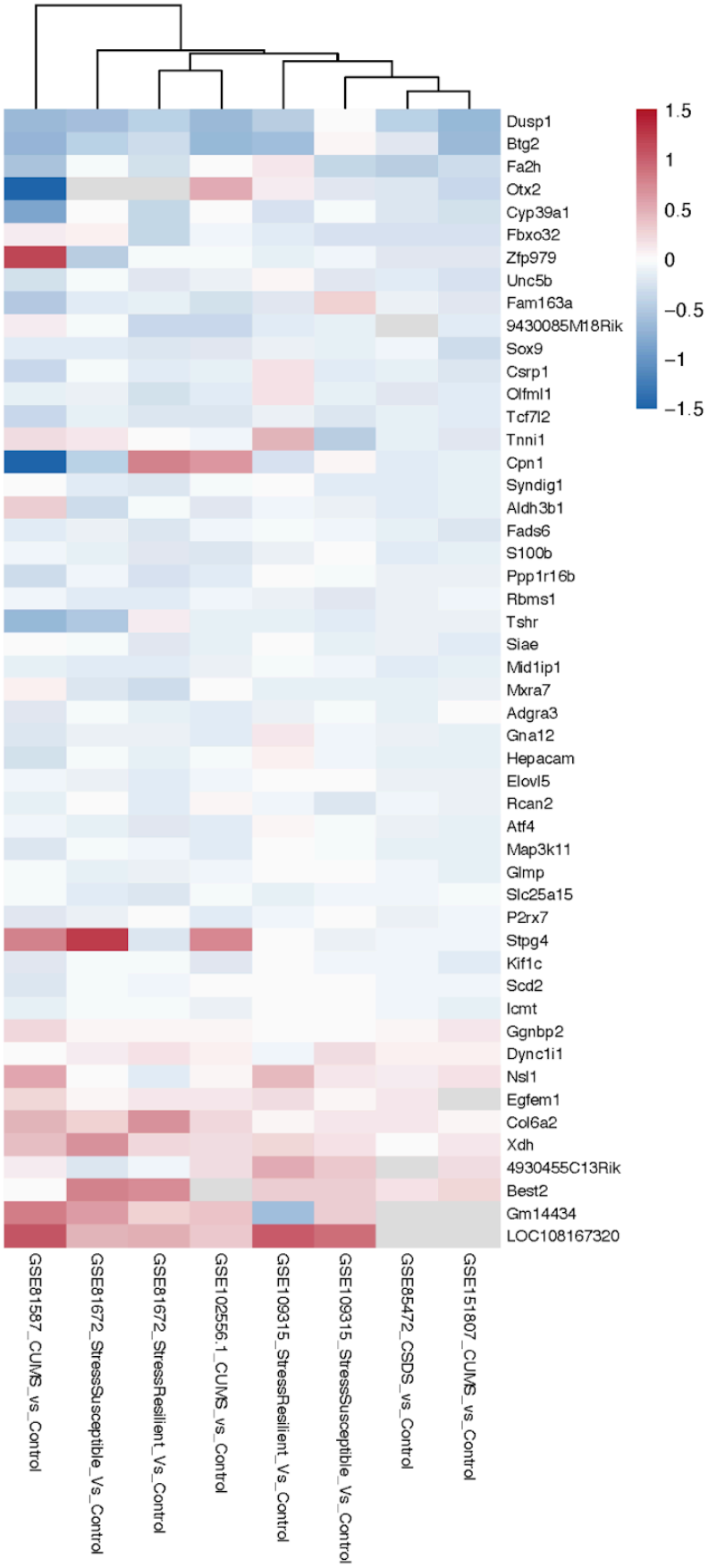

GSE81587_CUMS_vs_Control
GSE81672_StressSusceptible_Vs_Control
GSE81672_StressResilient_Vs_Control
GSE102556.1_CUMS_vs_Control
GSE109315_StressResilient_Vs_Control
GSE109315_StressSusceptible_Vs_Control
GSE85472_CSDS_vs_Control
GSE151807_CUMS_vs_Control
Dusp1
Btg2
Fa2h
Otx2
Cyp39a1
Fbxo32
Zfp979
Unc5b
Fam163a
9430085M18Rik
Sox9
Csrp1
Olfml1
Tcf7l2
Tnni1
Cpn1
Syndig1
Aldh3b1
Fads6
S100b
Ppp1r16b
Rbms1
Tshr
Siae
Mid1ip1
Mxra7
Adgra3
Gna12
Hepacam
Elovl5
Rcan2
Atf4
Map3k11
Glmp
Slc25a15
P2rx7
Stpg4
Kif1c
Scd2
Icmt
Ggnbp2
Dync1i1
Nsl1
Egfem1
Col6a2
Xdh
4930455C13Rik
Best2
Gm14434
LOC108167320
1.5
1
0.5
0
−0.5
−1
−1.5

Figure 2. Heatmap of the top 50 differentially expressed genes across all 8 chronic stress vs. control comparisons. Rows correspond to the 50 genes with the smallest FDR, columns indicate the Gene Expression Omnibus (GEO) dataset ID (GSE#...) and specific chronic stress vs. control comparison. Columns are ordered by unsupervised hierarchical clustering of log2 fold-change values so that chronic stress vs. control comparisons (contrasts) with similar results appear adjacent. The dendrogram at the top of the figure represents that similarity: the most similar items are joined at lower levels ("branches"), and less similar groups are joined higher up on the tree.Within the heatmap, pink indicates upregulation (positive Log2FC), and blue indicates down-regulation (negative Log2FC). Grey indicates that the gene lacks representation in the study.

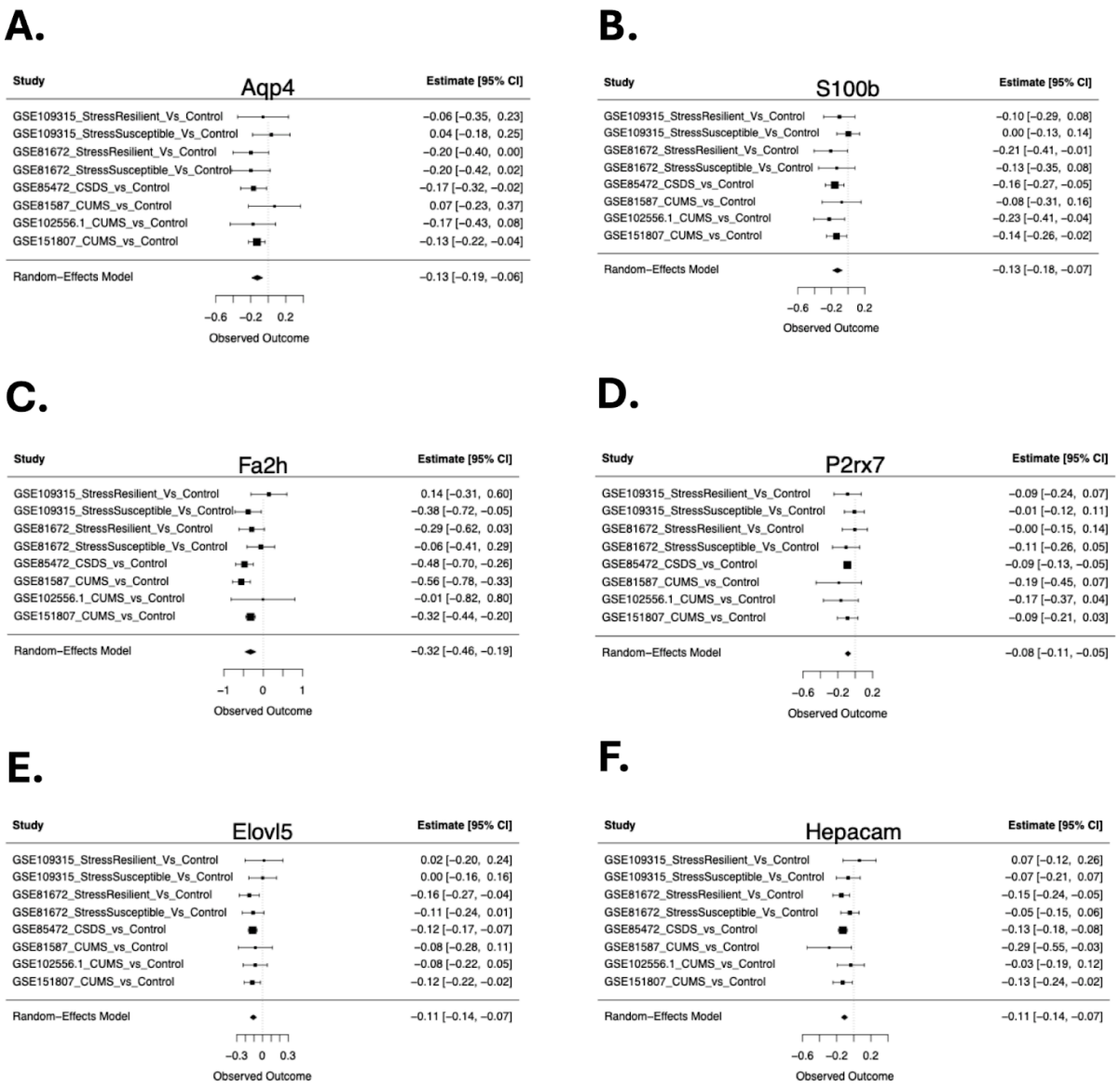


Figure 3. Genes related to glial development and function are down-regulated in the PFC in chronic stress models. Forest plots illustrate the consistency of effects across datasets and

conditions. Rows illustrate Log2FC (squares) with 95% confidence intervals (whiskers) for each of the datasets and the meta-analysis random effects model (RE Model). **(A)** A forest plot showing the down-regulation of Aquaporin 4 (*Aqp4*) in chronic stress models. **(B)** A forest plot showing the down-regulation of S100 calcium-binding protein B (*S100b*) in chronic stress models. **(C)** A forest plot showing the down-regulation of Fatty acid 2-hydroxylase (*Fa2h*) in chronic stress models. **(D)** A forest plot showing the down-regulation of P2X purinoceptor 7 (*P2rx7*) in chronic stress models. **(E)** A forest plot showing the down-regulation of ELOVL fatty acid elongase 5 (*Elovl5*) in chronic stress models. **(F)** A forest plot showing the down-regulation of hepatocyte cell adhesion molecule (*Hepacam*) in chronic stress models.

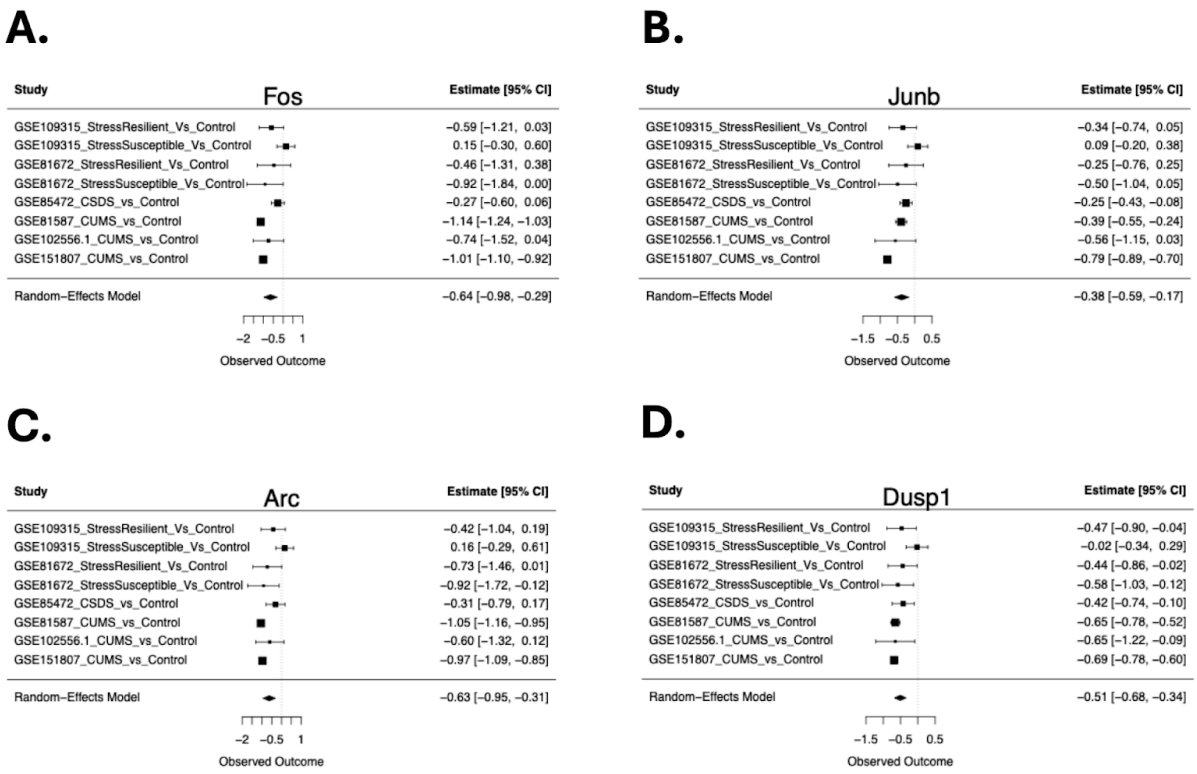


Figure 4. Immediate early genes are down-regulated in the PFC in chronic stress models. Formatting follows the conventions of Figure 3. **(A)** A forest plot showing the down-regulation of Fos proto-oncogene, AP-1 transcription factor subunit (*Fos*) in chronic stress models. **(B)** A forest plot showing the down-regulation of JunB proto-oncogene, AP-1 transcription factor subunit (*Junb*) in chronic stress models. **(C)** A forest plot showing the down-regulation of Activity-regulated cytoskeleton-associated protein (*Arc*) in chronic stress models. **(D)** A forest plot showing the down-regulation of Dual specificity phosphatase 1 (*Dusp1*) in chronic stress models.

