The Effects of Antidepressants on the Hippocampus: A Meta-Analysis of Public Transcriptional Profiling Data

Eva M. Geoghegan[1], Megan H. Hagenauer Ph.D.[2*], Erin Hernandez[3], Sophia Espinoza[4], Elizabeth Flandreau Ph.D.[5], Phi T. Nguyen Ph.D.[1], Mubashshir Ra'eed Bhuiyan[2], Sophie Mensch[2], Stanley Watson Jr. M.D., Ph.D.[2], Huda Akil Ph.D.[2], René Hen Ph.D.[1]

1. Columbia University, New York, NY, USA
2. University of Michigan, Ann Arbor, MI, USA
3. University of Chicago, Chicago, IL, USA
4. Michigan State University, East Lansing, MI, USA
5. Grand Valley State University, Allendale, MI, USA

Corresponding author:

Megan Hagenauer

Michigan Neuroscience Institute

University of Michigan

Ann Arbor, MI 48109

hagenaue@umich.edu

Acknowledgements:

This work was completed as part of the *Brain Data Alchemy Project* and supported by the Hope for Depression Research Foundation (HDRF: HA, RH), University of Michigan Undergraduate Research Opportunities Program (SE), Grinnell College Center for Careers, Life, and Service (EH & TQD), National Institute on Drug Abuse (NIDA U01 DA043098: HA), and the Pritzker Neuropsychiatric Disorders Research Foundation (HA & SJW). Funders and sponsors had no active role in the review. In addition, a thank you to all the other members of the Brain Data Alchemy Project 2024 cohort who helped with critical discussions, ideas and feedback: Lakshmi Chennupati, Ashlee Lewis, Anna Drozman, Brandon Hughes, Duy Nguyen and Toni Duan.

Competing Interests

The authors declare no potential conflict of interests. Several authors are members of the Pritzker Neuropsychiatric Disorders Research Consortium (MHH, HA, SJW), which is supported by the Pritzker Neuropsychiatric Disorders Research Fund L.L.C. A shared intellectual property agreement exists between this philanthropic fund and the University of Michigan, Stanford University, the Weill Medical College of Cornell University, the University of California at Irvine, and the HudsonAlpha Institute for Biotechnology to encourage the development of appropriate findings for research and clinical applications.

CRediT statement

EMG - 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
EH: Conceptualization, Methodology, Software, Formal analysis, Investigation, Data Curation, Writing - Original Draft, Writing - Review & Editing, Visualization
SE: Conceptualization, Methodology, Software, Writing - Review & Editing
EIF: Conceptualization, Methodology, Writing - Review & Editing
PTN: Writing - Review & Editing
MRB: Conceptualization, Methodology, Writing - Review & Editing
SM: Conceptualization, Methodology, Writing - Review & Editing
SJW: Writing - Review & Editing, Funding acquisition
HA: Writing - Review & Editing, Supervision, Funding acquisition
RH: Conceptualization, Methodology, Writing - Review & Editing, Supervision, Funding acquisition

Abstract

Background: Major depressive disorder (MDD) is characterized by persistent depressed mood and loss of interest and pleasure in life, known as anhedonia. The first line of treatment for MDD is antidepressant medication that enhances signaling by monoamine neurotransmitters, such as serotonin and norepinephrine. Other treatments include non-pharmaceutical treatments, such as electroconvulsive therapy and transmagnetic stimulation, and non-traditional pharmaceutical antidepressants that function via alternative, often unknown, mechanisms.

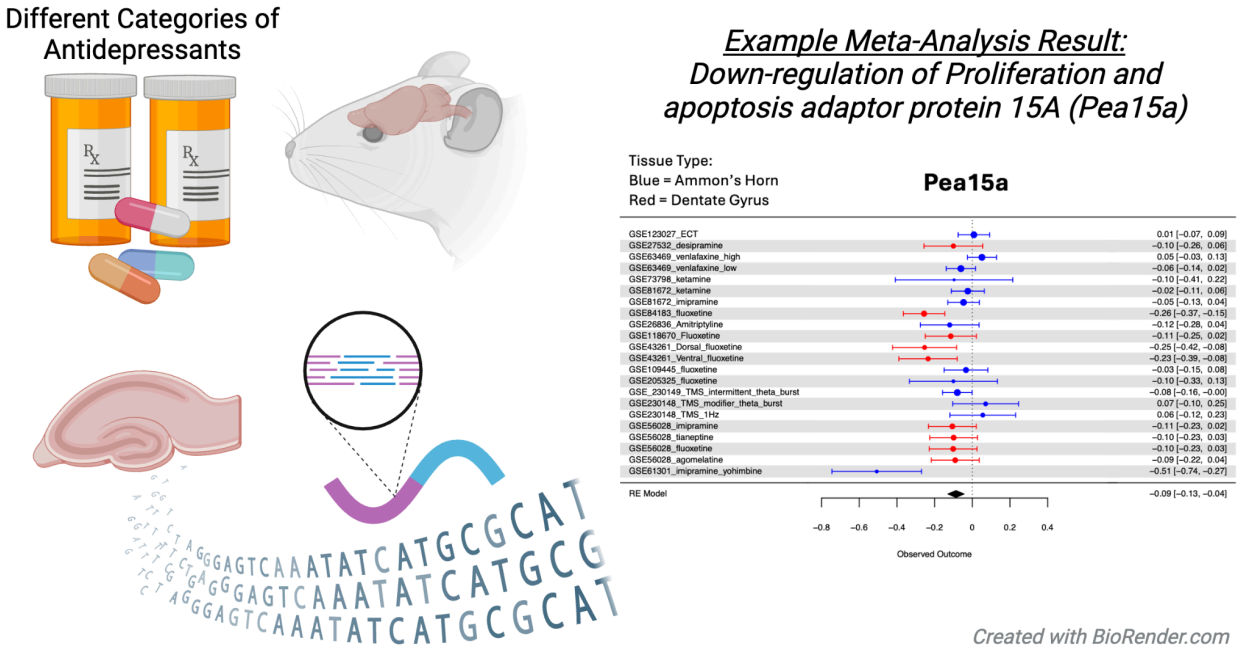
Methods: To identify mechanisms of action shared across antidepressant categories, we examined changes in gene expression following treatment with both traditional and non-traditional antidepressants, using a meta-analysis of public transcriptional profiling data from laboratory rodents (rats, mice). We focused on the hippocampus, which is a brain region that is well-documented via neuro-imaging to show morphological changes in depression that reverse with antidepressant usage. We specifically focused on treatment during adulthood, and included both clinically-used antidepressants (both pharmaceutical and non-pharmaceutical) and treatments demonstrated to effectively treat depressive mood symptoms. The outcome variable was gene expression in bulk dissected hippocampus as measured by microarray or RNA-Seq. To conduct our project, we systematically reviewed available datasets in the Gemma database of curated, reprocessed transcriptional profiling data using pre-defined search terms and inclusion/exclusion criteria. We identified 15 relevant studies containing a total of 22 antidepressant vs. control group comparisons (collective n=352). For each gene, a random effects meta-analysis model was then fit to the antidepressant vs. control effect sizes (Log2 Fold Changes) extracted from each study.

Results: Our meta-analysis yielded stable estimates for 16,439 genes, identifying 58 genes that were consistently differentially expressed (False Discovery Rate<0.05) across antidepressant experiments and categories. Of these genes, 23 were upregulated and 35 were downregulated. The functions associated with the differentially expressed genes were diverse, including modulation of the stress response, immune regulation, neurodevelopment and neuroplasticity.

Conclusion: The genes that we identified as consistently differentially expressed across antidepressant categories may be worth investigating as potential linchpins for antidepressant efficacy or as targets for novel therapies.

Keywords: Antidepressant, Hippocampus, Meta-analysis, RNA-Seq

Graphical Abstract



Key Points

- Depression can be treated with traditional antidepressants targeting monoaminergic function, as well as multiple other drug classes and non-pharmaceutical interventions.
- Understanding the congruent effects of different types of antidepressant treatments on sensitive brain regions, such as the hippocampus, can highlight essential mechanisms of action.
- A meta-analysis of fifteen public transcriptional profiling datasets identified 58 genes that are differentially expressed in the hippocampus across antidepressant categories.

