<u>Short Report</u>: A Meta-Analysis of the Effects of Sleep Deprivation on the Cortical Transcriptome in Animal Models

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Competing Interests

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CRediT Statement

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

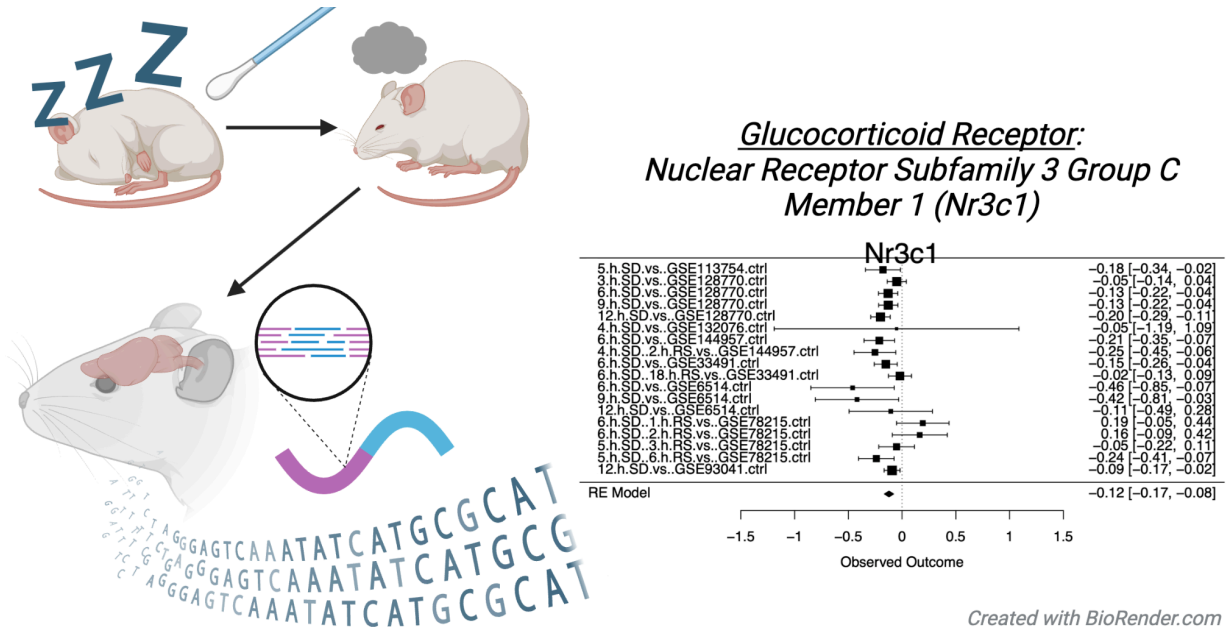
Data Availability Statement
All datasets used in this publication are publicly available In the National Center for Biotechnology Information (NCBI) Repository Gene Expression Omnibus (GEO, https://www.ncbi.nlm.nih.gov/geo/) under the accession numbers GSE6514, GSE33491, GSE78215, GSE93041, GSE113754, GSE128770, GSE132076, and GSE144957.

Abstract

Sleep deprivation (SD) causes large disturbances in mood and cognition. The molecular basis for these effects can be explored using transcriptional profiling to quantify brain gene expression. In this report, we used a meta-analysis of public transcriptional profiling data to discover effects of SD on gene expression that are consistent across studies and paradigms. To conduct the meta-analysis, we used pre-specified search terms related to rodent SD paradigms to identify relevant studies within *Gemma*, a database containing >19,000 re-analyzed microarray and RNA-Seq datasets. Eight studies met our systematic inclusion/exclusion criteria, characterizing the effect of 18 SD interventions on gene expression in the mouse cerebral cortex (collective *n*=293). For each gene with sufficient data (n=16,290), we fit a random effects meta-analysis model to the SD effect sizes (log(2) fold changes). Our meta-analysis revealed 182 differentially expressed genes in response to SD (false discovery rate<0.05), 104 of which were upregulated and 78 downregulated. Gene-set enrichment analysis revealed down-regulation in pathways related to stress response (e.g., glucocorticoid receptor *Nr3c1*), cell death and cell differentiation, and upregulation related to hypoxia and inflammation. Exploratory analyses found that the duration of SD (range: 3-12 hrs) did not significantly influence the magnitude of differential expression. Recovery sleep, which was included in three studies (range: 2-18 hrs), reversed the impact of SD on four transcripts. Our meta-analysis illustrates the diverse molecular impact of SD on the rodent cerebral cortex, producing effects that occasionally parallel those seen in the periphery.