Functional Patterns: We performed a fast gene set enrichment analysis (*fGSEA*) using a database containing both brain-related (*Brain.GMT*) and traditional gene ontology gene sets. Of

the 10,847 gene sets included in the results, 49 were enriched with down-regulation following chronic stress and 4 enriched with upregulation (FDR<0.05, **Table S2**).

Chronic stress altered gene sets that are associated with several brain cell types (**Table 2**), with glial cells appearing to be central responders. The most prominent changes involved oligodendrocytes (8 out of 53) and developing oligodendrocytes (4 out of 53), which were uniformly downregulated. Gene sets related to astrocytes and astrocytic functions (4 out of 53), radial-glia-like signatures (3 out of 53), and vasculature (4 out of 53) were also downregulated after chronic stress. Only one neuronal-related gene set was affected, and one gene set broadly related to cell differentiation was downregulated.

Our meta-analysis results showed an enrichment of differential expression in gene sets representing a variety of stress paradigms (**Table 3**), providing some cross-validation. Notably, we observed enrichment in gene sets that were previously shown to be upregulated after CSDS, even though the source experiments were not included in our meta-analysis (*GSE72343,* PFC-specific results were unavailable within the Gemma database (Bagot et al., 2016); *GSE149195:* PFC not profiled (DiSabato et al., 2021)). This convergence suggests that the molecular program we identified captures core elements of the brain's chronic stress response that can be generalized to other brain regions. We also observed an enrichment in gene sets related to hormonal response and MDD, highlighting the relevance of our findings to stress-related psychopathology.

There was also enrichment in gene sets from other stress paradigms. Two gene sets comprising downregulated genes from contextual fear conditioning in the hippocampus were enriched with down-regulation in our meta-analysis. In contrast, several other stress gene sets were enriched but shifted in the opposite direction, including contextual fear conditioning, trace fear conditioning, forced swim stress, restraint stress, and novel stress. These oppositely shifting gene sets were largely driven by classic IEGs including *Fos*, *Arc*, *Dusp1*, *Egr1*.

Gene Set	*p*-value	FDR	ES	NES	Size	Leading genes
Oligodendrocytes - Mature & Developing						
Ensheathment of Neurons *(GOBP)*	0.000193	0.0422	-0.637	-2.11	121	*Fa2h,Lpar1*
Oligodendrocyte Differentiation *(GOBP)*	0.000195	0.0422	-0.614	-1.95	92	*Fa2h,Lpar1,Sox9*
Oligodendrocyte Cells *(Cahoy et al. 2008, JNeuro)*	0.000194	0.0422	-0.826	-2.30	41	*Fa2h,Lgi3*
Oligodendrocyte Cells *(Zeisel et al. 2015, Science)*	0.000188	0.0422	-0.535	-2.02	389	*S1pr5,Fbxo32,Nipal4,Bfsp2,Tnni1,Fads6,Lgi3,Ppp1r16b,Gna12,Desi1,Smad7,Vangl2*
Myelinating Oligodendrocyte Cells *(Zhang et al. 2014, JNeuro)*	0.000195	0.0422	-0.810	-2.21	37	*Prr18,Trp53inp2*
Hippocampal Oligodendrocytes, Cluster marker Tfr *(DropViz)*	0.000192	0.0422	-0.821	-2.66	104	*Fa2h,S1pr5,Prr18,Lpar1,Csrp1,Tnni1*
Striatal Oligodendrocytes, Cluster marker Tfr *(DropViz)*	0.000192	0.0422	-0.803	-2.71	137	*Fa2h,S1pr5,Lpar1,Unc5b,Bfsp2,Csrp1,Olfml1,Tnni1,Lgi3,Desi1,Scd2*
Embryonic Brain Cortical Oligodendrocytes *(MSigDB: Fan)*	0.000182	0.0422	-0.495	-1.95	700	*Fa2h,S1pr5,Fbxo32,Prr18,Lpar1,Nipal4,Unc5b,Csrp1,S100b,Lgi3,Ppp1r16b,Desi1,Smad7,Reep3,Mtus1,Trp53inp2,P2rx7,Ubl3*
Prefrontal Cortical Oligodendrocyte Progenitor Cells *(MSigDB: Zhong)*	0.000195	0.0422	-0.598	-1.89	87	*Arc,S100b,Anxa5,Car10*
Fetal Cerebellar Oligodendrocytes *(MSigDB: Descartes)*	0.000198	0.0422	-0.696	-2.04	56	*Arc,Car10*
Fetal Oligodendrocytes *(MSigDB: Descartes)*	0.000196	0.0422	-0.700	-2.13	68	*Arc,Fa2h,Car10*
Oligodendrocyte Markers *(MSigDB: Lein)*	0.000194	0.0422	-0.772	-2.37	72	*Fa2h,S1pr5,Csrp1*
Astrocytes						
Hippocampal Astrocytes, Cluster Marker Gja1 *(DropViz)*	0.000193	0.0422	-0.641	-2.15	132	*Sox9,S100b,Aqp4,Hepacam*
Striatal Astrocytes, Cluster Marker Gja1 *(DropViz)*	0.000191	0.0422	-0.552	-1.87	145	*Sox9,Aqp4,Hepacam*
Prefrontal Cortical Astrocytes *(MSigDB: Zhong)*	0.000188	0.0422	-0.512	-1.89	307	*Sox9,Tcf7l2,S100b,Aqp4,Ddr1,Elovl5,Anxa5,Alpl,Ubl3*
GSE117758: Upregulated in Nucleus Accumbens Astrocytes *(Gemma)*	0.000182	0.0422	-0.487	-1.92	732	*Fos,Ccn1,Dusp1,Otx2,Fam163a,Sox9,BC034090,Csrp1,Olfml1,Aldh3b1,S100b,Aqp4,Mid1ip1,Adgra3,Gna12,Hepacam,Mmgt2,Elovl5,Gm973,Anxa5,Alpl,Ppp1r15a,Sft2d2,Kif1c*
Other Glia						
Embryonic Brain Cortical Glial Cells *(MSigDB: Fan)*	0.000193	0.0422	-0.509	-1.69	126	*S100b,Anxa5*
Midbrain Human Radial Glia 2B *(MSigDB: Manno)*	0.000187	0.0422	-0.439	-1.65	385	*Fos,Ccn1,Egr1,Sox9,Tcf7l2,Aqp4,Hepacam,Ubl3*
Midbrain Human Radial Glia 2A *(MSigDB: Manno)*	0.000183	0.0422	-0.404	-1.56	530	*Fos,Ccn1,Ier2,Egr1,Sox9,Aqp4,Hepacam,Anxa5,Ubl3*
Vasculature						
Embryonic Brain Cortical Endothelial Cells *(MSigDB: Fan)*	0.000187	0.0422	-0.409	-1.53	349	*Unc5b,Kdr,Tek,Slc39a8,Reep3,Pde8b*
Midbrain Human Endothelial Cells *(MSigDB: Manno)*	0.000181	0.0422	-0.398	-1.58	827	*Fos,Arc,Ccn1,Dusp1,Ier2,Egr1,Csrnp1,Unc5b,Csrp1,Kdr,Rbms1,Tek,Slc39a8,Anxa5,Smad7,Reep3,Map3k11,Mtus1,Alpl*
Midbrain Human Pericytes *(MSigDB: Manno)*	0.000183	0.0422	-0.418	-1.65	723	*Fos,Ccn1,Ier2,Egr1,Csrnp1,Unc5b,Olfml1,Rbms1,Anxa5,Reep3,Mtus1,Pde8b*
Adult Olfactory Neuroepithelium Vascular Smooth Muscle Cells *(MSigDB: Durante)*	0.000195	0.0422	-0.645	-1.99	76	*Fos,Egr1,Csrp1,Rcan2*
Neuron						
GSE117758: Downregulated in Nucleus Accumbens Neurons *(Gemma)*	0.000182	0.0422	-0.490	-1.94	784	*Fa2h,S1pr5,Unc5b,Sox9,Csrp1,Olfml1,Tcf7l2,Aqp4,Lgi3,Mid1ip1,Mmgt2,Elovl5,Anxa5,Car10,Bag3*
General Cell Type						
Positive Regulation of Cell Differentiation *(GOBP)*	0.000183	0.0422	-0.351	-1.38	719	*Fos,Ccn1,Dnai3,Sox9,Tcf7l2,Ngf,Kdr,Rnd2,Smad7*

Table 2. Functional gene sets that are enriched with the effects of chronic stress are related to various cell types. Size: size of gene set. Leading genes: A list of the leading genes in the gene set that were significantly differentially expressed following chronic stress (FDR < 0.05) in the meta-analysis. Abbreviations: ES, enrichment score; FDR, false discovery rate; NES, normalized enrichment score. Gene set names have been reformatted for clarity.

Gene Set	*p*-value	FDR	ES	NES	Size	Leading genes
Stress: Contradictory Direction of Effect						
GSE100236: Genes upregulated by swim stress in the hippocampus *(Gemma)*	0.000192	0.0422	-0.716	-2.30	99	*Fos,Arc,Ccn1,Dusp1,Btg2,Ier2,Egr1, Csrnp1,Ppp1r15a*
GSE100236: Genes upregulated by novelty stress in the hippocampus *(Gemma)*	0.000193	0.0422	-0.666	-2.19	115	*Fos,Arc,Ccn1,Dusp1,Btg2,Ier2,Egr1, Csrnp1,Ppp1r15a*
GSE100236: Genes upregulated by restraint stress in the hippocampus *(Gemma)*	0.000192	0.0422	-0.682	-2.23	112	*Fos,Arc,Ccn1,Dusp1,Btg2,Ier2,Egr1, Csrnp1,Ppp1r15a*
GSE16158: Genes upregulated by trace fear conditioning in the hippocampus, timepoint 0.5h *(Gemma)*	0.000195	0.0422	-0.901	-2.16	20	*Fos,Arc,Dusp1,Btg2,Egr1*
GSE16158: Genes upregulated by trace fear conditioning in the hippocampus, timepoint 2h *(Gemma)*	0.000195	0.0422	-0.876	-2.10	20	*Fos,Arc,Dusp1,Egr1*
GSE50423: Genes upregulated by contextual fear conditioning in the hippocampus (*Gemma)*	0.000193	0.0422	-0.929	-1.93	10	*Fos,Arc,Dusp1,Btg2*
GSE63412: Genes upregulated by contextual fear conditioning memory retrieval (*Gemma)*	0.000193	0.0422	-0.932	-2.04	13	*Fos,Arc,Ccn1,Dusp1,Btg2*
GSE63412: Genes upregulated by contextual fear conditioning (*Gemma)*	0.000193	0.0422	-0.932	-2.04	13	*Fos,Arc,Ccn1,Dusp1,Btg2*
GSE74966: Genes upregulated by contextual fear conditioning (*Gemma)*	0.000194	0.0422	-0.659	-2.09	90	*Fos,Egr1,Kdr*
GSE74966: Genes upregulated by contextual fear conditioning and electric shock (*Gemma)*	0.000195	0.0422	-0.662	-2.10	92	*Fos,Egr1,Kdr*
Stress: Confirmatory Direction of Effect						
GSE50423: Genes downregulated by contextual fear conditioning in the hippocampus, timepoint 4h (*Gemma)*	0.000184	0.0422	-0.423	-1.61	464	*Fos,Arc,Ccn1,Dusp1,Btg2,Egr1,Atf4*
GSE50423: Genes downregulated by contextual fear conditioning in the hippocampus, timepoint 24h	0.000191	0.0422	-0.517	-1.79	173	*Fos,Arc,Ccn1,Dusp1,Btg2,Egr1*
GSE72343: Genes upregulated in stress resilient mice following chronic social defeat stress *(Gemma)*	0.000205	0.0422	0.779	2.21	44	*Xdh*
GSE72343: Genes upregulated in stress susceptible mice following chronic social defeat stress *(Gemma)*	0.000205	0.0422	0.779	2.21	44	*Xdh*
GSE149195: Genes upregulated following social defeat stress *(Gemma)*	0.000206	0.0422	0.791	2.02	26	
Stress-Related:						
Response to Hormone *(GOBP)*	0.000183	0.0422	-0.348	-1.38	763	*Fos,Dusp1,Btg2,Egr1,Fbxo32,Cpn1, Tshr,Tek,Alpl*
Genes downregulated in Major Depressive Disorder *(MSigDB: Aston)*	0.000191	0.0422	-0.570	-1.94	148	*Lpar1,P2rx7*
GSE95740: Genes upregulated in the dentate gyrus following environmental enrichment *(Gemma)*	0.000195	0.0422	-0.608	-1.87	74	*Fos,Arc,Dusp1,Csrnp1,Syndig1*

Table 3. Functional gene sets that are enriched with the effects of chronic stress are related to various types of stress, hormonal response, and MDD. Size: size of gene set. Leading genes: A list of the leading genes in the gene set that were significantly differentially expressed following chronic stress (FDR<0.05) in the meta-analysis. Abbreviations: ES, enrichment score; FDR, false discovery rate; NES, normalized enrichment score. Gene set names have been reformatted for clarity.