Plain Language Summary

Major depressive disorder is characterized by persistent depressed mood and loss of interest and pleasure in life. Worldwide, an estimated 5% of adults suffer from depression, making it a leading cause of disability. The current standard of care for depressed individuals includes psychotherapy and antidepressant medications that enhance signaling by monoamine neurotransmitters, such as serotonin and norepinephrine. Other treatments include non-traditional antidepressants that function via alternative, often unknown, mechanisms. To identify mechanisms of action shared across different categories of antidepressants, we performed a meta-analysis using fifteen public datasets to characterize changes in gene expression (mRNA) following treatment with both traditional and non-traditional antidepressants. We focused on the hippocampus, which is a brain region that is sensitive to both depression and antidepressant usage. We found 23 genes that had consistently higher levels of expression (mRNA) and 35 genes that had consistently lower levels of expression (mRNA) across antidepressant categories. The functions associated with these genes were diverse, including regulation of stress response, the immune system, brain growth and adaptability. These genes are worth investigating further as potential linchpins for antidepressant efficacy or as targets for novel therapies.

Introduction

MDD is a serious disorder that is characterized by consistent depressed mood or markedly diminished pleasure in daily activities [1]. An estimated 14.5 million adults in the United States (US) had at least one major depressive episode with severe impairment in 2021 [2]. Worldwide, an estimated 5% of adults suffer from depression making it a leading cause of disability [3,4]. Depression is associated with increased mortality, and with physical disorders including cancer and cardiovascular disease [5]. Although antidepressant treatments are effective for some patients, around 30 - 40% of patients fail to respond to first-line treatment [6]. Therefore, continued investigation into the mechanisms of action of both traditional pharmacological treatments and non-traditional antidepressant treatments is warranted to better understand both their congruent and differing neurobiological effects for improving individualized treatment options.

It has been widely acknowledged that the treatment of depression is not one-size-fits-all. The current standard of care includes evidence-based psychotherapies and specific classes of drugs, which may be guided by specific blood biomarkers that may act as predictors of treatment outcomes [7,8]. Many first-line antidepressants target monoamine neurotransmitter function, such as selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs), which all enhance monoamine neurotransmission [9,10], [11]. With that said, monoamine potentiation may not be the direct mechanism of action for these antidepressant drugs as there is a clear difference in the timescales of monoamine potentiation and clinical improvement which usually requires several weeks [10].

Other varying classes of pharmacological treatments have also shown promise for treating depression. Ketamine, a N-Methyl-D-aspartate receptor (NMDAR) antagonist, has been shown to have rapid acting antidepressant effects that are sustained for up to seven days. The potential mechanisms of action for ketamine at subanesthetic doses include blocking NMDA receptors on GABAergic inhibitory interneurons and subsequent disinhibition of downstream excitatory pyramidal neurons, with the ventral hippocampus-medial prefrontal cortex pathway being crucial for the antidepressant response [12,13] [14]. Alpha-2 adrenergic antagonists have therapeutic value for accelerating the treatment response times of traditional pharmacological treatments by reversing a desensitization of alpha-2 adrenoceptors that has been associated with chronic administration of certain TCAs [15,16]. Agomelatine is an antidepressant approved in Europe and Australia and is an agonist of both melatonin and some serotonin receptors. Its synergistic action on both receptor types influences serotonin and melatonin levels, brain-derived neurotrophic factor (BDNF) expression and circadian rhythms [6,17,18]. Tianeptine, an atypical antidepressant that is approved for use in some countries, had initially conflicting data regarding its mechanisms of action [19]. It is now believed to be its agonistic activity on the μ-opioid receptor that is responsible for its antidepressant effects [20,21].

Brain stimulation therapies such as electroconvulsive therapy (ECT) and transcranial magnetic stimulation (TMS) are also used to treat depression. ECT has a faster onset of therapeutic response in comparison to traditional pharmacological treatments, and theories of its mechanisms of antidepressant action include increased GABAergic function and increased neurogenesis, but the specific mechanism of action is unclear [22,23]. The antidepressant effects of TMS are not immediate and maximum therapeutic effect is accumulated over multiple sessions. It is accepted that it facilitates synaptic plasticity within the target site (most commonly the dorsolateral prefrontal cortex) [24].

In general, many antidepressant treatments may alleviate depressive symptoms via effects on the hippocampus. In neuroimaging studies, hippocampal volume reduction is common in patients with depression, potentially due to prolonged exposure to glucocorticoids and stress-induced reduction in neurotrophic factors and neurogenesis [25]. Reduced hippocampal volume may also be a pre-existing risk factor for depression [26–28]. Antidepressants reverse or prevent the trend of hippocampal atrophy in depression. This reversal may be due to stopping stress-induced dendritic retraction or increasing adult

hippocampal neurogenesis (AHN) in the dentate gyrus [29–31]. AHN has been seen to be necessary for the antidepressant effects of treatments, specifically for fluoxetine (SSRI) and imipramine (TCA) [31,32]. Other treatments such as ECT have also been seen to increase AHN, and a recent study showed increased immunoreactivity of the neuroplasticity marker doublecortin in the dentate gyrus (DG) of post-mortem samples of depressed donors who had received ECT [33,34]. Despite this growing evidence, it is still unclear whether increases in hippocampal neuroplasticity and AHN are a necessary and sufficient mechanism for the antidepressant effects of all treatment classes.

In order to better understand the effects of antidepressant treatments on the hippocampus, we conducted a meta-analysis of publically-available rodent transcriptional profiling data from hippocampal tissue. Transcriptional profiling technologies quantify gene expression in tissues. By conducting a meta-analysis across studies using different classes of antidepressants, we hoped to identify patterns of gene expression common to a wide variety of antidepressant treatments while also increasing statistical power to provide stronger insights into patterns of gene expression underlying functional changes in the hippocampus.

Methods

The meta-analysis project was conducted using a standardized pipeline (protocol: [35], *not pre-registered*) and associated code repository (https://github.com/hagenaue/BrainDataAlchemy). The code used for the project is available at: https://github.com/evageoghegan/AntidepressantMetaAnalysis. R (v.4.4.1) and RStudio (v.2024.9.9.365) were used for statistical computing [36,37].

Information source

The Gemma Database was used to access comprehensive curated and reprocessed public transcriptional profiling data [38,39]. The Gemma database contains differential expression results for nearly 20,000 publicly available transcriptional profiling datasets, representing approximately 600,000 samples [39,40]. We focused on the Gemma database to provide consistency in our meta-analysis input: the Gemma project adheres to a strict, standardized pipeline for dataset curation, preprocessing, and re-analysis [38,39]. During preprocessing, Gemma realigns the datasets to an updated genome. Quality control measures include identification and removal of outlier samples, removal of genes (rows) with minimal variance in expression values (either zero variance or <70% distinct values), and manual curation for common issues such as batch effects [38]. Differential expression is calculated using the limma or limma-voom pipeline, and statistical output is available for the full model (omnibus) and individual contrasts.

Dataset identification and search

For our meta-analysis, we focused on treatments that specifically target depressive mood symptoms [41]. To identify potential datasets, a list of common traditional antidepressants, corresponding brand names and drug classes was compiled (**Fig. 1**). Non-traditional antidepressant treatments were added if there was peer-reviewed evidence available linking it to potential antidepressant effects. These included electroconvulsive therapy (ECT), transmagnetic stimulation (TMS), deep brain stimulation, ketamine, 3,4-methylenedioxymethamphetamine (MDMA), psilocybin, tianeptine and agomelatine [17,42–47], [48]. The scope for the search included publicly available transcriptional profiling datasets from laboratory rats (*Rattus norvegicus*) or laboratory mice (*Mus musculus*) using bulk tissue dissections that targeted the full or large representative portion of the transcriptome. Search terms were initially generated by the first author (EMG) and decisions were then reviewed and approved by co-authors (MHH, RH, SE, MRB, SM). Our search was conducted using Gemma's application programming interface (API) and the packages *gemma.R* (v.3.1.6), *plyr* (v.1.8.9) and *dplyr* (v.1.8.9) [39,49,50].