Keywords: Sleep, RNA-Seq, Microarray, Cerebral Cortex, Meta-Analysis

Graphical Abstract



Introduction

Sleep disruption, restriction, or deprivation (SD) negatively impacts many aspects of mood and cognition, causing depression, anxiety, impaired memory and cognitive abilities (Medic et al., 2017; Van Dongen et al., 2003). These effects are accompanied by large changes in cortical activity (Van Dongen et al., 2003). To gain insight into the molecular basis for these effects, gene expression (mRNA) can be quantified in the cortex following SD using transcriptional profiling methods such as microarray and RNA-Seq.

Transcriptional profiling provides rich information but also presents many challenges, including methodological variability due to sample mislabeling (Toker et al., 2016), batch effects (Zhou et al., 2019), and dissection heterogeneity (Hagenauer et al., 2018). Also, due to expense, sample sizes in transcriptional profiling experiments tend to be small, providing low statistical power and increased risk of false negative and false positive findings (Button et al., 2013).

To overcome these challenges, we used meta-analysis to identify consistent effects of SD on the cerebral cortex within public transcriptional profiling datasets. Our meta-analysis focused on the effects of SD in laboratory rodents, induced by various methods for waking the animal soon after sleep initiation. As rodents have shorter sleep-wake cycles than humans, rodent SD interventions tend to occur on the scale of hours instead of days (Pires et al., 2016), with longer periods of SD expected to result in more dramatic effects (Van Dongen et al., 2003). We included a variety of SD paradigms and subject characteristics in our meta-analysis to increase the generalizability of our findings. When possible, we used standardized, systematic methods for dataset identification, selection, and result extraction to reduce bias and improve the quality of our results.

Methods

The R code (R v.4.2.0, R studio v.2022.02.4) and detailed methods used for our meta-analysis can be found at: *https://github.com/rhoadsco/Sleep-Deprivation-MetaAnalysis*.

General Overview: This meta-analysis was completed 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 (pipeline for 2022: *dx.doi.org/10.17504/protocols.io.j8nlk84jxl5r/v1*, *not pre-registered*), leveraging 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.

Dataset Identification and Selection: Potential datasets were identified in the *Gemma* database using search terms related to rodent SD paradigms (n=106), and narrowed using standardized inclusion/exclusion criteria (**Figure 1,** criteria: *dx.doi.org/10.17504/protocols.io.j8nlk84jxl5r/v1*, completed by researcher CAR). Datasets were then removed that lacked relevant SD differential

expression results in *Gemma* or samples from the murine or rat cerebral cortex. An additional dataset was removed due to brain collection occurring multiple days (192 hrs) following sleep deprivation. Following exclusions, 8 relevant datasets remained containing 18 SD interventions (SD vs. control contrasts) (**Table 1**). At this stage, all inclusion/exclusion decisions were reviewed by a second researcher (MHH) and final decisions discussed with the full 2022 cohort of the *Brain Data Alchemy Project* (CAR, MHH, EF, JX, EH, DMN, AS).