Similarities with Previous Studies Examining the Effects of Stress & Glucocorticoids:

Some of our DEGs showed effects resembling those reported in previous meta-analyses examining the effects of chronic stress on the prefrontal cortex transcriptome. For example, a

meta-analysis of the effects of 10 days of CSDS ((Reshetnikov et al., 2022): *n*=56 subjects) provided results for 1968 genes surviving a nominal *p*<0.05 threshold, including 21 of our 133 DEGs. For these 21 genes, there was a strong positive correlation between the Log2FCs for the two meta-analyses (*R*=0.73, *p*=0.000147; *Rho*=0.78, *p*=4.32e-05, **Figure 5A**), despite minimal overlap in included samples (15%: *n*=18 of our 117 subjects). Whether this strong positive correlation would persist for our DEGs with unavailable results is unknown. Similar parallels were not observed with the results from a smaller meta-analysis of the effects of 30 days of CSDS ((Reshetnikov et al., 2022), *n*=20 subjects). Only 14 DEGs from our meta-analysis were represented in their provided results (3132 genes surviving a *p*<0.05 threshold), and their associated Log2FCs showed minimal correlation with our findings (*R*=-0.021, *p*=0.944; *Rho*=0.068, *p*=0.820, **Figure 5B**). We also observed limited overlap with the results from a meta-analysis of the effects of chronic stress more broadly defined (CSDS, CUMS, or chronic restraint) ((Gururajan, 2022), n=101 subjects). For this study, only results for genes surviving a stricter FDR<0.05 threshold were available (160 genes), of which only one (*Xdh*) was included in our DEGs, making comparison difficult.

We were able to more unambiguously document a positive correlation with results from large studies related to chronic stress with result reporting for more genes. For example, results were available for 92 of our DEGs within a meta-analysis of the long-term effects of early life stress on the prefrontal transcriptome ((Duan et al., 2025): *n*=89 subjects), eleven of which showed nominal significance (*p*<0.05). The Log2FCs for these genes correlated positively with the Log2FCs in our meta-analysis (92 genes: *R*=0.52, *p*=1.44e-07; *Rho*=0.35, *p*=0.000795, **Figure 5D**), suggesting parallels between the effects of early life stress and adult chronic stress. Our results were also weakly correlated with the effects of chronic daily corticosterone on the hippocampal transcriptome ((Juszczak et al., 2025): *n*=48 subjects, **Figure 5C**), with 110 of our genes represented in their results, 48 of which showed nominal significance (*p*<0.05). For these genes, the Log2FCs showed a small positive correlation with the Log2FCs in our meta-analysis (110 genes: *R*=0.13, *p*=0.179; *Rho*=0.31, *p*=0.00103). Additional DEGs had previous relationships with chronic stress (either medium duration or prolonged stress) documented in a large review of the literature characterizing the effects of stress on the brain transcriptome (Stankiewicz et al., 2022) (**Table S3**). Altogether, these comparisons suggest that our findings add to a growing body of results documenting the effects of stress on brain gene expression.

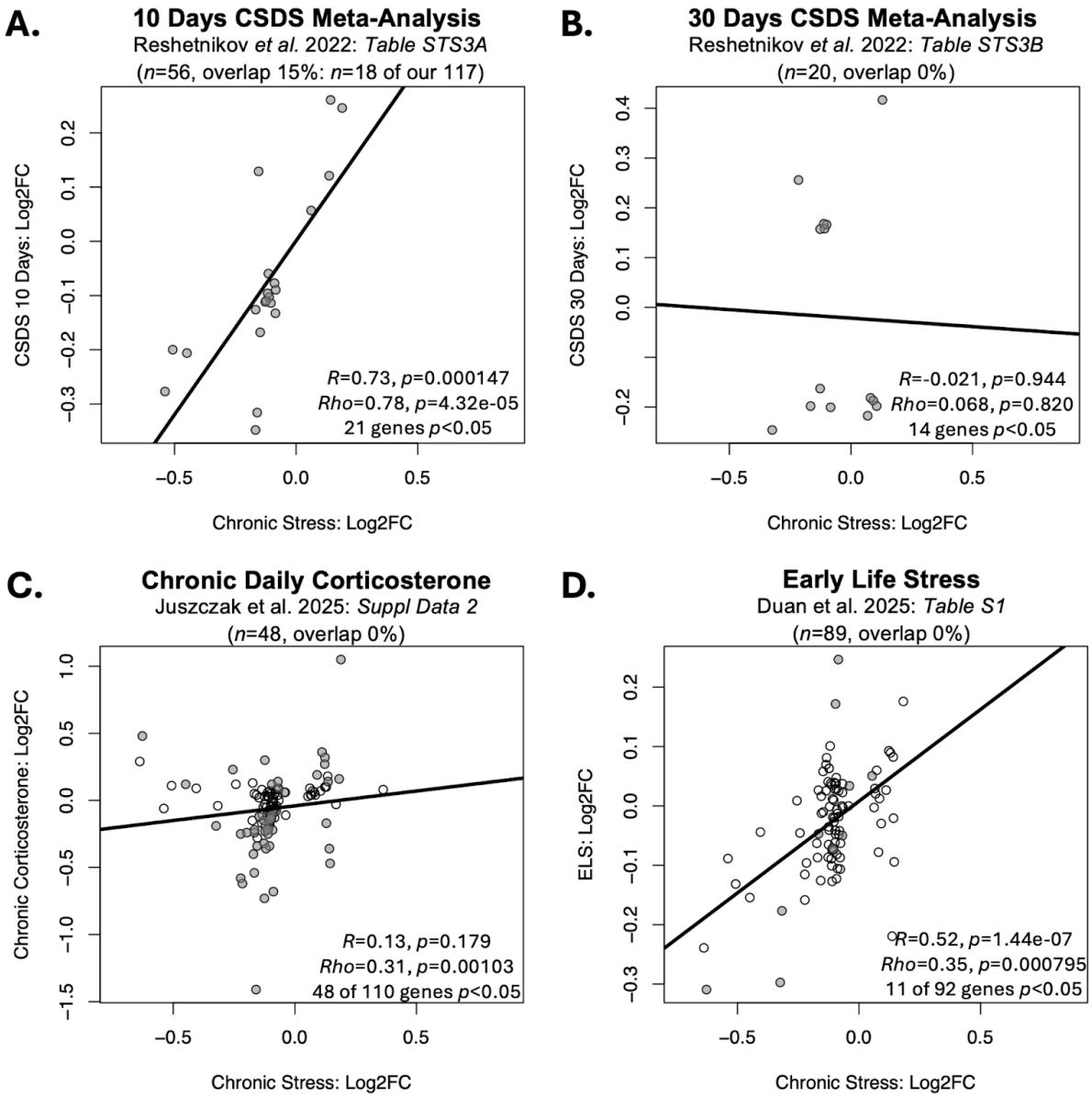


Figure 5. The DEGs from our current meta-analysis show similar effects in previous large studies characterizing the effects of chronic stress and glucocorticoids on the brain transcriptome. A-D: Scatterplots illustrate the correlation between the effects of chronic stress within our meta-analysis (Log2FC: x-axis) and the effects of stress within previous studies (Log2FC: y-axis) for any of our 133 identified DEGs (FDR<0.05) that had results available in the referenced publication. Data points are shaded grey if the effects within the previous publication were nominally significant (p<0.05). Trend lines illustrate the relationship between the two sets of results as identified by simple linear regression. **A.** Differential expression results were available for 21 of our DEGs within a previously published meta-analysis of the effects of 10 days of CSDS on the PFC ((Reshetnikov et al., 2022): n=56 subjects, only nominally significant results available). For these genes, there was a strong positive correlation between the Log2FCs from the two meta-analyses (21 genes: R=0.73, Rho=0.78). **B.** Differential expression

results were available for 14 of our DEGs within a small previously published meta-analysis of the effects of 30 days of CSDS on the PFC ((Reshetnikov et al., 2022): n=20 subjects, only nominally significant results available). For these genes, there was minimal correlation between the Log2FCs from the two meta-analyses (14 genes: R=-0.021, Rho=0.068). **C.** Differential expression results were available for 110 of our DEGs within a large study of the effects of chronic daily corticosterone on the hippocampal transcriptome ((Juszczak et al., 2025): n=48 subjects). For these genes, there was a small positive correlation with the Log2FCs in our meta-analysis (110 genes: R=0.13, Rho=0.31). **D.** Differential expression results were available for 92 of our DEGs within a meta-analysis of the long-term effects of early life stress on the prefrontal transcriptome ((Duan et al., 2025): n=89 subjects). For these genes, there was a positive correlation with the Log2FCs in our meta-analysis (92 genes: R=0.52, Rho=0.35).

Similarities with Previous Studies Examining the Effects of Stress-Related Psychiatric Disorders:

Some of our DEGs showed effects resembling those reported in previous meta-analyses examining the effects of stress-related psychiatric disorders on the cortical transcriptome. Of 221 genes previously found to be differentially expressed in meta-analyses of the effects of suicide in the frontal cortex (Piras et al., 2022), seven were amongst our 133 DEGs, all of which showed the same direction of effect. Amongst 40 genes that had previously shown consistent differential expression in association with PTSD in the frontal cortex (Stankiewicz et al., 2022), three were amongst our DEGs, all of which also showed the same direction of effect.

When examining the Log2FCs for our DEGs, we also found a consistent positive correlation with the Log2FCs identified in previous psychiatric meta-analyses (**Figure 6**). Across diagnoses, this relationship appeared to be primarily driven by a small group of downregulated IEGs, such that the strong correlations disappeared when using non-parametric methods. This included effects of Alcohol Abuse Disorder (AAD, n=32, **Figure 6A**), MDD (n=176, **Figure 6B**), Bipolar Disorder (BPD, n=197, **Figure 6C**), and Schizophrenia (SCHIZ, n=314, **Figure 6E**) in the cortex as measured by microarray ((Gandal et al., 2018), *MDD:* R=0.32, p=0.0011, *Rho*=0.04, p=0.702, 20 of 102 genes p<0.05; *BPD:* R=0.22, p=0.0655**trend*, *Rho*=-0.074, p=0.531, 26 of 74 genes p<0.05; *SCHIZ*: R=0.40, p=0.000363; *Rho*=0.11, p=0.314; 35 of 74 genes p<0.05; *AAD:* R=0.21, p=0.0368, *Rho*=0.15, p=0.142, 18 of 98 genes p<0.05), and effects of BPD (n=171, **Figure 6D**) and SCHIZ (n=384, **Figure 6F**) on the frontal cortex as measured by RNA-Seq ((Gandal et al., 2018), *BPD:* R=0.58, p=7.60e-09; *Rho*=0.11, p=0.328; 15 of 85 genes p<0.05; *SCHIZ:* R=0.37, p=0.000505; *Rho*=0.033, p=0.766; 23 of 85 genes p<0.05). In contrast, the DEGs driving the correlations with other animal chronic stress studies, and similarities with PTSD and Suicide, seemed to more closely reflect glial dysregulation (**Table S3**).