Filtering

Following input of search terms with Boolean operators (**Fig. 1)**, organism part was filtered using the formal hierarchical ontology term for the hippocampus (UBERON_0002421). Metadata records were filtered down to publicly available datasets, which were not labeled problematic within the Gemma database. The identified datasets were then scrutinized for inclusion/exclusion based on the systematic criteria [35]. Initial filtering was performed by the first author (EMG) and then decisions were reviewed and approved by co-authors (MHH, RH). Forty-one studies were removed because either 1) treatment was administered during development, 2) brain collection was during development instead of adulthood, 3) the studies were epigenetic studies, or 4) the manipulation was unrelated to antidepressant treatment.

For the remaining studies, the metadata for the differential expression results were downloaded and reviewed to ensure that there was a specific experimental manipulation relevant to antidepressant treatment and related statistical contrasts. The publications associated with the datasets were also referenced, focusing exclusively on the methodological information to determine inclusion/exclusion. Following this review, two datasets were removed - one due to being neuron-specific and another due to having a sample size of n=1 per subgroup (**Fig. 1**). At this stage, all inclusion/exclusion decisions were reviewed and finalized by the entire 2024 cohort of the *Brain Data Alchemy Project* (MHH, SE, EIF, SM, RB, LTC, AL, DMN, TQD) and the laboratory PI (RH). Overall, the risk of systematic bias within the datasets from the individual transcriptional profiling studies was deemed low for any particular gene-level result, as the original publications conducted full genome analyses. That said, it should be noted that the overall bias in the literature against negative results may generally inflate effect sizes represented in publicly-released transcriptional profiling datasets, but in a manner that should be impartial to direction-of-effect.

Reprocessing

Four studies required reprocessing: GSE118670, GSE26836, GSE84183 and GSE43261. For GSE118670 and GSE26836, the differential expression model included multiple tissue types rather than just hippocampal tissue. For GSE84183, the expression data was accidentally log(2) transformed twice during Gemma's preprocessing. For GSE43261, the differential expression model included organism part as a variable rather than providing differential expression results for each brain region independently, and used treatment sensitivity phenotype as the variable of interest rather than the treatment itself.

To re-analyze these datasets, we followed Gemma's analysis pipeline as much as possible to maintain consistency. We used the *Gemma.R* (v.0.99.41) and *tidyverse* (v.2.0.0) [38,40] packages to import the preprocessed log(2) expression data and sample metadata from the Gemma database (import date: 10/22/2024). Each dataset was then subsetted to only hippocampal tissue, and the Gemma Diagnostics tab was consulted to determine whether outlier samples or batch effects had been previously identified (none found). In the case of GSE118670, the adult and developing comparison mice were also excluded, as they were not included in either the antidepressant treatment or control treatment conditions.

We then filtered out genes (rows) lacking log(2) expression data or that had insufficient variability within the antidepressant treatment or control groups. The design matrix was constructed so that antidepressant treatment was defined as a factor, with the control group for the antidepressant treatment defined as the reference level (intercept). Any additional experimental variables present in the metadata were included as co-variates (GSE84183: stress treatment, with a reference level of no stress, GSE118670, GSE43261, and GSE26836: no co-variates). The differential expression model was then fit using the *limma* pipeline (package: *limma* (v.3.17) with a correction for heteroskedasticity (mean-variance trend) and an empirical Bayes correction [51]. False discovery rate (FDR) was calculated using the Benjamini-Hochberg method.

Result Extraction

The differential expression results for the antidepressant treatment vs. control statistical contrasts from each included study were extracted. The Log(2) Fold Change (Log2FC) was extracted for each gene from

each study, and standard error (SE) and sampling variance calculated. In the case that more than one result represented a gene, the Log2FC and SE were averaged. Results were then aligned across species using EntrezID and the Jackson Labs Mouse Ortholog Database [52]. For a gene to be included in the meta-analysis, a minimum number of 11 results (contrasts) needed to be available. The *metafor* package was used to run a simple (intercept-only) random effects meta-analysis [53]. This resulted in an output for each gene including estimated Log2FC change, with respective standard error, confidence intervals and p-value, as well as the number of contrasts included. A false discovery rate (FDR) correction using the Benjamin-Hockberg method was applied to the nominal p-values (*multtest* v.1.32.0) [54]. The final sample size was not deemed large enough to conduct reliable analyses to formally assess sources of heterogeneity amongst the datasets, because two of the most important variables of interest (antidepressant category and transcriptional profiling platform) were strongly correlated with dissection (Ammon's horn vs. dentate gyrus): all three of the RNA-Seq datasets and 7 of the 9 statistical contrasts containing non-traditional antidepressants represented Ammon's horn tissue.

Functional Patterns

Gene set enrichment analysis was used to determine whether our meta-analysis results, ranked by effect size (Log2FC value), were enriched with down-regulation or upregulation in sets of genes associated with known biological pathways and previous experimental results. Fast gene set enrichment analysis was carried out using the *fgsea* (v.1.32.0) package [55]. Enrichment within the ranked gene list was evaluated using traditional gene ontology gene sets and custom brain-related gene sets [56]. StringDB was used to explore potential protein-protein interactions (PPI) between significant differentially expressed genes (58 genes at $FDR<0.05$) [57]. A PPI network was created using medium confidence PPIs (interaction score ≥ 0.4) with *Mus musculus* as the species of interest. The statistical background for examining functional enrichment within the PPI network was defined within StringDB as all genes included in the meta-analysis.

Results

Fifty-eight datasets were identified using our prespecified antidepressant search terms (**Fig. 1**). Of these 58 datasets, 15 survived our inclusion/exclusion criteria, leaving a final collective sample size of n=352. The majority of datasets were collected using microarray technology and the remaining were collected using Ribonucleic acid-sequencing (RNA-seq). Two-thirds of datasets were derived from Ammon's horn's tissue, with the remaining datasets specified as dentate gyrus. Out of 15 datasets, 6 used *Rattus norvegicus* and the remainder used *Mus musculus*. All samples were male (**Table. 1**).

These fifteen selected datasets included 22 antidepressant vs. control comparisons, representing a total of 11 different types of treatments. These included pharmacological treatments: SSRIs (fluoxetine), TCAs (imipramine, desipramine, amitriptyline), SNRIs (venlafaxine), NMDA receptor antagonists (ketamine), Alpha-2 adrenergic antagonists combined with TCAS (yohimbine and imipramine), atypical antidepressants (tianeptine) and MASSAs (agomelatine). Non-pharmaceutical treatments included ECT and TMS (**Table. 1**). These antidepressant treatments were tested using a variety of rodent depression models, including chronic unpredictable mild stress (CUMS), olfactory bulbectomy (OBX), lipopolysaccharide (LPS) induced depression-like model, chronic corticosterone treatment, stress-induced analgesia (SIA) and chronic social defeat stress (CSDS) [58–64]. Three datasets included aged subjects, with cognitive impairment induced using transgenic mice lines (TgAD) and behavioral testing for cognitive impairment [65,66]. A number of datasets utilized no depression model [67–69].

To be included in the meta-analysis, a gene needed to be present in a minimum of 11 antidepressant vs. control comparisons. 16,494 genes fulfilled this requirement, and 16,439 genes produced stable meta-analysis estimates. Fifty-eight genes were significantly differentially expressed (FDR <0.05), of which 23 were upregulated and 35 were downregulated. Approximately 60% of the significantly differentially expressed genes had effect sizes estimated using 19 or more comparisons (**Table. 2, Table.**

3). Examples of genes that are significantly upregulated and down-regulated following a variety of antidepressant treatments can be found in **Figures 2 - 6**.