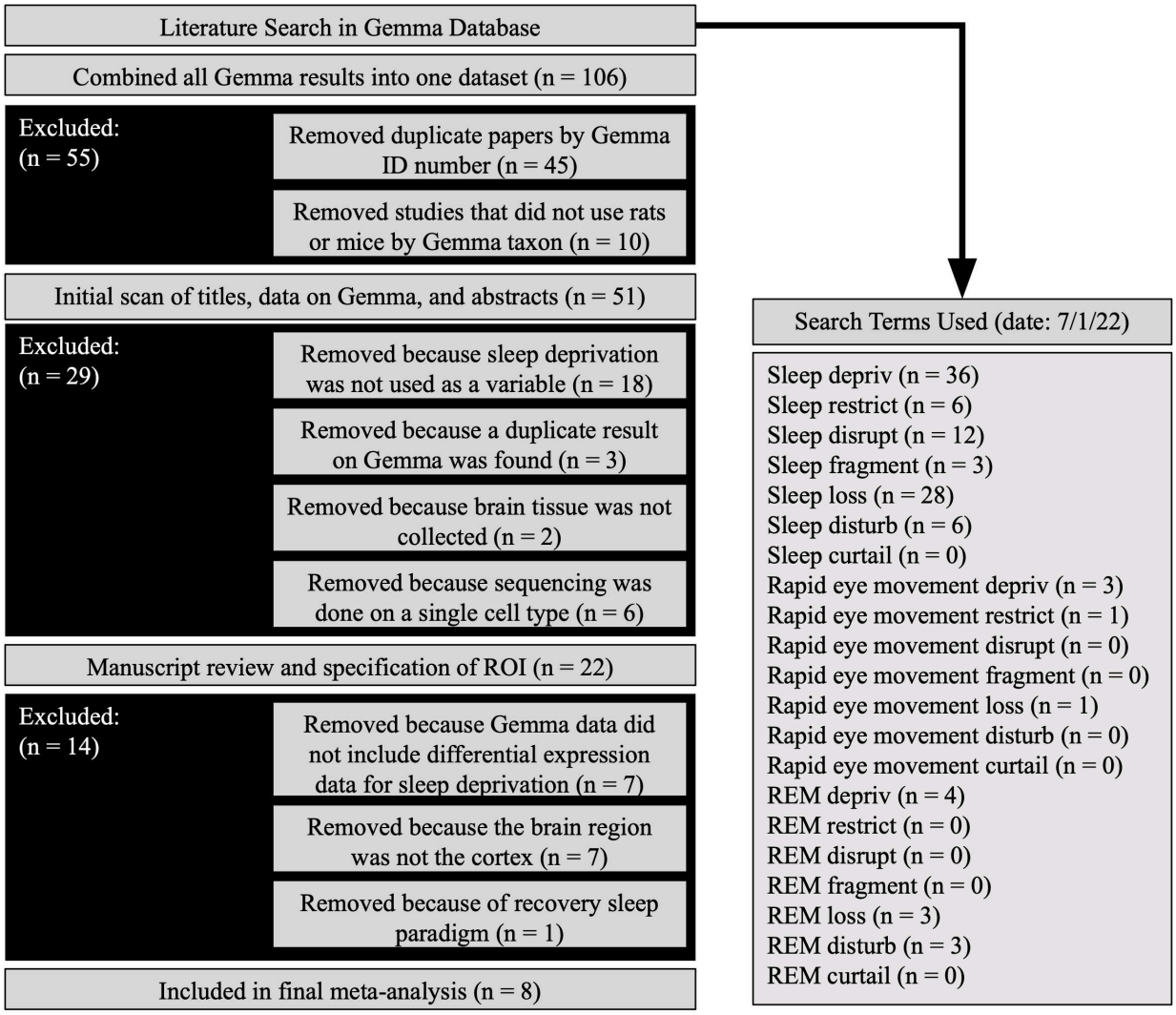


***Figure 1**. Diagram illustrating the dataset search terms and selection criteria used for the meta-analysis. Abbreviations: ROI (Region of Interest), n (number of datasets)*

The eight selected datasets all used the gentle handling SD method in mice, with paradigms that varied between 3-12 hours of SD. Three datasets included some duration of recovery sleep (RS: 2-18 hrs), defined as the period between an SD treatment and sacrifice of the animal, during which time the animal was freely allowed to sleep. The final collective sample size was *n*=293, with sufficient power (80%) to detect medium effect sizes using a traditional alpha (0.05).