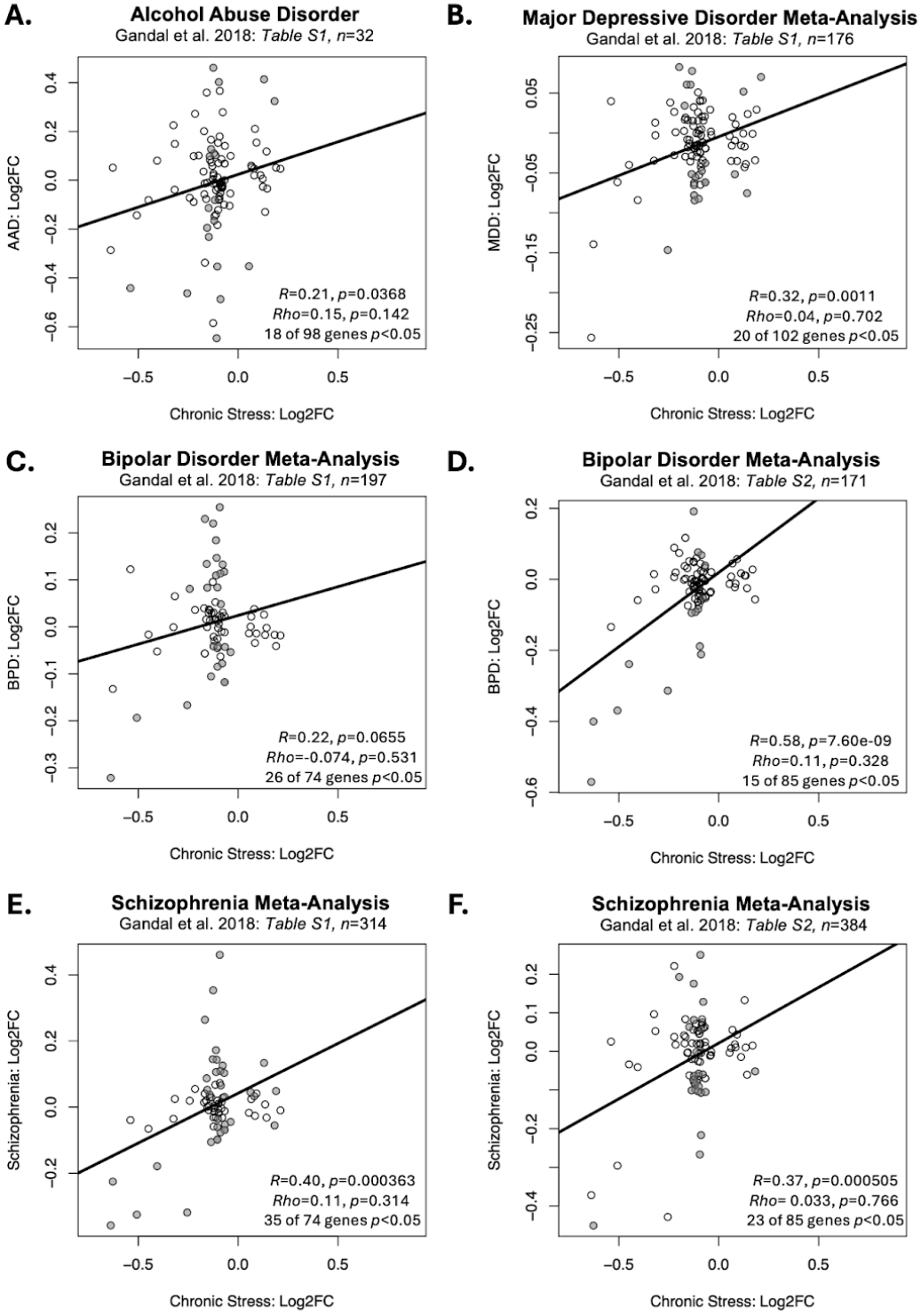


Figure 6. Some of the DEGs from our current meta-analysis show similar effects in previous large studies characterizing the effects of stress-related psychiatric disorders on the brain transcriptome. A-F) Scatterplots illustrate the correlation between the effects of chronic stress within our meta-analysis (Log2FC: x-axis) and the effects of stress-related

psychiatric disorders in previous studies (Log2FC: y-axis) for any of our 133 identified DEGs (FDR<0.05) that had results available in the referenced publication. Data points are shaded grey if the effects within the previous publication were nominally significant (p<0.05). Trend lines illustrate the relationship between the two sets of results as identified by simple linear regression. Across diagnoses, these positive findings appeared to be primarily driven by a small group of downregulated immediate early genes, such that the strong correlations typically disappeared when using non-parametric methods. **A-C, E)** These scatterplots illustrate the relationship between the effects of chronic stress within our meta-analysis and the effects of each psychiatric disorder on the cortical transcriptome as measured by microarray ((Gandal et al., 2018), Table S1). Note that the Bipolar Disorder and Schizophrenia meta-analyses share overlapping control subjects and thus cannot be considered fully independent. **D, F)** These scatterplots illustrate the relationship between the effects of chronic stress within our meta-analysis and the effects of each psychiatric disorder on the frontal cortical transcriptome as measured by RNA-Seq ((Gandal et al., 2018), Table S2). Note that the Bipolar Disorder and Schizophrenia meta-analyses share overlapping control subjects and thus cannot be considered fully independent. **A)** Alcohol Abuse Disorder (n=32: R=0.21, Rho=0.15), **B)** MDD (n=176: R=0.32, Rho=0.04), **C)** Bipolar Disorder (n=197: R=0.22, Rho=-0.074), **D)** Bipolar Disorder (n=171: R=0.58, Rho=0.11), **E)** Schizophrenia (n=314: R=0.40, Rho=0.11), **F)** Schizophrenia (n=384: R=0.37, Rho= 0.033).

Discussion

Chronic stress has been shown to have lasting effects on the brain, contributing to cognitive impairments and risk of psychiatric disorders (Girotti et al., 2024). Examining the PFC under chronic stress is critical due to its involvement in stress-sensitive cognitive and emotional functions (Shansky & Lipps, 2013). Our results documenting the effects of chronic stress on PFC gene expression add to growing evidence that the PFC remains plastic and vulnerable to stress into adulthood (Algaidi, 2025).

To identify effects of chronic stress that were consistent across laboratories and models, we performed a meta-analysis of six independent mouse studies using chronic social defeat (CSDS) and chronic unpredictable stress (CUMS) paradigms (total *n*=117). Across studies 97 transcripts were consistently downregulated and 36 upregulated. The downregulated genes were highly enriched for markers of glial cells (especially astrocytes and oligodendrocytes), neurovasculature, myelination, and inflammatory or immune processes, suggesting that chronic stress broadly disrupts glial and vascular support functions in the PFC in a manner that seems to parallel previous observations from patients with PTSD and suicide. We also observed consistent down-regulation of IEGs across multiple datasets, paralleling what has been observed in multiple human neuropsychiatric disorders.

Astrocyte and Neurovascular Function: Our meta-analysis revealed that chronic stress causes consistent down-regulation of gene sets associated with astrocytic function and neurovascular integrity in the PFC, with *Aqp4*, *S100b,* and *Hepacam* amongst the leading contributors. Evidence from both clinical and preclinical studies supports the down-regulation of these genes under chronic stress.

Aqp4 encodes aquaporin-4, a water channel protein highly enriched in astrocytic endfeet that is related to blood-brain barrier water homeostasis and glymphatic clearance (Mader &

Brimberg, 2019, Papadopoulos & Verkman, 2013). Similar to our results, *Aqp4* was downregulated in the anterior cortex of mice following CUMS (Wei et al., 2019) and in the hippocampus following chronic corticosterone exposure (Juszczak et al., 2025). This finding may be clinically relevant, as *AQP4* expression is reduced in the post-mortem orbitofrontal cortex (Rajkowska et al., 2013) and hippocampus (Medina et al., 2016) of patients with MDD, and in the frontal cortex of subjects who died of suicide (Piras et al., 2022).

Gene expression related to astrocyte development was downregulated. *S100b* is an astrocyte-derived calcium binding protein that promotes glial and neuronal proliferation, survival, and differentiation (Hernández-Ortega et al., 2024). Similar to our results, chronic unpredictable stress reduced S100B protein in the PFC of rats (Luo et al., 2010) and *S100b* mRNA in the PFC of male mice (Bollinger et al., 2025), resembling the down-regulation produced by chronic corticosterone (Juszczak et al., 2025). *Hepacam* encodes an astroglial adhesion molecule regulating astrocyte competition for territory and morphological complexity during development (Baldwin et al., 2021). *Hepacam* expression in the PFC has not been previously linked to chronic stress. However, *Hepacam* is sensitive to glucocorticoids (Juszczak & Stankiewicz, 2018) and, in humans, *HEPACAM* shows a gene-based association with suicidality, with effects moderated by environmental factors (Wendt et al., 2021). The down-regulation of *S100b* and *Hepacam* we observed may indicate stress-induced astrocytic structural remodeling.

Disrupted astrocytic and neurovascular gene expression following chronic stress may underlie impaired astrocyte network function. Prior work shows that chronic stress induces astrocytic atrophy without reducing cell number (Tynan et al., 2013), weakening astrocyte syncytial networks (Aten et al., 2023), dysregulating astrocyte-neuron metabolic coupling (Descalzi, 2020); and altering blood-brain barrier integrity ((Menard et al., 2017); (Dudek et al., 2020)). These mechanisms are all increasingly thought to be related to mood disorders.

Oligodendrocytes: Chronic stress produced down-regulation in gene sets representing mature oligodendrocytes, developing oligodendrocyte precursor cells, and myelination processes in the PFC. This included down-regulation of two enzymes, *Fa2h* and *Elovl5,* that are responsible for the synthesis of critical components of the myelin sheath, 2-hydroxylated fatty acids (Potter et al., 2011), and long-chain polyunsaturated fatty acids (Hoxha et al., 2021). Consistent with our results, *Fa2h* was similarly downregulated in the hippocampus following chronic corticosterone (Juszczak et al., 2025), and in the PFC following CSDS (Cathomas et al., 2019) and potentially early life stress (Duan et al., 2025). *Elovl5* was also down-regulated following chronic corticosterone (Juszczak et al., 2025). These findings could be clinically important, as *ELOVL5* is reduced in the postmortem frontal cortex in patients with MDD (McNamara & Liu, 2011), alcohol abuse disorder (Gandal et al., 2018), and suicide (Piras et al., 2022). These molecular changes align with a broader pattern of oligodendrocyte impairment reported in stress-related disorders including MDD, as post-mortem evidence showed oligodendrocyte abnormalities in the PFC of MDD and BD patients (Czéh & Nagy, 2018).

Glial Communication: Chronic stress suppressed genes related to glial communication, including *P2rx7*. *P2rx7* encodes a purinergic receptor involved in numerous inflammation pathways (Adinolfi et al., 2018). The protein receptor P2X7R is activated by stress-elevated extracellular ATP, triggering downstream neuroinflammation linked to depression (von Muecke-Heim et al., 2021). In chronic stress models, P2X7R antagonists were found to

consistently blunt depressive-like behaviors and reverse immune changes (Ribeiro et al., 2019). The down-regulation of *P2rx7* in our meta-analysis and in previous studies of MDD (Aston et al., 2005) might reflect a homeostatic or compensatory response to chronic overstimulation of this pathway, limiting excessive inflammation in the PFC. Overall, the down-regulation of multiple glial-driven gene sets suggests that chronic stress may impair the glial-neuron communication, potentially disrupting neuroimmune signaling within PFC circuits.

Immediate Early Genes: Chronic stress suppressed immediate early genes (IEGs) linked to neuronal activity and plasticity, such as *Fos*, *Junb*, *Arc*, and *Dusp1* (**Figure 4**). Functionally, *Fos* and *Junb* encode proteins that are core components of the activator protein-1 (AP-1) transcription factor complex (Abate et al., 1991). *Arc* supports synaptic plasticity and is crucial for memory consolidation (Korb & Finkbeiner, 2011). *Dusp1* encodes a phosphatase that provides negative feedback to MAPK/ERK signaling (Chen et al., 2019). A comprehensive review of the literature reported that these IEGs are reliably induced by acute stressors but down-regulated after chronic stress across multiple regions, including the hippocampus and PFC (Flati et al., 2020). Notably, the regulation of *Dusp1* appears to be context-dependent. While we observed a consistent down-regulation of *Dusp1* with chronic stress in PFC, some studies have found the opposite pattern in certain conditions (*e.g.,* (Zhao et al., 2017)). A similar down-regulation of IEG expression was also observed in the frontal cortex across a variety of other psychiatric disorders, including alcohol abuse disorder, MDD, bipolar disorder, and schizophrenia (Gandal et al., 2018).