Although our meta-analysis identified 58 genes that were differentially expressed following a variety of antidepressant treatments, we did not observe a clear pattern of functional implications. Contrary to expectations, constructing a protein-protein interaction (PPI) network using the top genes identified as significantly differentially expressed following antidepressant treatment in our meta-analysis (58 genes with FDR>0.05) did not show a density of PPIs beyond what would be expected by random chance (StringDB enrichment value of 0.364, average local clustering coefficient of 0.258), indicating a lack of strong functional association. Similarly, we did not find a significant enrichment of differential expression within functional gene sets using fast gene set enrichment analysis (all 10,976 gene sets FDR>0.10).

Discussion

Our meta-analysis provides a view into the shared mechanisms of actions of diverse antidepressant treatments in the hippocampus. A wide variety of treatments were represented in our meta-analysis, including SSRIs, SNRIs, TCAs, NMDA receptor agonists, alpha-2 adrenergic antagonists and TCAs combined, MASSAs, ECT and TMS. The aggregation of data from 15 datasets also provided strong statistical power, with a collective sample size of n=352. Altogether, our meta-analysis identified a comprehensive list of 58 differentially expressed genes, with 60% of those present in 19 or more treatment datasets. We did not find strong evidence for an overarching functional pattern in the differential expression. That said, many of the top genes upregulated or downregulated following antidepressant treatment are associated with functions previously implicated in depression.

Differential Expression Related to Stress Responses

Stress and its effects on the hippocampus are well-documented in the pathophysiology of depression, with the hippocampus acting as target and regulator of stress [70]. Therefore, it is interesting that several of our top differentially expressed genes have been previously implicated in stress responses. For example, *MER proto-oncogene tyrosine kinase* (*Mertk*) was down-regulated following antidepressant exposure (**Fig. 2A**). Early life stress models in mice have highlighted *Mertk* activation as part of a glucocorticoid receptor (GR) dependent pathway in astrocytes that induces brain and behavior abnormalities [71]. *Cdk5 And Abl Enzyme Substrate 1* (*Cables1*) was downregulated following antidepressant treatment and is known to be modulated by corticosteroids and is responsible for progression of the cell cycle (**Fig. 2B**) [72]. *T-box Transcription Factor 19* (*Tbx19*) was upregulated and is an important factor in the hypothalamus-pituitary (HPA) axis that regulates stress responses. *Tbx19* has been identified as a genetic marker for certain neurotic traits (**Fig. 2C**) [73]. Altogether, these results suggest that multiple types of antidepressants may act by similarly modulating stress pathways implicated in depression.

Differential Expression Related to Hippocampal Morphology

Neuroimaging studies have consistently shown volume reduction in patients with depression, with stress playing a key role in the development of morphological irregularities [25,31]. Several of the top downregulated genes have been identified as of interest in hippocampal morphology. *Proliferation and apoptosis adaptor protein 15A* (*Pea15a*) was downregulated across all 22 comparisons and is an abundant phosphoprotein in astrocytes that modulates apoptosis and cell proliferation signaling pathways [74,75] (**Fig. 3A**). *Pea15a* was spotlighted as a single gene positively correlated with ECT induced grey matter volume increases in the bilateral hippocampus in patients with depression [76]. *Ankyrin repeat domain 7* (*Ankrd7*) was downregulated across 20 datasets (**Fig. 3B**). Overexpression of another member of the *Ankrd* family, *Ankrd37*, has been causally associated with decreased hippocampal volume in humans [77]. Enrichment of ankyrin-repeat domain proteins have also been implicated in genome-wide association studies for a number of neuropsychiatric diseases [78]. These results together with previous research suggest a pathway for antidepressant effects involving reversal of hippocampal atrophy.

Differential Expression Related to Neurodevelopment and Neuroplasticity

Genes related to neurodevelopment and neuroplasticity are of particular interest when analyzing how antidepressants function to reverse depression. Depressive behaviors have been associated with hippocampal neuronal atrophy and impairments of neuroplasticity due to a cascade of effects following chronic stress such as decreased BDNF expression [79]. Within our meta-analysis we found that multiple genes related to neurodevelopment were upregulated following antidepressant exposure. *Left-right determination factor 1* (*Lefty1*) was upregulated and encodes signaling proteins of the transforming growth factor-beta protein family (**Fig. 4A**). Within the hippocampus it is a midline marker of CA1 clusters [80,81]. Several zinc finger or related genes were also upregulated (*Glis 1, Zfp41, Zfp691, Zfp324, Zfp773, Zc3h15)* (see **Fig. 4B** for *Glis1*). The functions of these proteins in the hippocampus are not well-documented, however *GLIS family zinc finger 1* (*Glis1*) promotes generation of induced pluripotent stem cells (IPSCs) during neural development [82]. *Dual Specificity Protein Phosphatase 9* (*Dusp9*) was also upregulated (**Fig. 4C**). Other DUSP proteins are linked to depression and they modulate several neuronal functions including neurogenesis [83].

In contrast, multiple genes responsible for neuronal signaling were downregulated, including *Unc-13 homolog C* (*Unc13c*), *Potassium Two Pore Domain Channel Subfamily K Member 10* (*Kcnk10*) and *Neurensin 1* (*Nrsn1*) (**Fig. 5**). *Unc13c* is linked to the mediation of excitatory neurotransmitters and is a member of a family of proteins involved in exocytosis and synaptic plasticity [84]. *Nrsn1* is a brain-specific gene that may be important for neural plasticity and transduction of nerve signals [85,86]. *Kcnk10* was found in 22 comparisons and downregulated overall (**Fig. 5B**). *Kcnk10* encodes potassium channel proteins that are regulated by stretch, voltage and temperature and stimulated by arachidonic acid (AA). AA imbalances have been implicated in the development of depression [87,88]. Other potassium channels (*Kcnk2*) knockout mice appear resistant to depression [89,90]. In contrast, *Syntaxin Binding Protein 5* (*Stxbp5*) was upregulated following antidepressant exposure, and encodes the protein tomosyn, which is highly expressed in glutamatergic synapses in the hippocampus [91,92]. Collectively, these findings suggest molecular targets that may mediate antidepressant effects on growth and plasticity.

Differential Expression Related to Immune Function

Immune dysregulation as a stress response is a prominent theory in depression [93]. Environmental stressors lead to increased immune response via an estimated 20 - 200% activation of microglial cells in the hippocampus [79,94]. Therefore, it is interesting that several of our top upregulated genes have been implicated in immune responses and microglial function. For example, *C-C motif chemokine receptor-like 2* (*Ccrl2*) was upregulated and enables chemokine receptor binding activity which facilitates immune cell recruitment (**Fig. 6B**). *Guanylate Binding Protein 2 (Gbp2)* was upregulated across 12 comparisons, which has been associated with microglial activation in the hippocampus (**Fig. 6C**) [95]. Microglia can be activated in two states - 'classical' (M1) and 'alternative' (M2), the former producing inflammatory cytokines and the latter releasing neurotrophic factors and reducing neuroinflammation [96]. *Gbp2* has high expression in M1 microglia, with downregulated *Gbp2* reducing neuronal damage and inducing M1 to M2 polarization [97]. *Toll-like receptor 9* (*Tlr9*) plays a role in immune response as a pattern-recognition receptor. It is expressed in microglia in the hippocampus and modulates immune homeostasis [98,99] by triggering production of the cytokines Interleukin-6 and Interleukin-10 [99].

However, the overall effect of antidepressants on immune-related signaling is unclear. Several downregulated genes also have roles in immune response. For example, *Mertk* is present in microglia and astrocytes in the central nervous system and mediates clearing of apoptotic cells [71,100,101]. Likewise, effects on immune-related gene *Tlr9* seemed potentially specific to tissue-type, antidepressant type and depression model (**Fig. 6A**), and a previous study of *Tlr* profiles in patients showed a normalization of elevated levels following a variety of antidepressants [99]. Therefore, it may be worthwhile to explore the

effect of antidepressants on molecular immune signatures in tissue-specific comparisons and depression models.