Dataset ID	n	Species	Authors	Year	Region	Platform	Type of Sleep Dep	Comparisons of Interest
GSE6514	45	Mouse (C57BL/6J)	Mackiewicz et al.	2007	Cerebral Cortex	Affymetrix GeneChip Mouse Genome 430 2.0 Array	Gentle Handling	6h SD vs. Ctrl 9h SD vs. Ctrl 12h SD vs Ctrl
GSE33491	9	Mouse (C57BL/6J)	Hinard et al.	2012	Cerebral Cortex	Affymetrix Mouse Exon 1.0 ST Array	Unknown	6h SD vs. Ctrl 6h SE + 18h RS vs. Ctrl
GSE78215	65	Mouse (C57BL/6J)	Gerstner et al.	2016	Cerebral Cortex	Affymetrix Mouse Gene 2.1 ST Array	Gentle handling	6h SD + 1h RS vs. Ctrl 6h SD + 2h RS vs. Ctrl 5h SD + 3h RS vs. Ctrl 5h SD + 6h RS vs. Ctrl
GSE93041	9	Mouse (C57BL6/J)	Orozco- Solis et al.	2017	Anterior Cingulate Cortex	Affymetrix Mouse Gene 2.0 ST Array	Constant movement	12h SD vs. Ctrl
GSE113754	20	Mouse (C57BL6/J)	Ingiosi et al.	2019	Prefrontal Cortex	RNA-Seq	Gentle handling	5h SD vs. Ctrl
GSE128770	108	Mouse (C57BL6/J)	Guo et al.	2019	Medial Prefrontal Cortex	RNA-Seq	Gentle handling	3h SD vs. Ctrl 6h SD vs. Ctrl 9h SD vs. Ctrl 12h SD vs. Ctrl
GSE132076	4	Mouse (C57BL6/J)	Muheim et al.	2019	Cerebral Cortex	RNA-Seq	Gentle handling	4h SD vs. Ctrl
GSE144957	33	Mouse (C57BL6/J)	Bjorness et al.	2020	Frontal Cortex	RNA-Seq	Gentle handling	6h SD vs. Ctrl 4h SD + 2h RS vs. Ctrl

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) for the subset of the dataset used in the differential expression analysis, authors and year of publication (Bjorness et al., 2020; Gerstner et al., 2016; Guo et al., 2019; Hinard et al., 2012; Ingiosi et al., 2019; Mackiewicz et al., 2007; Muheim et al., 2019; Orozco-Solis et al., 2017), brain region sampled, and transcriptional profiling platform. Study details include the sleep deprivation paradigm and specific experimental groups included in the statistical contrasts extracted for inclusion in the meta-analysis. Abbreviations: h (hour), SD (sleep deprivation), RS (recovery sleep).*

Result Extraction: The differential expression results for each of the relevant 18 statistical contrasts (SD vs. control group comparisons) were imported into R using Gemma's API. Rows lacking unambiguous gene symbol annotation were excluded, and gene-level average effect sizes (log2 fold change or Log2FC) and their respective standard errors 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 SD effect sizes (Log2FC values) and accompanying SV for each gene that was represented in at least 13 of the 18 statistical contrasts derived from the 8 studies (n=16,290). Due to limited dataset availability, we used a simple, intercept-only model as our main outcome. As a secondary (exploratory) outcome, we re-ran the meta-analysis with SD duration included as a numeric predictor (centered on average duration)

and recovery sleep (RS) included as a factor (intercept=no recovery sleep). 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*) was performed on the meta-analysis results (Sergushichev, 2016), ranked by estimated Log2FC, using the *Brain.GMT* gene set database (v1: (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.

Results

Planned Meta-Analysis: Eight datasets examining the effects of SD on the cortex survived our inclusion/exclusion criteria (Bjorness et al., 2020; Gerstner et al., 2016; Guo et al., 2019; Hinard et al., 2012; Ingiosi et al., 2019; Mackiewicz et al., 2007; Muheim et al., 2019; Orozco-Solis et al., 2017), and the differential expression results from eighteen relevant SD vs. control statistical contrasts (group comparisons) from those datasets were extracted for inclusion in our meta-analysis (collective n=293). Of the 16,290 genes included in the meta-analysis, 16,255 produced stable meta-analysis estimates (full results: **Table S1)**. Our meta-analysis revealed 182 differentially expressed genes ("DEGs": FDR<0.05), 104 of which were upregulated and 78 downregulated (examples: **Figure 2**).