Upregulation of Xdh: Finally, we observed an upregulation of *Xdh* that was consistent with nominal findings from two other chronic stress-related meta-analyses (Gururajan, 2022; Reshetnikov et al., 2022), chronic corticosterone exposure (Juszczak et al., 2025), prolonged stress exposure (Stankiewicz et al., 2022b), and schizophrenia (Gandal et al., 2018) (**Table S3**). *Xdh* encodes the protein xanthine oxidoreductase (XOR), the terminal enzyme of purine catabolism that exists in two forms: xanthine dehydrogenase (XDH) and xanthine oxidase (XO) (Furuhashi, 2020). In mice, chronic stress increased cortical XOR activity and resulted in cerebrovascular dysfunction and cognitive deficits (Burrage et al., 2023). The upregulation of *Xdh* observed in our results, along with previous findings, may suggest a shift towards increased oxidative stress at the neurovascular interface caused by different types of stress exposure.

Strengths and Limitations: Compared to the original studies, our meta-analysis provides greater statistical power, allowing more robust identification of DEGs, and better generalizability of findings. However, our analysis has several limitations. Response to chronic stress has been shown to be sex-specific. For example, six days of variable stress could induce depression-associated behaviors in female mice but not in males (Hodes et al., 2015). Since our datasets only included male subjects, the findings may be limited to male mice. Likewise, the limited number of comparisons between stress susceptible and resilient groups did not allow us to examine how stress susceptibility affects PFC gene expression, but a recent meta-analysis of CSDS effects on the PFC was able to pursue this question, revealing that down-regulation of myelin-related genes may be more pronounced in susceptible mice (Reshetnikov et al., 2022). Future analyses with more comparisons should dig deeper into these variables.

Conclusion: Chronic stress is a significant public health concern in the United States, contributing to the onset and the exacerbation of psychiatric conditions, including MDD and PTSD (Davis et al., 2017). Human studies often have modest effect sizes and complex designs,

making it difficult to identify targets. By releasing our full meta-analysis results **(Table S1**: 21,379 genes, with 133 DEGs) and gene set enrichment results (**Table S2**: 10,847 gene sets, with 53 with FDR<0.05), we provide a useful reference database that can be compared to the transcriptional profiling results from stress-induced psychiatric and neurological conditions to distinguish stress-associated factors. Moreover, our convergent analyses with prior human transcriptomic reports highlighted patterns that are consistent across species, providing insight for mechanistic and translational follow-up.

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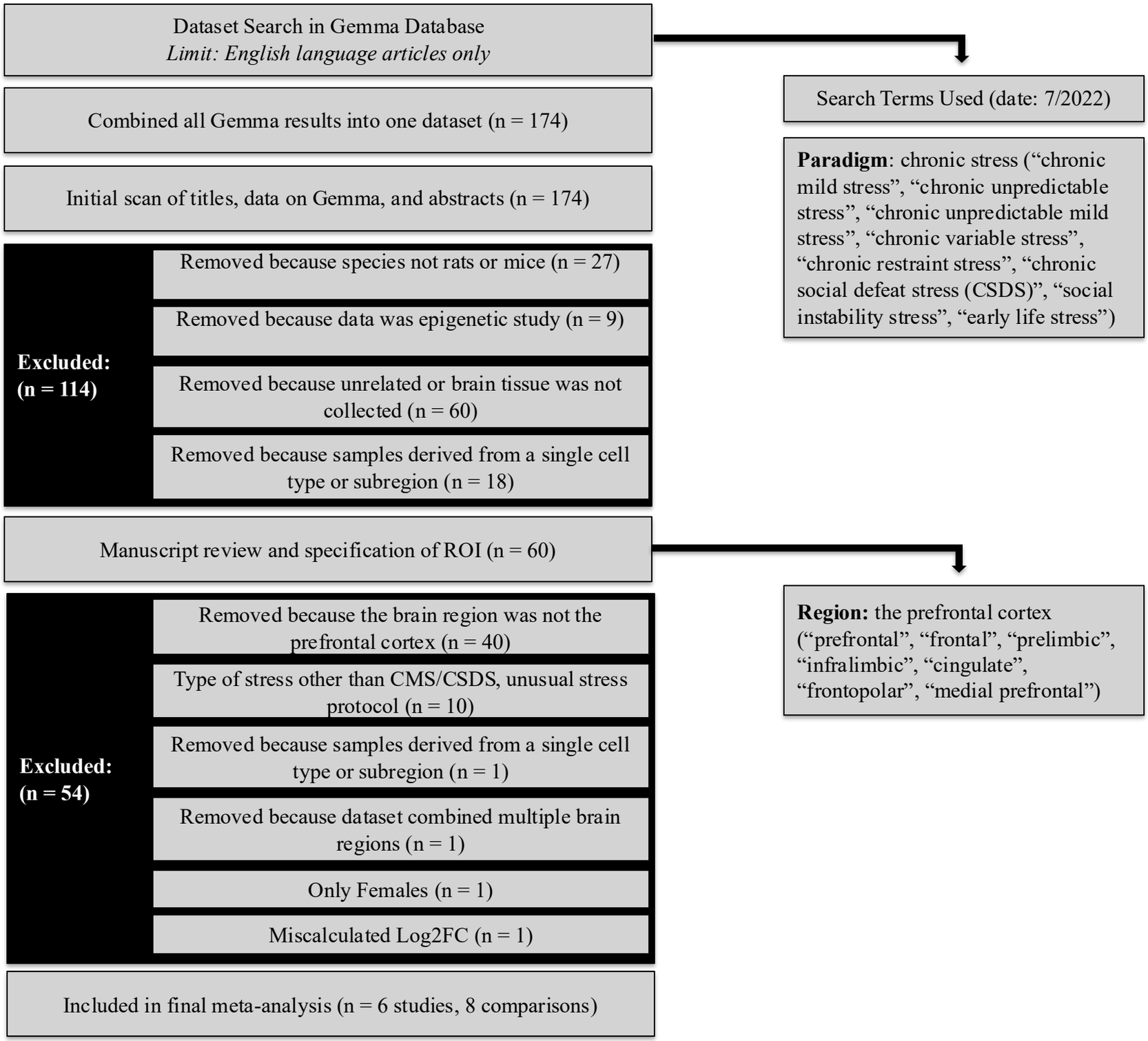
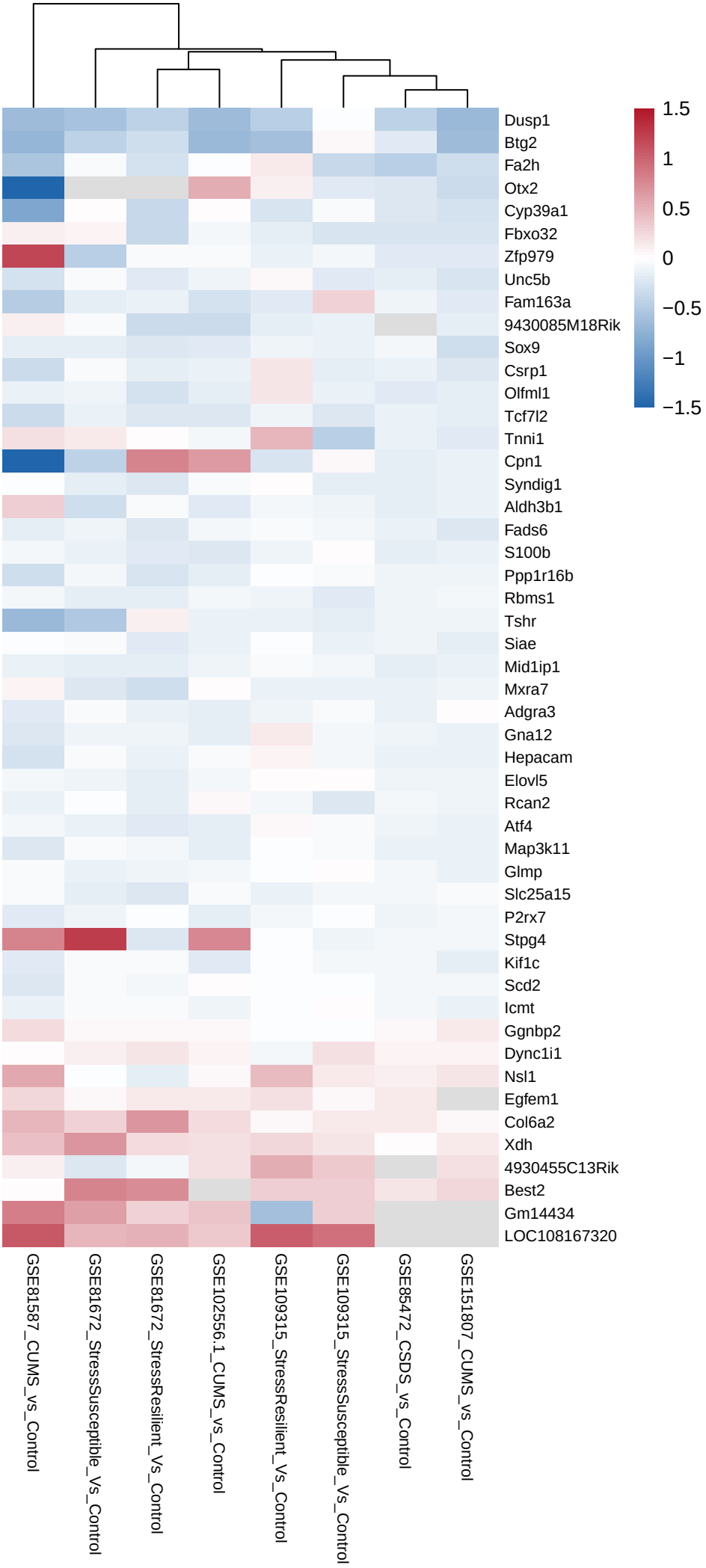

Dataset Search in Gemma Database
Limit: English language articles only
Search Terms Used (date: 7/2022)
Paradigm: chronic stress ("chronic mild stress", "chronic unpredictable stress", "chronic unpredictable mild stress", "chronic variable stress", "chronic restraint stress", "chronic social defeat stress (CSDS)", "social instability stress", "early life stress")
Combined all Gemma results into one dataset (n = 174)
Initial scan of titles, data on Gemma, and abstracts (n = 174)
Excluded: (n = 114)
Removed because species not rats or mice (n = 27)
Removed because data was epigenetic study (n = 9)
Removed because unrelated or brain tissue was not collected (n = 60)
Removed because samples derived from a single cell type or subregion (n = 18)
Manuscript review and specification of ROI (n = 60)
Region: the prefrontal cortex ("prefrontal", "frontal", "prelimbic", "infralimbic", "cingulate", "frontopolar", "medial prefrontal")
Excluded: (n = 54)
Removed because the brain region was not the prefrontal cortex (n = 40)
Type of stress other than CMS/CSDS, unusual stress protocol (n = 10)
Removed because samples derived from a single cell type or subregion (n = 1)
Removed because dataset combined multiple brain regions (n = 1)
Only Females (n = 1)
Miscalculated Log2FC (n = 1)
Included in final meta-analysis (n = 6 studies, 8 comparisons)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GSE81587_CUMS_vs_Control
GSE81672_StressSusceptible_Vs_Control
GSE81672_StressResilient_Vs_Control
GSE102556.1_CUMS_vs_Control
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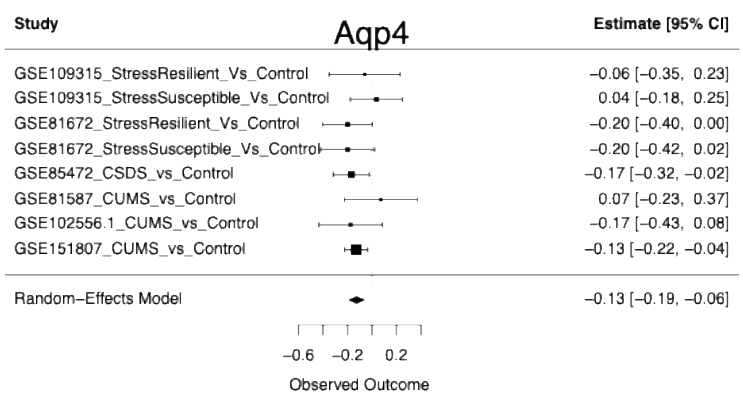
GSE151807_CUMS_vs_Control