Strengths and Limitations

Future work should address some of the weaknesses in our analysis. First, the scope of our search included datasets not derived from depression models. This may be important, as prior primate research has indicated that antidepressants may affect neural structures of nondepressed subjects differently to depressed subjects [102], and a recent transcriptional profiling meta-analysis suggested that the effects of fluoxetine on the hippocampus may differ in stressed and control animals [103]. A recent meta analysis in human patients also showed no effect of antidepressant treatment on the cognitive function of non-depressed patients [104]. The depression models used in the studies included in our meta-analysis also varied, representing highly divergent pathways to depressive-like behavior, including chronic stress, inflammation, and olfactory bulbectomy, which may be optimally reversed by different forms of treatment. Second, the samples were all male. This is an important weakness to acknowledge, as there are well-documented sex differences in the neurobiological and transcriptional effects of depression in pre-clinical and clinical studies [105]. Finally, the datasets included a mixture of dissection types (whole hippocampus vs. dentate gyrus). We have previously found that dissection can be one of the largest sources of variability in transcriptional profiling datasets [106]**.** This mixture of dissection types may make it difficult to infer a specific transcriptomic signature across multiple studies, especially since the neurogenesis effects of antidepressants on the hippocampus would be restricted to the dentate gyrus [29–34]. Future studies using scRNA-Seq or spatial transcriptomics could help clarify this issue.

Finally, our meta-analysis was designed to identify convergent results across antidepressant categories, with the hope of identifying shared functional pathways that could be targeted to construct novel treatments. That said, an intuitive follow-up question would be how categories of antidepressants differ in their effects on the hippocampus, with the goal of shedding light on treatment resistance or variable treatment response. Unfortunately, our final sample size was not large enough to conduct reliable analyses to formally assess the differential effects of antidepressant categories, because the choice of antidepressant used in the experiments included in our meta-analysis strongly correlated with a highly influential technical variable (choice of dissection method). That said, many of the genes identified as differentially expressed within our meta-analysis are within functional pathways previously linked to the effects of fluoxetine on the hippocampus in a recent transcriptional profiling meta-analysis (*e.g.,* glucocorticoid response, synaptic plasticity: [103]. This convergence provides additional evidence supporting the role of these pathways in antidepressant effects, as only 66% of the samples included in the 2022 fluoxetine meta-analysis were included in our own meta-analysis due to differing inclusion/exclusion criteria, contributing only 25% to our final sample size. Our findings further demonstrate that the effects on gene expression within these pathways occur in response to other categories of antidepressant, including ketamine, agomelatine, tianeptine, and ECT (**Fig 2**, **Figs 4-5**).

Conclusion

Altogether, our meta-analysis identified a comprehensive list of 58 genes that were consistently differentially expressed following treatment with a variety of antidepressants. These genes are worth investigating further as potential linchpins for antidepressant efficacy or as targets for novel therapies. We were unable to detect an enrichment of differential expression within gene sets representing documented functional pathways, but many of the top genes upregulated or downregulated following antidepressant treatment are associated with functions previously implicated in depression. For future work, we would like to address some weaknesses in our analysis, including variability in antidepressant response in relationship to depression model, biological sex, and hippocampal region. For future research, running smaller meta-analyses based on tissue type or depression models may better link antidepressant categories

and functional patterns. We also plan to compare our results to meta-analyses using other brain regions relevant to depression, such as the prefrontal cortex (PFC), or using environmental factors that alleviate depression, such as environmental enrichment and exercise, to provide further insight into convergent antidepressant mechanisms.

References

[1] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. Fifth Edition. American Psychiatric Association; 2013. https://doi.org/10.1176/appi.books.9780890425596.

[2] National Institute of Mental Health. Major Depression. Major Depress n.d. https://www.nimh.nih.gov/health/statistics/major-depression (accessed November 7, 2024).

[3] World Health Organization. Depressive Disorder (Depression) 2023. https://www.who.int/news-room/fact-sheets/detail/depression (accessed November 7, 2024).

[4] Friedrich MJ. Depression Is the Leading Cause of Disability Around the World. JAMA 2017;317:1517. https://doi.org/10.1001/jama.2017.3826.

[5] Kessler RC, Bromet EJ. The epidemiology of depression across cultures. Annu Rev Public Health 2013;34:119–38. https://doi.org/10.1146/annurev-publhealth-031912-114409.

[6] Norman TR, Olver JS. Agomelatine for depression: expanding the horizons? Expert Opin Pharmacother 2019;20:647–56. https://doi.org/10.1080/14656566.2019.1574747.

[7] Cohen ZD, DeRubeis RJ. Treatment Selection in Depression. Annu Rev Clin Psychol 2018;14:209–36. https://doi.org/10.1146/annurev-clinpsy-050817-084746.

[8] Uher R, Tansey KE, Dew T, Maier W, Mors O, Hauser J, et al. An Inflammatory Biomarker as a Differential Predictor of Outcome of Depression Treatment With Escitalopram and Nortriptyline. Am J Psychiatry 2014;171:1278–86. https://doi.org/10.1176/appi.ajp.2014.14010094.

[9] Gautam S, Jain A, Gautam M, Vahia V, Grover S. Clinical Practice Guidelines for the management of Depression. Indian J Psychiatry 2017;59:34. https://doi.org/10.4103/0019-5545.196973.

[10] Harmer CJ, Duman RS, Cowen PJ. How do antidepressants work? New perspectives for refining future treatment approaches. Lancet Psychiatry 2017;4:409–18. https://doi.org/10.1016/S2215-0366(17)30015-9.

[11] Artigas F, Nutt DJ, Shelton R. Mechanism of action of antidepressants. Psychopharmacol Bull 2002;36 Suppl 2:123–32.

[12] Zanos P, Gould TD. Mechanisms of ketamine action as an antidepressant. Mol Psychiatry 2018;23:801–11. https://doi.org/10.1038/mp.2017.255.

[13] Homayoun H, Moghaddam B. NMDA Receptor Hypofunction Produces Opposite Effects on Prefrontal Cortex Interneurons and Pyramidal Neurons. J Neurosci 2007;27:11496–500. https://doi.org/10.1523/JNEUROSCI.2213-07.2007.

[14] Carreno FR, Donegan JJ, Boley AM, Shah A, DeGuzman M, Frazer A, et al. Activation of a ventral hippocampus–medial prefrontal cortex pathway is both necessary and sufficient for an antidepressant response to ketamine. Mol Psychiatry 2016;21:1298–308. https://doi.org/10.1038/mp.2015.176.

[15] Invernizzi RW, Garattini S. Role of presynaptic α2-adrenoceptors in antidepressant action: recent findings from microdialysis studies. Prog Neuropsychopharmacol Biol Psychiatry 2004;28:819–27. https://doi.org/10.1016/j.pnpbp.2004.05.026.

[16] Smith CB, Hollingsworth PJ. α2-Adrenoceptors and antidepressant treatments. In: Paton W, Mitchell J, Turner P, Padgham C, Ashcroft E, editors. IUPHAR 9th Int. Congr. Pharmacol. Lond. 1984, London: Palgrave Macmillan UK; 1984, p. 131–6. https://doi.org/10.1007/978-1-349-17615-1_20.

[17] Guardiola-Lemaitre B, De Bodinat C, Delagrange P, Millan MJ, Munoz C, Mocaër E. Agomelatine: mechanism of action and pharmacological profile in relation to antidepressant properties. Br J Pharmacol 2014;171:3604–19. https://doi.org/10.1111/bph.12720.

[18] Racagni G, Riva MA, Molteni R, Musazzi L, Calabrese F, Popoli M, et al. Mode of action of agomelatine: Synergy between melatonergic and 5-HT_{2C} receptors. World J Biol Psychiatry 2011;12:574–87. https://doi.org/10.3109/15622975.2011.595823.

[19] Edinoff AN, Sall S, Beckman SP, Koepnick AD, Gold LC, Jackson ED, et al. Tianeptine, an Antidepressant with Opioid Agonist Effects: Pharmacology and Abuse Potential, a Narrative Review. Pain Ther 2023;12:1121–34. https://doi.org/10.1007/s40122-023-00539-5.