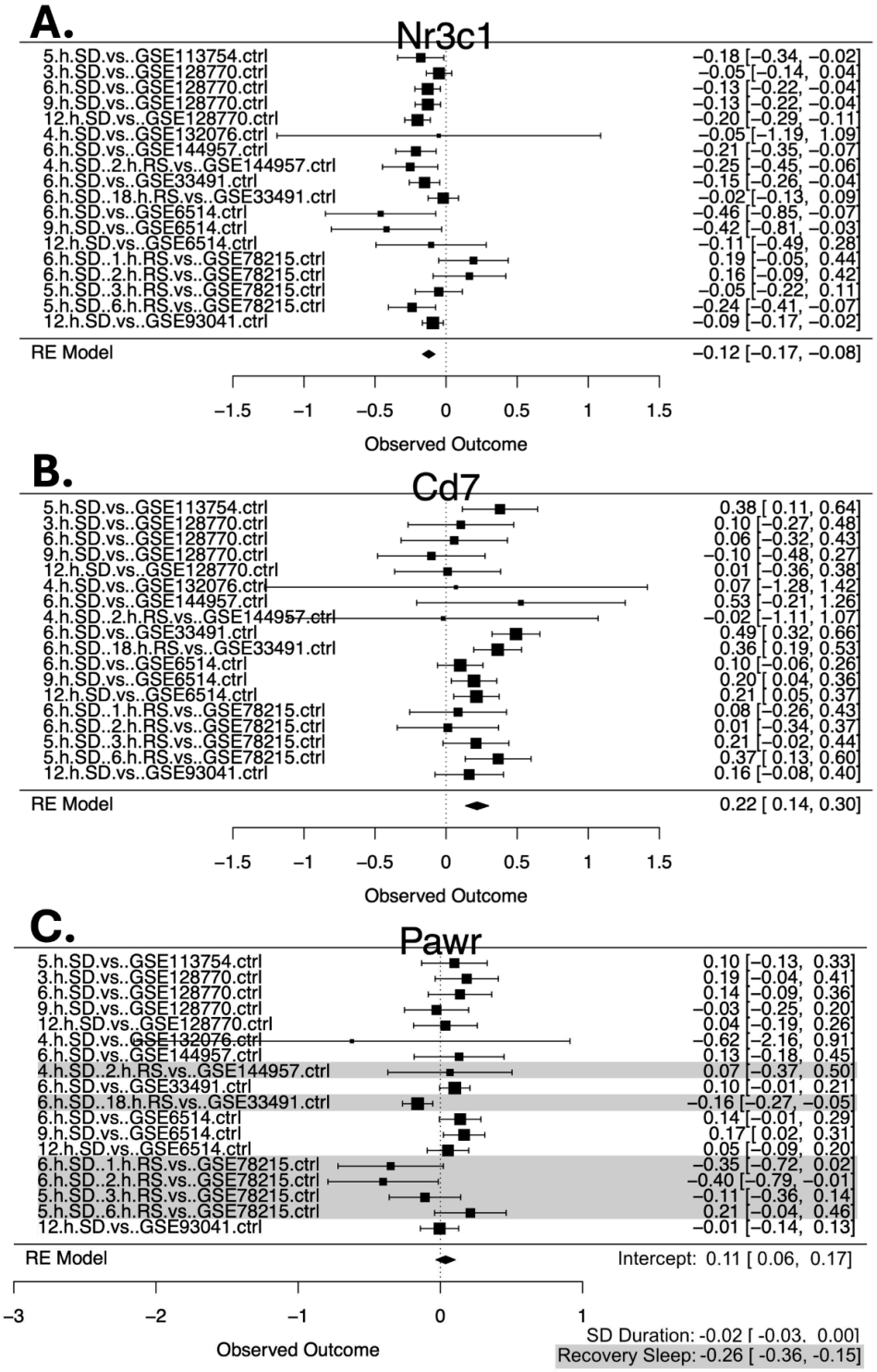


Figure 2. *Example forest plots that show genes that were identified as consistently differentially expressed in the cortex across SD paradigms and experiments in our meta-analysis. Rows illustrate the effect sizes (SD vs. control Log2FC) with squares, with 95% confidence intervals (whiskers), for each of the datasets and the meta-analysis random effects meta-analysis model ("RE Model"). Each study is named using the duration of SD in hours (h), the Gene Expression*