A.
Study
Aqp4
Estimate [95% CI]
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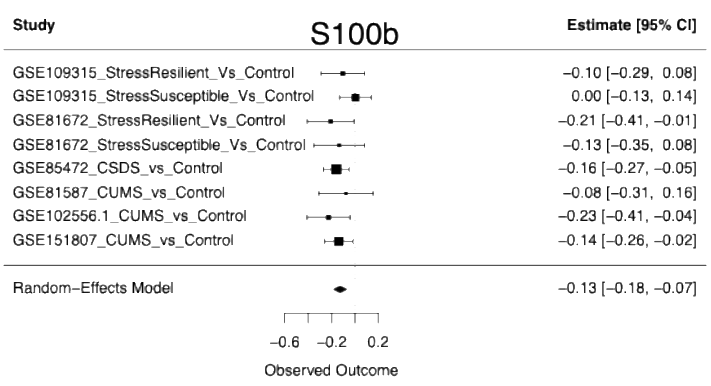
GSE109315_StressSusceptible_Vs_Control 0.04 [−0.18, 0.25]
GSE81672_StressResilient_Vs_Control −0.20 [−0.40, 0.00]
GSE81672_StressSusceptible_Vs_Control −0.20 [−0.42, 0.02]
GSE85472_CSDS_vs_Control −0.17 [−0.32, −0.02]
GSE81587_CUMS_vs_Control 0.07 [−0.23, 0.37]
GSE102556.1_CUMS_vs_Control −0.17 [−0.43, 0.08]
GSE151807_CUMS_vs_Control −0.13 [−0.22, −0.04]
Random−Effects Model −0.13 [−0.19, −0.06]
−0.6 −0.2 0.2
Observed Outcome


B.
Study
S100b
Estimate [95% CI]
GSE109315_StressResilient_Vs_Control −0.10 [−0.29, 0.08]
GSE109315_StressSusceptible_Vs_Control 0.00 [−0.13, 0.14]
GSE81672_StressResilient_Vs_Control −0.21 [−0.41, −0.01]
GSE81672_StressSusceptible_Vs_Control −0.13 [−0.35, 0.08]
GSE85472_CSDS_vs_Control −0.16 [−0.27, −0.05]
GSE81587_CUMS_vs_Control −0.08 [−0.31, 0.16]
GSE102556.1_CUMS_vs_Control −0.23 [−0.41, −0.04]
GSE151807_CUMS_vs_Control −0.14 [−0.26, −0.02]
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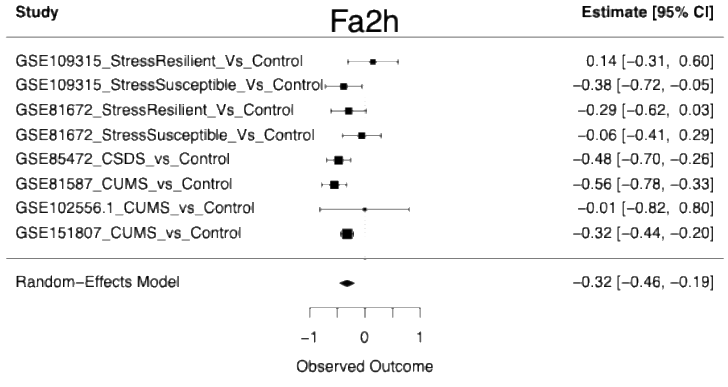
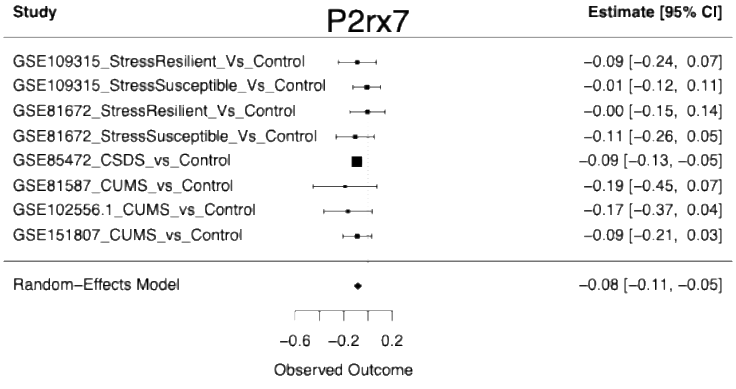
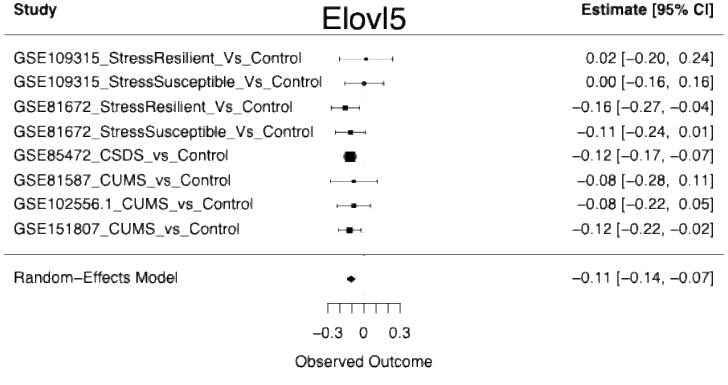
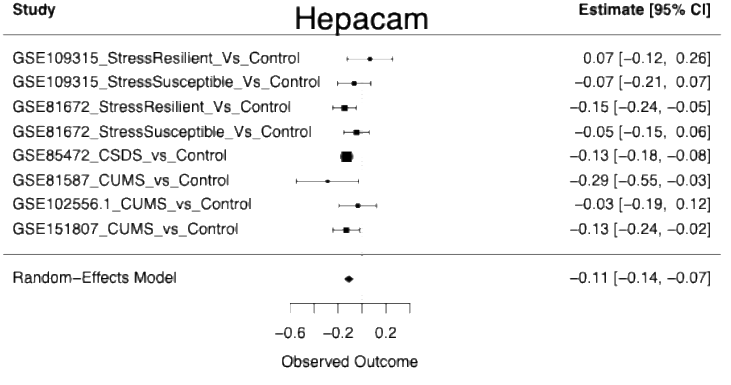
−0.6 −0.2 0.2
Observed Outcome

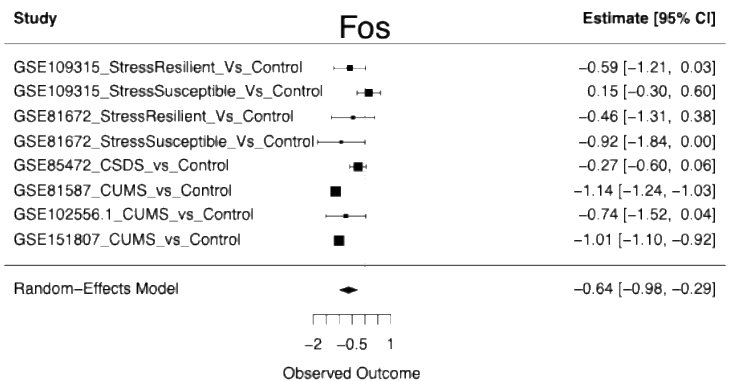

C.
Study
Fa2h
Estimate [95% CI]
GSE109315_StressResilient_Vs_Control 0.14 [−0.31, 0.60]
GSE109315_StressSusceptible_Vs_Control −0.38 [−0.72, −0.05]
GSE81672_StressResilient_Vs_Control −0.29 [−0.62, 0.03]
GSE81672_StressSusceptible_Vs_Control −0.06 [−0.41, 0.29]
GSE85472_CSDS_vs_Control −0.48 [−0.70, −0.26]
GSE81587_CUMS_vs_Control −0.56 [−0.78, −0.33]
GSE102556.1_CUMS_vs_Control −0.01 [−0.82, 0.80]
GSE151807_CUMS_vs_Control −0.32 [−0.44, −0.20]
Random−Effects Model −0.32 [−0.46, −0.19]
−1 0 1
Observed Outcome


D.
Study
P2rx7
Estimate [95% CI]
GSE109315_StressResilient_Vs_Control −0.09 [−0.24, 0.07]
GSE109315_StressSusceptible_Vs_Control −0.01 [−0.12, 0.11]
GSE81672_StressResilient_Vs_Control −0.00 [−0.15, 0.14]
GSE81672_StressSusceptible_Vs_Control −0.11 [−0.26, 0.05]
GSE85472_CSDS_vs_Control −0.09 [−0.13, −0.05]
GSE81587_CUMS_vs_Control −0.19 [−0.45, 0.07]
GSE102556.1_CUMS_vs_Control −0.17 [−0.37, 0.04]
GSE151807_CUMS_vs_Control −0.09 [−0.21, 0.03]
Random−Effects Model −0.08 [−0.11, −0.05]
−0.6 −0.2 0.2
Observed Outcome

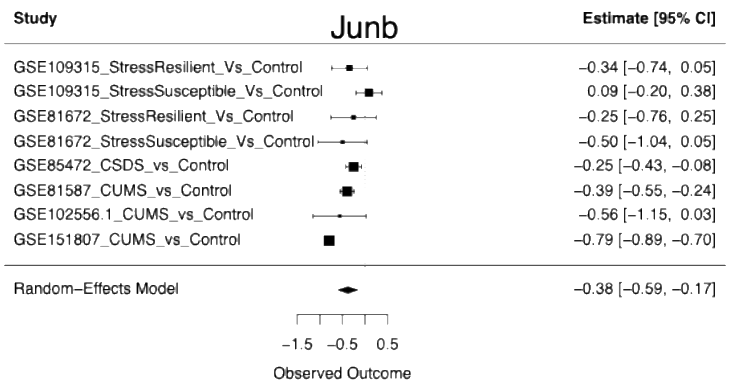

E.
Study
Elovl5
Estimate [95% CI]
GSE109315_StressResilient_Vs_Control 0.02 [−0.20, 0.24]
GSE109315_StressSusceptible_Vs_Control 0.00 [−0.16, 0.16]
GSE81672_StressResilient_Vs_Control −0.16 [−0.27, −0.04]
GSE81672_StressSusceptible_Vs_Control −0.11 [−0.24, 0.01]
GSE85472_CSDS_vs_Control −0.12 [−0.17, −0.07]
GSE81587_CUMS_vs_Control −0.08 [−0.28, 0.11]
GSE102556.1_CUMS_vs_Control −0.08 [−0.22, 0.05]
GSE151807_CUMS_vs_Control −0.12 [−0.22, −0.02]
Random−Effects Model −0.11 [−0.14, −0.07]
−0.3 0 0.3
Observed Outcome


F.
Study
Hepacam
Estimate [95% CI]
GSE109315_StressResilient_Vs_Control 0.07 [−0.12, 0.26]
GSE109315_StressSusceptible_Vs_Control −0.07 [−0.21, 0.07]
GSE81672_StressResilient_Vs_Control −0.15 [−0.24, −0.05]
GSE81672_StressSusceptible_Vs_Control −0.05 [−0.15, 0.06]
GSE85472_CSDS_vs_Control −0.13 [−0.18, −0.08]
GSE81587_CUMS_vs_Control −0.29 [−0.55, −0.03]
GSE102556.1_CUMS_vs_Control −0.03 [−0.19, 0.12]
GSE151807_CUMS_vs_Control −0.13 [−0.24, −0.02]
Random−Effects Model −0.11 [−0.14, −0.07]
−0.6 −0.2 0.2
Observed Outcome

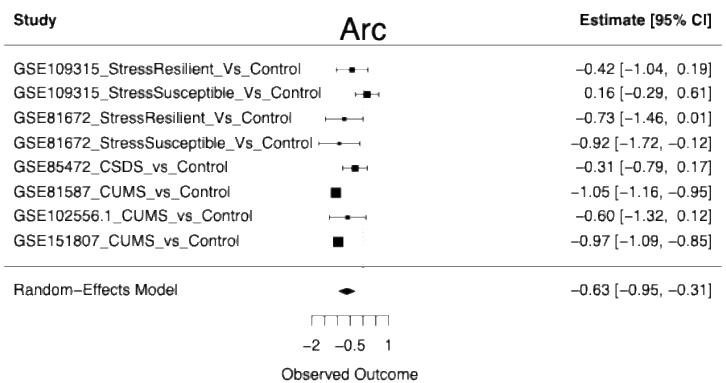
A.