[20] Samuels BA, Nautiyal KM, Kruegel AC, Levinstein MR, Magalong VM, Gassaway MM, et al. The Behavioral Effects of the Antidepressant Tianeptine Require the Mu-Opioid Receptor.

Neuropsychopharmacology 2017;42:2052–63. https://doi.org/10.1038/npp.2017.60.
[21] Han J, Andreu V, Langreck C, Pekarskaya EA, Grinnell SG, Allain F, et al. Mu opioid receptors on hippocampal GABAergic interneurons are critical for the antidepressant effects of tianeptine. Neuropsychopharmacology 2022;47:1387–97. https://doi.org/10.1038/s41386-021-01192-2.
[22] Singh A, Kar SK. How Electroconvulsive Therapy Works?: Understanding the Neurobiological Mechanisms. Clin Psychopharmacol Neurosci Off Sci J Korean Coll Neuropsychopharmacol 2017;15:210–21. https://doi.org/10.9758/cpn.2017.15.3.210.
[23] Deng Z-D, Robins PL, Regenold W, Rohde P, Dannhauer M, Lisanby SH. How electroconvulsive therapy works in the treatment of depression: is it the seizure, the electricity, or both? Neuropsychopharmacology 2024;49:150–62. https://doi.org/10.1038/s41386-023-01677-2.
[24] Downar J, Siddiqi SH, Mitra A, Williams N, Liston C. Mechanisms of Action of TMS in the Treatment of Depression. In: Browning M, Cowen PJ, Sharp T, editors. Emerg. Neurobiol. Antidepressant Treat., vol. 66, Cham: Springer International Publishing; 2024, p. 233–77. https://doi.org/10.1007/7854_2024_483.
[25] Belleau EL, Treadway MT, Pizzagalli DA. The Impact of Stress and Major Depressive Disorder on Hippocampal and Medial Prefrontal Cortex Morphology. Biol Psychiatry 2019;85:443–53. https://doi.org/10.1016/j.biopsych.2018.09.031.
[26] Roddy DW, Farrell C, Doolin K, Roman E, Tozzi L, Frodl T, et al. The Hippocampus in Depression: More Than the Sum of Its Parts? Advanced Hippocampal Substructure Segmentation in Depression. Biol Psychiatry 2019;85:487–97. https://doi.org/10.1016/j.biopsych.2018.08.021.
[27] Sheline YI. Depression and the Hippocampus: Cause or Effect? Biol Psychiatry 2011;70:308–9. https://doi.org/10.1016/j.biopsych.2011.06.006.
[28] Charney DS, Manji HK. Life Stress, Genes, and Depression: Multiple Pathways Lead to Increased Risk and New Opportunities for Intervention. Sci STKE 2004;2004. https://doi.org/10.1126/stke.2252004re5.
[29] Sapolsky RM. Depression, antidepressants, and the shrinking hippocampus. Proc Natl Acad Sci 2001;98:12320–2. https://doi.org/10.1073/pnas.231475998.
[30] Czéh B, Michaelis T, Watanabe T, Frahm J, De Biurrun G, Van Kampen M, et al. Stress-induced changes in cerebral metabolites, hippocampal volume, and cell proliferation are prevented by antidepressant treatment with tianeptine. Proc Natl Acad Sci 2001;98:12796–801. https://doi.org/10.1073/pnas.211427898.
[31] Sahay A, Hen R. Adult hippocampal neurogenesis in depression. Nat Neurosci 2007;10:1110–5. https://doi.org/10.1038/nn1969.
[32] Santarelli L, Saxe M, Gross C, Surget A, Battaglia F, Dulawa S, et al. Requirement of Hippocampal Neurogenesis for the Behavioral Effects of Antidepressants. Science 2003;301:805–9. https://doi.org/10.1126/science.1083328.
[33] Madsen TM, Treschow A, Bengzon J, Bolwig TG, Lindvall O, Tingström A. Increased neurogenesis in a model of electroconvulsive therapy. Biol Psychiatry 2000;47:1043–9. https://doi.org/10.1016/S0006-3223(00)00228-6.
[34] Loef D, Tendolkar I, Van Eijndhoven PFP, Hoozemans JJM, Oudega ML, Rozemuller AJM, et al. Electroconvulsive therapy is associated with increased immunoreactivity of neuroplasticity markers in the hippocampus of depressed patients. Transl Psychiatry 2023;13:355. https://doi.org/10.1038/s41398-023-02658-1.
[35] Hagenauer M, Manh Nguyen D, Flandreau E, Geoghegan E, Mensch S, Ra'eed Bhuiyan M, et al. Brain Data Alchemy Project: Meta-Analysis of Re-Analyzed Public Transcriptional Profiling Data in the Gemma Database (v.2024) v1 2024. https://doi.org/10.17504/protocols.io.yxmvmejkng3p/v1.
[36] R Core Team. _R: A Language and Environment for Statistical Computing_. 2024.
[37] RStudio Team. RStudio: Integrated Development for R. 2024.
[38] Lim N, Tesar S, Belmadani M, Poirier-Morency G, Mancarci BO, Sicherman J, et al. Curation of over 10 000 transcriptomic studies to enable data reuse. Database 2021;2021:baab006. https://doi.org/10.1093/database/baab006.
[39] University of British Columbia. Gemma 2024.
[40] Wickham H, Averick M, Bryan J, Chang W, McGowan L, François R, et al. Welcome to the Tidyverse. J Open Source Softw 2019;4:1686. https://doi.org/10.21105/joss.01686.