Omnibus accession number (GSE#), and, if relevant, the duration of recovery sleep (RS) in hours (hr). ***A.*** *Nuclear Receptor Subfamily 3 Group C Member 1 (Nr3c1) was consistently down-regulated across SD paradigms and experiments. Nr3c1 is a glucocorticoid receptor involved in stress response pathways.* ***B.*** *CD7 Molecule (Cd7) was consistently upregulated across SD paradigms and experiments. Cd7 is a member of the immunoglobulin superfamily and plays an important role in immune function.* ***C.*** *Exploratory Analysis: Pro-Apoptotic WT1 Regulator (Pawr) was upregulated with SD (RE Model: "Intercept") in a manner that did not seem to depend on SD Duration (RE Model: "SD Duration") but appeared reversed by recovery sleep (highlighted gray, RE Model: "Recovery Sleep"). Pawr promotes apoptosis, which is programmed cell death.*

Functional Ontology: Gene set enrichment analysis (fGSEA) revealed biological pathways enriched with differential expression following SD, as identified by our meta-analysis. Of the 10,436 gene sets included in the fGSEA analysis, 236 gene sets were enriched with differential expression (FDR<0.05, full results: **Table S2**), most of which were downregulated (200 of 236). These down-regulated gene sets were dominated by a correlated cluster of leading edge genes that included the DEG *Nuclear Receptor Subfamily 3 Group C Member 1* (*Nr3c1)*, which is the glucocorticoid receptor involved in stress response (**Figure 2A**), as well as many immediate early genes (*Fos Proto-Oncogene, AP-1 Transcription Factor Subunit* (*Fos), Early Growth Response 2 (Egr2), JunB Proto-Oncogene, AP-1 Transcription Factor Subunit (Junb)*, etc.) which weren't individually significant differentially expressed in the meta-analysis. These gene sets also tended to include two other DEGs from our meta-analysis: *Tropomodulin 3* (*Tmod3)* and *Nuclear Receptor Subfamily 2 Group E Member 1* (*Nr2e1)*. These down-regulated gene sets were predictably involved in the stress response and immediate early gene responses, but also pathways associated with plasticity, growth and development, and vasculature. In contrast, upregulated gene sets were associated with pathways related to adaptation challenges, such as stress, hypoxia, inflammation, and microglia, with leading edge genes including known mediator DEGs *Hypoxia Inducible Factor 3 Subunit Alpha* (*Hif3a)* and *CD7 Molecule* (*Cd7)* (**Figure 2B**).

Leading genes in gene set include:	**# of gene sets with FDR<0.05**
Immediate early genes and *Nr3c1*	155
Hif3a	10
Cd7	15
Total # of gene sets with FDR<0.05	**236**

Table 2. *The gene sets enriched with differential expression included many of the same genes/gene families. Note that the leading genes mentioned are not all of the leading genes in the gene set, just examples of genes present repeatedly in a large number of the enriched gene sets. Abbreviations: FDR: False Discovery Rate, Nr3c1: Nuclear Receptor Subfamily 3 Group C Member 1, Hif3a: Hypoxia Inducible Factor 3 Subunit Alpha, Cd7: CD7 Molecule.*

Exploratory Meta-Analysis: We ran a follow-up exploratory meta-analysis to examine whether the differential expression results were modulated by SD duration or the addition of recovery sleep (RS) following SD. Of the 8 datasets (n=18 contrasts) included in the meta-analysis, 3 (n=6 contrasts) included RS (ranging from 2-18 hours). We found that SD duration did not significantly influence differential expression (full results: **Table S3**). The addition of RS, however, induced a reversal of SD differential expression in a small set of genes with diverse functions: *Major urinary protein 3* (*Mup3)* and *PRKC, apoptosis, WT1, regulator* (*Pawr),* and *doublecortin like kinase 1 (Dclk1)* were upregulated with SD and downregulated with RS and *aminoadipate aminotransferase* (*Aadat)* was downregulated with SD and upregulated with RS.