Study
Fos
Estimate [95% CI]
GSE109315_StressResilient_Vs_Control −0.59 [−1.21, 0.03]
GSE109315_StressSusceptible_Vs_Control 0.15 [−0.30, 0.60]
GSE81672_StressResilient_Vs_Control −0.46 [−1.31, 0.38]
GSE81672_StressSusceptible_Vs_Control −0.92 [−1.84, 0.00]
GSE85472_CSDS_vs_Control −0.27 [−0.60, 0.06]
GSE81587_CUMS_vs_Control −1.14 [−1.24, −1.03]
GSE102556.1_CUMS_vs_Control −0.74 [−1.52, 0.04]
GSE151807_CUMS_vs_Control −1.01 [−1.10, −0.92]
Random−Effects Model −0.64 [−0.98, −0.29]
−2 −0.5 1
Observed Outcome

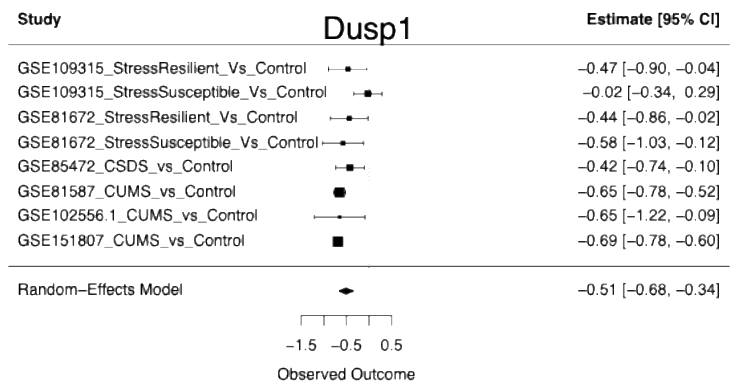
B.

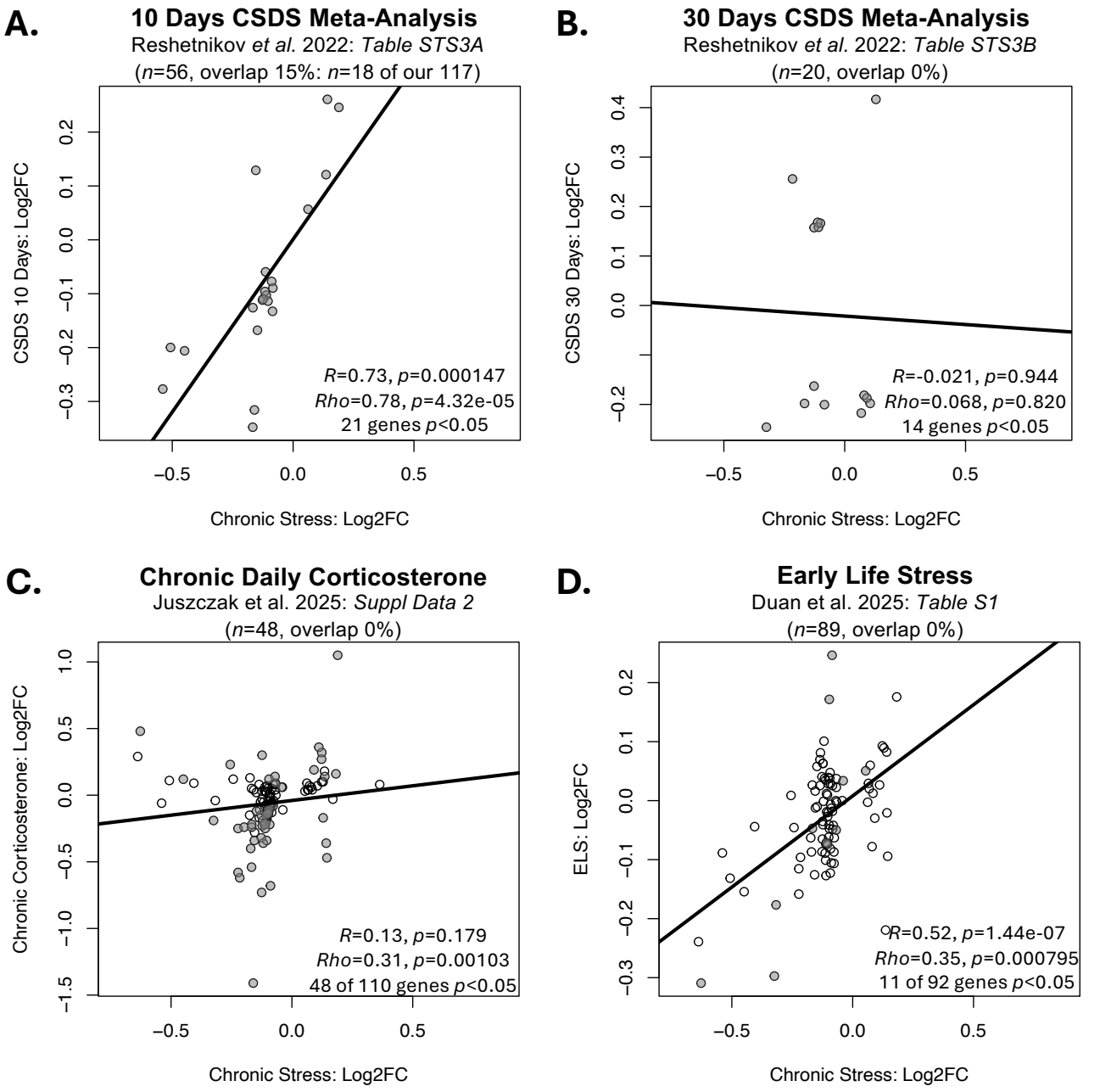

Study
Junb
Estimate [95% CI]
GSE109315_StressResilient_Vs_Control −0.34 [−0.74, 0.05]
GSE109315_StressSusceptible_Vs_Control 0.09 [−0.20, 0.38]
GSE81672_StressResilient_Vs_Control −0.25 [−0.76, 0.25]
GSE81672_StressSusceptible_Vs_Control −0.50 [−1.04, 0.05]
GSE85472_CSDS_vs_Control −0.25 [−0.43, −0.08]
GSE81587_CUMS_vs_Control −0.39 [−0.55, −0.24]
GSE102556.1_CUMS_vs_Control −0.56 [−1.15, 0.03]
GSE151807_CUMS_vs_Control −0.79 [−0.89, −0.70]
Random−Effects Model −0.38 [−0.59, −0.17]
−1.5 −0.5 0.5
Observed Outcome

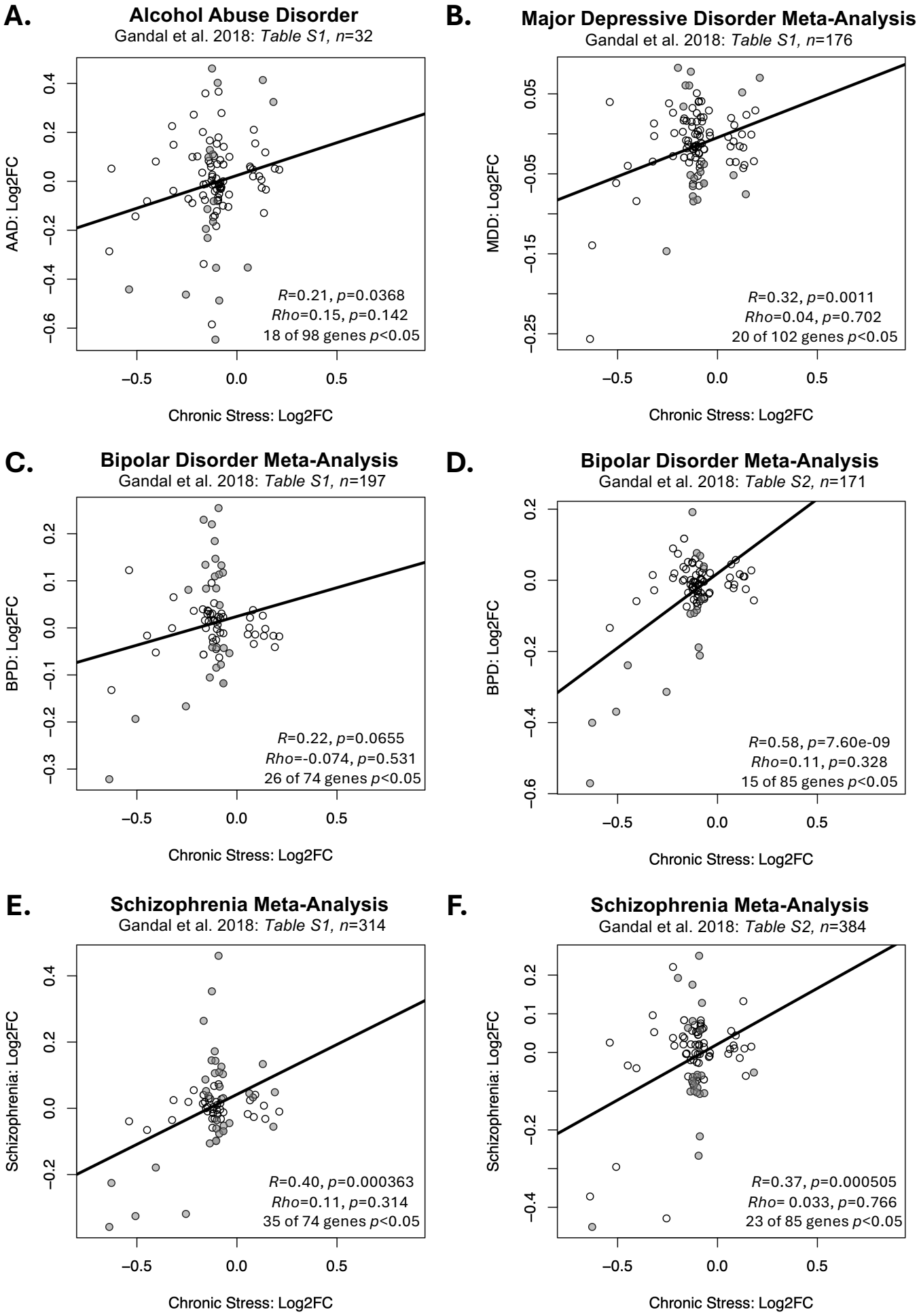
C.


Study
Arc
Estimate [95% CI]
GSE109315_StressResilient_Vs_Control −0.42 [−1.04, 0.19]
GSE109315_StressSusceptible_Vs_Control 0.16 [−0.29, 0.61]
GSE81672_StressResilient_Vs_Control −0.73 [−1.46, 0.01]
GSE81672_StressSusceptible_Vs_Control −0.92 [−1.72, −0.12]
GSE85472_CSDS_vs_Control −0.31 [−0.79, 0.17]
GSE81587_CUMS_vs_Control −1.05 [−1.16, −0.95]
GSE102556.1_CUMS_vs_Control −0.60 [−1.32, 0.12]
GSE151807_CUMS_vs_Control −0.97 [−1.09, −0.85]
Random−Effects Model −0.63 [−0.95, −0.31]
−2 −0.5 1
Observed Outcome

D.


Study
Dusp1
Estimate [95% CI]
GSE109315_StressResilient_Vs_Control −0.47 [−0.90, −0.04]
GSE109315_StressSusceptible_Vs_Control −0.02 [−0.34, 0.29]
GSE81672_StressResilient_Vs_Control −0.44 [−0.86, −0.02]
GSE81672_StressSusceptible_Vs_Control −0.58 [−1.03, −0.12]
GSE85472_CSDS_vs_Control −0.42 [−0.74, −0.10]
GSE81587_CUMS_vs_Control −0.65 [−0.78, −0.52]
GSE102556.1_CUMS_vs_Control −0.65 [−1.22, −0.09]
GSE151807_CUMS_vs_Control −0.69 [−0.78, −0.60]
Random−Effects Model −0.51 [−0.68, −0.34]
−1.5 −0.5 0.5
Observed Outcome


A.
10 Days CSDS Meta-Analysis
Reshetnikov et al. 2022: Table STS3A
(n=56, overlap 15%: n=18 of our 117)
CSDS 10 Days: Log2FC
Chronic Stress: Log2FC
R=0.73, p=0.000147
Rho=0.78, p=4.32e-05
21 genes p<0.05
B.
30 Days CSDS Meta-Analysis
Reshetnikov et al. 2022: Table STS3B
(n=20, overlap 0%)
CSDS 30 Days: Log2FC
Chronic Stress: Log2FC
R=-0.021, p=0.944
Rho=0.068, p=0.820
14 genes p<0.05
C.
Chronic Daily Corticosterone
Juszczak et al. 2025: Suppl Data 2
(n=48, overlap 0%)
Chronic Corticosterone: Log2FC
Chronic Stress: Log2FC
R=0.13, p=0.179
Rho=0.31, p=0.00103
48 of 110 genes p<0.05
D.
Early Life Stress
Duan et al. 2025: Table S1
(n=89, overlap 0%)
ELS: Log2FC
Chronic Stress: Log2FC
R=0.52, p=1.44e-07
Rho=0.35, p=0.000795
11 of 92 genes p<0.05