[41] Bains N, Abdijadid S. Major Depressive Disorder StatPearls [internet]. Treasure Island (FL): StatPearls Publishing; n.d.
[42] Gassaway MM, Rives M-L, Kruegel AC, Javitch JA, Sames D. The atypical antidepressant and neurorestorative agent tianeptine is a μ-opioid receptor agonist. Transl Psychiatry 2014;4:e411–e411. https://doi.org/10.1038/tp.2014.30.
[43] Kisely S, Li A, Warren N, Siskind D. A systematic review and meta-analysis of deep brain stimulation for depression. Depress Anxiety 2018;35:468–80. https://doi.org/10.1002/da.22746.
[44] Sonmez AI, Camsari DD, Nandakumar AL, Voort JLV, Kung S, Lewis CP, et al. Accelerated TMS for Depression: A systematic review and meta-analysis. Psychiatry Res 2019;273:770–81. https://doi.org/10.1016/j.psychres.2018.12.041.
[45] Bahji A, Vazquez GH, Zarate CA. Comparative efficacy of racemic ketamine and esketamine for depression: A systematic review and meta-analysis. J Affect Disord 2021;278:542–55. https://doi.org/10.1016/j.jad.2020.09.071.
[46] Pagnin D, De Queiroz V, Pini S, Cassano GB. Efficacy of ECT in Depression: A Meta-Analytic Review. Focus 2008;6:155–62. https://doi.org/10.1176/foc.6.1.foc155.
[47] Gill H, Gill B, Chen-Li D, El-Halabi S, Rodrigues NB, Cha DS, et al. The emerging role of psilocybin and MDMA in the treatment of mental illness. Expert Rev Neurother 2020;20:1263–73. https://doi.org/10.1080/14737175.2020.1826931.
[48] Patel R, Titheradge D. MDMA for the treatment of mood disorder: all talk no substance? Ther Adv Psychopharmacol 2015;5:179–88. https://doi.org/10.1177/2045125315583786.
[49] dplyr: A Grammar of Data Manipulation. R package version 1.1.4, https://github.com/tidyverse/dplyr, https://dplyr.tidyverse.org. 2023.
[50] Wickham H. plyr: Tools for Splitting, Applying and Combining Data 2023.
[51] Ritchie ME, Phipson B, Wu D, Hu Y, Law CW, Shi W, et al. limma powers differential expression analyses for RNA-sequencing and microarray studies. Nucleic Acids Res 2015;43:e47. https://doi.org/10.1093/nar/gkv007.
[52] Baldarelli RM, Smith CL, Ringwald M, Richardson JE, Bult CJ, Mouse Genome Informatics Group, et al. Mouse Genome Informatics: an integrated knowledgebase system for the laboratory mouse. GENETICS 2024;227:iyae031. https://doi.org/10.1093/genetics/iyae031.
[53] Viechtbauer W. Conducting Meta-Analyses in *R* with the **metafor** Package. J Stat Softw 2010;36. https://doi.org/10.18637/jss.v036.i03.
[54] Pollard KS, Dudoit S, Laan MJ van der. Multiple Testing Procedures: the multtest Package and Applications to Genomics. Bioinforma. Comput. Biol. Solut. Using R Bioconductor, Springer, New York, NY; 2005, p. 249–71. https://doi.org/10.1007/0-387-29362-0_15.
[55] Korotkevich G, Sukhov V, Budin N, Shpak B, Artyomov MN, Sergushichev A. Fast gene set enrichment analysis 2016. https://doi.org/10.1101/060012.
[56] Megan H. Hagenauer, Yusra Sannah, Elaine K. Hebda-Bauer, Cosette Rhoads, Angela M. O'Connor, Stanley J. Watson Jr., et al. Resource: A Curated Database of Brain-Related Functional Gene Sets (Brain.GMT) n.d. https://doi.org/10.1101/2024.04.05.588301.
[57] Szklarczyk D, Kirsch R, Koutrouli M, Nastou K, Mehryary F, Hachilif R, et al. The STRING database in 2023: protein–protein association networks and functional enrichment analyses for any sequenced genome of interest. Nucleic Acids Res 2023;51:D638–46. https://doi.org/10.1093/nar/gkac1000.
[58] Wang H, He Y, Sun Z, Ren S, Liu M, Wang G, et al. Microglia in depression: an overview of microglia in the pathogenesis and treatment of depression. J Neuroinflammation 2022;19:132. https://doi.org/10.1186/s12974-022-02492-0.
[59] Rimmerman N, Verdiger H, Goldenberg H, Naggan L, Robinson E, Kozela E, et al. Microglia and their LAG3 checkpoint underlie the antidepressant and neurogenesis-enhancing effects of electroconvulsive stimulation. Mol Psychiatry 2022;27:1120–35. https://doi.org/10.1038/s41380-021-01338-0.
[60] Samuels BA, Leonardo ED, Dranovsky A, Williams A, Wong E, Nesbitt AMI, et al. Global State Measures of the Dentate Gyrus Gene Expression System Predict Antidepressant-Sensitive Behaviors. PLoS ONE 2014;9:e85136. https://doi.org/10.1371/journal.pone.0085136.
[61] Lisowski P, Juszczak GR, Goscik J, Stankiewicz AM, Wieczorek M, Zwierzchowski L, et al. Stress

susceptibility-specific phenotype associated with different hippocampal transcriptomic responses to chronic tricyclic antidepressant treatment in mice. BMC Neurosci 2013;14:144. https://doi.org/10.1186/1471-2202-14-144.

[62] Patrício P, Mateus-Pinheiro A, Irmler M, Alves ND, Machado-Santos AR, Morais M, et al. Differential and Converging Molecular Mechanisms of Antidepressants' Action in the Hippocampal Dentate Gyrus. Neuropsychopharmacology 2015;40:338–49. https://doi.org/10.1038/npp.2014.176.

[63] Bagot RC, Cates HM, Purushothaman I, Vialou V, Heller EA, Yieh L, et al. Ketamine and Imipramine Reverse Transcriptional Signatures of Susceptibility and Induce Resilience-Specific Gene Expression Profiles. Biol Psychiatry 2017;81:285–95. https://doi.org/10.1016/j.biopsych.2016.06.012.

[64] Hervé M, Bergon A, Le Guisquet A-M, Leman S, Consoloni J-L, Fernandez-Nunez N, et al. Translational Identification of Transcriptional Signatures of Major Depression and Antidepressant Response. Front Mol Neurosci 2017;10:248. https://doi.org/10.3389/fnmol.2017.00248.

[65] Weiler M, Stieger KC, Shroff K, Klein JP, Wood WH, Zhang Y, et al. Transcriptional changes in the rat brain induced by repetitive transcranial magnetic stimulation. Front Hum Neurosci 2023;17:1215291. https://doi.org/10.3389/fnhum.2023.1215291.

[66] Chadwick W, Mitchell N, Caroll J, Zhou Y, Park S-S, Wang L, et al. Amitriptyline-Mediated Cognitive Enhancement in Aged 3×Tg Alzheimer's Disease Mice Is Associated with Neurogenesis and Neurotrophic Activity. PLoS ONE 2011;6:e21660. https://doi.org/10.1371/journal.pone.0021660.

[67] Husain BFA, Nanavaty IN, Marathe SV, Rajendran R, Vaidya VA. Hippocampal transcriptional and neurogenic changes evoked by combination yohimbine and imipramine treatment. Prog Neuropsychopharmacol Biol Psychiatry 2015;61:1–9. https://doi.org/10.1016/j.pnpbp.2015.03.004.

[68] Ficek J, Zygmunt M, Piechota M, Hoinkis D, Rodriguez Parkitna J, Przewlocki R, et al. Molecular profile of dissociative drug ketamine in relation to its rapid antidepressant action. BMC Genomics 2016;17:362. https://doi.org/10.1186/s12864-016-2713-3.

[69] Hagihara H, Ohira K, Miyakawa T. Transcriptomic evidence for immaturity induced by antidepressant fluoxetine in the hippocampus and prefrontal cortex. Neuropsychopharmacol Rep 2019;39:78–89. https://doi.org/10.1002/npr2.12048.

[70] Dranovsky A, Hen R. Hippocampal Neurogenesis: Regulation by Stress and Antidepressants. Biol Psychiatry 2006;59:1136–43. https://doi.org/10.1016/j.biopsych.2006.03.082.

[71] Byun YG, Kim N-S, Kim G, Jeon Y-S, Choi JB, Park C-W, et al. Stress induces behavioral abnormalities by increasing expression of phagocytic receptor MERTK in astrocytes to promote synapse phagocytosis. Immunity 2023;56:2105-2120.e13. https://doi.org/10.1016/j.immuni.2023.07.005.

[72] Gulyaeva NV. Functional Neurochemistry of the Ventral and Dorsal Hippocampus: Stress, Depression, Dementia and Remote Hippocampal Damage. Neurochem Res 2019;44:1306–22. https://doi.org/10.1007/s11064-018-2662-0.

[73] Wasserman D, Geijer T, Sokolowski M, Rozanov V, Wasserman J. Genetic variation in the hypothalamic–pituitary–adrenocortical axis regulatory factor, T-box 19, and the angry/hostility personality trait. Genes Brain Behav 2007;6:321–8. https://doi.org/10.1111/j.1601-183X.2006.00259.x.

[74] Park J-Y, Kang T-C. The differential roles of PEA15 phosphorylations in reactive astrogliosis and astroglial apoptosis following status epilepticus. Neurosci Res 2018;137:11–22. https://doi.org/10.1016/j.neures.2018.02.003.

[75] Araujo H, Danziger N, Cordier J, Glowinski J, Chneiweiss H. Characterization of PEA-15, a major substrate for protein kinase C in astrocytes. J Biol Chem 1993;268:5911–20. https://doi.org/10.1016/S0021-9258(18)53407-4.

[76] Sun H, Bai T, Zhang X, Fan X, Zhang K, Zhang J, et al. Molecular mechanisms underlying structural plasticity of electroconvulsive therapy in major depressive disorder. Brain Imaging Behav 2024;18:930–41. https://doi.org/10.1007/s11682-024-00884-9.