Discussion

Investigating the effects of sleep deprivation (SD) on the brain is important due to the prevalence of sleep disorders and sleep disruption (Li et al., 2018; Patel et al., 2010). Our meta-analysis revealed that SD has varied and multi-directional effects on gene expression in the rodent cerebral cortex. We found an enrichment of differential expression within many functional gene sets, with downregulation related to the stress response, immediate early genes, plasticity, growth, and vasculature, and upregulation related to hypoxia and inflammation. In this respect, the effects that we identified in the cortex parallel dysregulation observed following SD in peripheral stress response (Medic et al., 2017), cardiovascular and immune systems (Tobaldini et al., 2017).

Many effects were remarkably consistent across SD paradigms and laboratories, with a period of SD as small as 3 hours inducing differential expression in implicated biological pathways. Surprisingly, within an exploratory analysis, SD duration did not significantly modulate our differential expression results. This could suggest a plateau in measurable SD effects on cortical expression, such that the SD paradigms used in our meta-analysis had similar biological consequences. That said, our power to detect relationships between SD duration and gene expression was smaller than our power to detect simple SD effects. As expected, we did find that recovery sleep (RS) following SD reduced the effect of SD, but only for a handful of genes, again most likely due to limited power. As future datasets are released, updating our meta-analysis will likely result in additional findings.

In conclusion, by performing a meta-analysis of eight publicly available transcriptional profiling studies characterizing the effects of SD on the cerebral cortex (collective *n*=293), we improved the reliability and generalizability of our inferences regarding SD effects on cortical gene expression. By releasing the full meta-analysis results (**Table S1:** 16,255 genes, with 182 DEGs) and gene set enrichment results (**Table S2:** 10,436 gene sets, with 236 with FDR<0.05), we provide a useful resource to compare to cortical transcriptional profiling results from patients with conditions characterized by chronic sleep disruption, including psychiatric, neurodegenerative, and neurodevelopmental disorders. Future directions include elucidating mechanisms by which identified DEGs might mediate behavioral and physiological consequences of SD, and exploring translation from animal models to clinical applications.

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Supplemental Table Legends

Table S1. The full meta-analysis results (16,290 genes, 16,255 stable meta-analysis estimates). *This .xlsx file includes two worksheets: 1) The worksheet "SleepDeprivation_MetaAnalysisResults" provides the full meta-analysis results, with each row representing the results for one gene, and each column providing either gene annotation or meta-analysis statistical output. The results are ordered by p-value, so that the top rows in the worksheet are the genes with the smallest p-values. 2) The worksheet "ColumnDefinitions" provides the definitions for the variables present in each column in "SleepDeprivation_MetaAnalysisResults".*

Table S2: The full fast Gene Set Enrichment Analysis (fGSEA) results (10,436 gene sets). *This .xlsx file includes two worksheets: 1) The worksheet "fGSEA_Results" provides the full fGSEA results, with each row representing the results for one gene set, and each column providing the fGSEA statistical output. The results are ordered by p-value, so that the top rows in the worksheet are the gene sets with the smallest p-values. 2) The worksheet "ColumnDefinitions" provides the definitions for the variables present in each column in "fGSEA_Results".*

Table S3. The full exploratory meta-analysis results (16,290 genes, 16,248 stable meta-analysis estimates). *This .xlsx file includes two worksheets: 1) The worksheet "ExploratoryMeta_FullResults" provides the full exploratory meta-analysis results, with each row representing the results for one gene, and each column providing either gene annotation or meta-analysis statistical output. The results are ordered by p-value for the effect of recovery sleep (RS), so that the top rows in the worksheet are the genes with the smallest p-values. 2) The worksheet "ColumnDefinitions" provides the definitions for the variables present in each column in "ExploratoryMeta_FullResults".*