A.
Alcohol Abuse Disorder
Gandal et al. 2018: Table S1, n=32
AAD: Log2FC
Chronic Stress: Log2FC
R=0.21, p=0.0368
Rho=0.15, p=0.142
18 of 98 genes p<0.05
B.
Major Depressive Disorder Meta-Analysis
Gandal et al. 2018: Table S1, n=176
MDD: Log2FC
Chronic Stress: Log2FC
R=0.32, p=0.0011
Rho=0.04, p=0.702
20 of 102 genes p<0.05
C.
Bipolar Disorder Meta-Analysis
Gandal et al. 2018: Table S1, n=197
BPD: Log2FC
Chronic Stress: Log2FC
R=0.22, p=0.0655
Rho=-0.074, p=0.531
26 of 74 genes p<0.05
D.
Bipolar Disorder Meta-Analysis
Gandal et al. 2018: Table S2, n=171
BPD: Log2FC
Chronic Stress: Log2FC
R=0.58, p=7.60e-09
Rho=0.11, p=0.328
15 of 85 genes p<0.05
E.
Schizophrenia Meta-Analysis
Gandal et al. 2018: Table S1, n=314
Schizophrenia: Log2FC
Chronic Stress: Log2FC
R=0.40, p=0.000363
Rho=0.11, p=0.314
35 of 74 genes p<0.05
F.
Schizophrenia Meta-Analysis
Gandal et al. 2018: Table S2, n=384
Schizophrenia: Log2FC
Chronic Stress: Log2FC
R=0.37, p=0.000505
Rho= 0.033, p=0.766
23 of 85 genes p<0.05

ID Number	n	Species	Authors	Year	Platform	Tissue	Type of Stress	Stress Duration	Comparisons of Interest
GSE84572	12	mouse	Lehmann et al.	2017	Microarray (Affymetrix)	mPFC	CSDS	14 days, 5 min/day	Susceptible vs. Control
GSE109315	32	mouse	Laine et al.	2018	RNA-seq	mPFC	CSDS	10 days, 10 min/day	Susceptible vs. Control, Resilient vs. Control
GSE81672	25	mouse	Bagot et al.	2017	RNA-seq	PFC	CSDS	10 days, 5 min/day	Susceptible vs. Control, Resilient vs. Control
GSE81587	4	mouse	Ma et al.	2016	RNA-seq	mPFC	CUMS	3 weeks	CUMS vs. Control
GSE102556.1	38	mouse	Labonté et al.	2017	RNA-seq	PFC	CUMS	3 weeks	CUMS vs. Control
GSE151807	6	mouse	Yu et al.	2021	Microarray (Affymetrix)	PFC	CUMS	4 weeks	CUMS vs. Control

Gene Set	*p*-value	FDR	ES	NES	Size	Leading genes
Oligodendrocytes - Mature & Developing						
Ensheathment of Neurons *(GOBP)*	0.000193	0.0422	-0.637	-2.11	121	*Fa2h,Lpar1*
Oligodendrocyte Differentiation *(GOBP)*	0.000195	0.0422	-0.614	-1.95	92	*Fa2h,Lpar1,Sox9*
Oligodendrocyte Cells *(Cahoy et al. 2008, JNeuro)*	0.000194	0.0422	-0.826	-2.30	41	*Fa2h,Lgi3*
Oligodendrocyte Cells *(Zeisel et al. 2015, Science)*	0.000188	0.0422	-0.535	-2.02	389	*S1pr5,Fbxo32,Nipal4,Bfsp2,Tnni1,Fads6,Lgi3,Ppp1r16b,Gna12,Desi1,Smad7,Vangl2*
Myelinating Oligodendrocyte Cells *(Zhang et al. 2014, JNeuro)*	0.000195	0.0422	-0.810	-2.21	37	*Prr18,Trp53inp2*
Hippocampal Oligodendrocytes, Cluster marker Tfr *(DropViz)*	0.000192	0.0422	-0.821	-2.66	104	*Fa2h,S1pr5,Prr18,Lpar1,Csrp1,Tnni1*
Striatal Oligodendrocytes, Cluster marker Tfr *(DropViz)*	0.000192	0.0422	-0.803	-2.71	137	*Fa2h,S1pr5,Lpar1,Unc5b,Bfsp2,Csrp1,Olfml1,Tnni1,Lgi3,Desi1,Scd2*
Embryonic Brain Cortical Oligodendrocytes *(MSigDB: Fan)*	0.000182	0.0422	-0.495	-1.95	700	*Fa2h,S1pr5,Fbxo32,Prr18,Lpar1,Nipal4,Unc5b,Csrp1,S100b,Lgi3,Ppp1r16b,Desi1,Smad7,Reep3,Mtus1,Trp53inp2,P2rx7,Ubl3*
Prefrontal Cortical Oligodendrocyte Progenitor Cells *(MSigDB: Zhong)*	0.000195	0.0422	-0.598	-1.89	87	*Arc,S100b,Anxa5,Car10*
Fetal Cerebellar Oligodendrocytes *(MSigDB: Descartes)*	0.000198	0.0422	-0.696	-2.04	56	*Arc,Car10*
Fetal Oligodendrocytes *(MSigDB: Descartes)*	0.000196	0.0422	-0.700	-2.13	68	*Arc,Fa2h,Car10*
Oligodendrocyte Markers *(MSigDB: Lein)*	0.000194	0.0422	-0.772	-2.37	72	*Fa2h,S1pr5,Csrp1*
Astrocytes						
Hippocampal Astrocytes, Cluster Marker Gja1 *(DropViz)*	0.000193	0.0422	-0.641	-2.15	132	*Sox9,S100b,Aqp4,Hepacam*
Striatal Astrocytes, Cluster Marker Gja1 *(DropViz)*	0.000191	0.0422	-0.552	-1.87	145	*Sox9,Aqp4,Hepacam*
Prefrontal Cortical Astrocytes *(MSigDB: Zhong)*	0.000188	0.0422	-0.512	-1.89	307	*Sox9,Tcf7l2,S100b,Aqp4,Ddr1,Elovl5,Anxa5,Alpl,Ubl3*
GSE117758: Upregulated in Nucleus Accumbens Astrocytes *(Gemma)*	0.000182	0.0422	-0.487	-1.92	732	*Fos,Ccn1,Dusp1,Otx2,Fam163a,Sox9,BC034090,Csrp1,Olfml1,Aldh3b1,S100b,Aqp4,Mid1ip1,Adgra3,Gna12,Hepacam,Mmgt2,Elovl5,Gm973,Anxa5,Alpl,Ppp1r15a,Sft2d2,Kif1c*
Other Glia						
Embryonic Brain Cortical Glial Cells *(MSigDB: Fan)*	0.000193	0.0422	-0.509	-1.69	126	*S100b,Anxa5*
Midbrain Human Radial Glia 2B *(MSigDB: Manno)*	0.000187	0.0422	-0.439	-1.65	385	*Fos,Ccn1,Egr1,Sox9,Tcf7l2,Aqp4,Hepacam,Ubl3*
Midbrain Human Radial Glia 2A *(MSigDB: Manno)*	0.000183	0.0422	-0.404	-1.56	530	*Fos,Ccn1,Ier2,Egr1,Sox9,Aqp4,Hepacam,Anxa5,Ubl3*
Vasculature						
Embryonic Brain Cortical Endothelial Cells *(MSigDB: Fan)*	0.000187	0.0422	-0.409	-1.53	349	*Unc5b,Kdr,Tek,Slc39a8,Reep3,Pde8b*
Midbrain Human Endothelial Cells *(MSigDB: Manno)*	0.000181	0.0422	-0.398	-1.58	827	*Fos,Arc,Ccn1,Dusp1,Ier2,Egr1,Csrnp1,Unc5b,Csrp1,Kdr,Rbms1,Tek,Slc39a8,Anxa5,Smad7,Reep3,Map3k11,Mtus1,Alpl*
Midbrain Human Pericytes *(MSigDB: Manno)*	0.000183	0.0422	-0.418	-1.65	723	*Fos,Ccn1,Ier2,Egr1,Csrnp1,Unc5b,Olfml1,Rbms1,Anxa5,Reep3,Mtus1,Pde8b*
Adult Olfactory Neuroepithelium Vascular Smooth Muscle Cells *(MSigDB: Durante)*	0.000195	0.0422	-0.645	-1.99	76	*Fos,Egr1,Csrp1,Rcan2*
Neuron						
GSE117758: Downregulated in Nucleus Accumbens Neurons *(Gemma)*	0.000182	0.0422	-0.490	-1.94	784	*Fa2h,S1pr5,Unc5b,Sox9,Csrp1,Olfml1,Tcf7l2,Aqp4,Lgi3,Mid1ip1,Mmgt2,Elovl5,Anxa5,Car10,Bag3*
General Cell Type						
Positive Regulation of Cell Differentiation *(GOBP)*	0.000183	0.0422	-0.351	-1.38	719	*Fos,Ccn1,Dnai3,Sox9,Tcf7l2,Ngf,Kdr,Rnd2,Smad7*

Gene Set	*p*-value	FDR	ES	NES	Size	Leading genes
Stress: Contradictory Direction of Effect						
GSE100236: Genes upregulated by swim stress in the hippocampus *(Gemma)*	0.000192	0.0422	-0.716	-2.30	99	*Fos,Arc,Ccn1,Dusp1,Btg2,Ier2,Egr1, Csrnp1,Ppp1r15a*
GSE100236: Genes upregulated by novelty stress in the hippocampus *(Gemma)*	0.000193	0.0422	-0.666	-2.19	115	*Fos,Arc,Ccn1,Dusp1,Btg2,Ier2,Egr1, Csrnp1,Ppp1r15a*
GSE100236: Genes upregulated by restraint stress in the hippocampus *(Gemma)*	0.000192	0.0422	-0.682	-2.23	112	*Fos,Arc,Ccn1,Dusp1,Btg2,Ier2,Egr1, Csrnp1,Ppp1r15a*
GSE16158: Genes upregulated by trace fear conditioning in the hippocampus, timepoint 0.5h *(Gemma)*	0.000195	0.0422	-0.901	-2.16	20	*Fos,Arc,Dusp1,Btg2,Egr1*
GSE16158: Genes upregulated by trace fear conditioning in the hippocampus, timepoint 2h *(Gemma)*	0.000195	0.0422	-0.876	-2.10	20	*Fos,Arc,Dusp1,Egr1*
GSE50423: Genes upregulated by contextual fear conditioning in the hippocampus (*Gemma)*	0.000193	0.0422	-0.929	-1.93	10	*Fos,Arc,Dusp1,Btg2*
GSE63412: Genes upregulated by contextual fear conditioning memory retrieval (*Gemma)*	0.000193	0.0422	-0.932	-2.04	13	*Fos,Arc,Ccn1,Dusp1,Btg2*
GSE63412: Genes upregulated by contextual fear conditioning (*Gemma)*	0.000193	0.0422	-0.932	-2.04	13	*Fos,Arc,Ccn1,Dusp1,Btg2*
GSE74966: Genes upregulated by contextual fear conditioning (*Gemma)*	0.000194	0.0422	-0.659	-2.09	90	*Fos,Egr1,Kdr*
GSE74966: Genes upregulated by contextual fear conditioning and electric shock (*Gemma)*	0.000195	0.0422	-0.662	-2.10	92	*Fos,Egr1,Kdr*
Stress: Confirmatory Direction of Effect						
GSE50423: Genes downregulated by contextual fear conditioning in the hippocampus, timepoint 4h (*Gemma)*	0.000184	0.0422	-0.423	-1.61	464	*Fos,Arc,Ccn1,Dusp1,Btg2,Egr1,Atf4*
GSE50423: Genes downregulated by contextual fear conditioning in the hippocampus, timepoint 24h	0.000191	0.0422	-0.517	-1.79	173	*Fos,Arc,Ccn1,Dusp1,Btg2,Egr1*
GSE72343: Genes upregulated in stress resilient mice following chronic social defeat stress *(Gemma)*	0.000205	0.0422	0.779	2.21	44	*Xdh*
GSE72343: Genes upregulated in stress susceptible mice following chronic social defeat stress *(Gemma)*	0.000205	0.0422	0.779	2.21	44	*Xdh*
GSE149195: Genes upregulated following social defeat stress *(Gemma)*	0.000206	0.0422	0.791	2.02	26	
Stress-Related:						
Response to Hormone *(GOBP)*	0.000183	0.0422	-0.348	-1.38	763	*Fos,Dusp1,Btg2,Egr1,Fbxo32,Cpn1, Tshr,Tek,Alpl*
Genes downregulated in Major Depressive Disorder *(MSigDB: Aston)*	0.000191	0.0422	-0.570	-1.94	148	*Lpar1,P2rx7*
GSE95740: Genes upregulated in the dentate gyrus following environmental enrichment *(Gemma)*	0.000195	0.0422	-0.608	-1.87	74	*Fos,Arc,Dusp1,Csrnp1,Syndig1*