[77] Xu J, Xia X, Li Q, Dou Y, Suo X, Sun Z, et al. A causal association of ANKRD37 with human hippocampal volume. Mol Psychiatry 2022;27:4432–45.

https://doi.org/10.1038/s41380-022-01800-7.
[78] Yoon S, Piguel NH, Penzes P. Roles and mechanisms of ankyrin-G in neuropsychiatric disorders. Exp Mol Med 2022;54:867–77. https://doi.org/10.1038/s12276-022-00798-w.
[79] Price RB, Duman R. Neuroplasticity in cognitive and psychological mechanisms of depression: an integrative model. Mol Psychiatry 2020;25:530–43. https://doi.org/10.1038/s41380-019-0615-x.
[80] Hamada H, Meno C, Watanabe D, Saijoh Y. Establishment of vertebrate left–right asymmetry. Nat Rev Genet 2002;3:103–13. https://doi.org/10.1038/nrg732.
[81] Yao Z, Van Velthoven CTJ, Nguyen TN, Goldy J, Sedeno-Cortes AE, Baftizadeh F, et al. A taxonomy of transcriptomic cell types across the isocortex and hippocampal formation. Cell 2021;184:3222-3241.e26. https://doi.org/10.1016/j.cell.2021.04.021.
[82] Al-Naama N, Mackeh R, Kino T. C2H2-Type Zinc Finger Proteins in Brain Development, Neurodevelopmental, and Other Neuropsychiatric Disorders: Systematic Literature-Based Analysis. Front Neurol 2020;11:32. https://doi.org/10.3389/fneur.2020.00032.
[83] An N, Bassil K, Al Jowf GI, Steinbusch HWM, Rothermel M, De Nijs L, et al. Dual-specificity phosphatases in mental and neurological disorders. Prog Neurobiol 2021;198:101906. https://doi.org/10.1016/j.pneurobio.2020.101906.
[84] Ansari U, Chen V, Sedighi R, Syed B, Muttalib Z, Ansari K, et al. Role of the UNC13 family in human diseases: A literature review. AIMS Neurosci 2023;10:388–400. https://doi.org/10.3934/Neuroscience.2023029.
[85] Lencer R, Mills LJ, Alliey-Rodriguez N, Shafee R, Lee AM, Reilly JL, et al. Genome-wide association studies of smooth pursuit and antisaccade eye movements in psychotic disorders: findings from the B-SNIP study. Transl Psychiatry 2017;7:e1249–e1249. https://doi.org/10.1038/tp.2017.210.
[86] Cho J, Yu N-K, Choi J-H, Sim S-E, Kang SJ, Kwak C, et al. Multiple repressive mechanisms in the hippocampus during memory formation. Science 2015;350:82–7. https://doi.org/10.1126/science.aac7368.
[87] Regulska M, Szuster-Głuszczak M, Trojan E, Leśkiewicz M, Basta-Kaim A. The Emerging Role of the Double-Edged Impact of Arachidonic Acid- Derived Eicosanoids in the Neuroinflammatory Background of Depression. Curr Neuropharmacol 2020;19:278–93. https://doi.org/10.2174/1570159X18666200807144530.
[88] Dong YY, Pike ACW, Mackenzie A, McClenaghan C, Aryal P, Dong L, et al. K2P channel gating mechanisms revealed by structures of TREK-2 and a complex with Prozac. Science 2015;347:1256–9. https://doi.org/10.1126/science.1261512.
[89] Heurteaux C, Lucas G, Guy N, El Yacoubi M, Thümmler S, Peng X-D, et al. Deletion of the background potassium channel TREK-1 results in a depression-resistant phenotype. Nat Neurosci 2006;9:1134–41. https://doi.org/10.1038/nn1749.
[90] Gordon JA, Hen R. TREKing toward new antidepressants. Nat Neurosci 2006;9:1081–3. https://doi.org/10.1038/nn0906-1081.
[91] Barak B, Williams A, Bielopolski N, Gottfried I, Okun E, Brown MA, et al. Tomosyn expression pattern in the mouse hippocampus suggests both presynaptic and postsynaptic functions. Front Neuroanat 2010;4:149. https://doi.org/10.3389/fnana.2010.00149.
[92] Batten SR, Matveeva EA, Whiteheart SW, Vanaman TC, Gerhardt GA, Slevin JT. Linking kindling to increased glutamate release in the dentate gyrus of the hippocampus through the STXBP5/tomosyn-1 gene. Brain Behav 2017;7:e00795. https://doi.org/10.1002/brb3.795.
[93] Miller AH, Raison CL. The role of inflammation in depression: from evolutionary imperative to modern treatment target. Nat Rev Immunol 2016;16:22–34. https://doi.org/10.1038/nri.2015.5.
[94] Calcia MA, Bonsall DR, Bloomfield PS, Selvaraj S, Barichello T, Howes OD. Stress and neuroinflammation: a systematic review of the effects of stress on microglia and the implications for mental illness. Psychopharmacology (Berl) 2016;233:1637–50. https://doi.org/10.1007/s00213-016-4218-9.
[95] Zhang Z, Guo Z, Jin P, Yang H, Hu M, Zhang Y, et al. Transcriptome Profiling of Hippocampus After Cerebral Hypoperfusion in Mice. J Mol Neurosci 2023;73:423–36. https://doi.org/10.1007/s12031-023-02123-0.
[96] Hu X, Leak RK, Shi Y, Suenaga J, Gao Y, Zheng P, et al. Microglial and macrophage

polarization—new prospects for brain repair. Nat Rev Neurol 2015;11:56–64. https://doi.org/10.1038/nrneurol.2014.207.

[97] You J-E, Kim E-J, Kim HW, Kim J-S, Kim K, Kim P-H. Exploring the Role of Guanylate-Binding Protein-2 in Activated Microglia-Mediated Neuroinflammation and Neuronal Damage. Biomedicines 2024;12:1130. https://doi.org/10.3390/biomedicines12051130.

[98] Matsuda T, Murao N, Katano Y, Juliandi B, Kohyama J, Akira S, et al. TLR9 signalling in microglia attenuates seizure-induced aberrant neurogenesis in the adult hippocampus. Nat Commun 2015;6:6514. https://doi.org/10.1038/ncomms7514.

[99] Hung Y-Y, Huang K-W, Kang H-Y, Huang GY-L, Huang T-L. Antidepressants normalize elevated Toll-like receptor profile in major depressive disorder. Psychopharmacology (Berl) 2016;233:1707–14. https://doi.org/10.1007/s00213-015-4087-7.

[100] Scott RS, McMahon EJ, Pop SM, Reap EA, Caricchio R, Cohen PL, et al. Phagocytosis and clearance of apoptotic cells is mediated by MER. Nature 2001;411:207–11. https://doi.org/10.1038/35075603.

[101] Nguyen LT, Aprico A, Nwoke E, Walsh AD, Blades F, Avneri R, et al. Mertk-expressing microglia influence oligodendrogenesis and myelin modelling in the CNS. J Neuroinflammation 2023;20:253. https://doi.org/10.1186/s12974-023-02921-8.

[102] Willard SL, Uberseder B, Clark A, Daunais JB, Johnston WD, Neely D, et al. Long term sertraline effects on neural structures in depressed and nondepressed adult female nonhuman primates. Neuropharmacology 2015;99:369–78. https://doi.org/10.1016/j.neuropharm.2015.06.011.

[103] Ibrahim EC, Gorgievski V, Ortiz-Teba P, Belzeaux R, Turecki G, Sibille E, et al. Transcriptomic Studies of Antidepressant Action in Rodent Models of Depression: A First Meta-Analysis. Int J Mol Sci 2022;23:13543. https://doi.org/10.3390/ijms232113543.

[104] Prado CE, Watt S, Crowe SF. A meta-analysis of the effects of antidepressants on cognitive functioning in depressed and non-depressed samples. Neuropsychol Rev 2018;28:32–72. https://doi.org/10.1007/s11065-018-9369-5.

[105] Eid RS, Gobinath AR, Galea LAM. Sex differences in depression: Insights from clinical and preclinical studies. Prog Neurobiol 2019;176:86–102. https://doi.org/10.1016/j.pneurobio.2019.01.006.

[106] Hagenauer MH, Schulmann A, Li JZ, Vawter MP, Walsh DM, Thompson RC, et al. Inference of cell type content from human brain transcriptomic datasets illuminates the effects of age, manner of death, dissection, and psychiatric diagnosis. PLOS ONE 2018;13:e0200003. https://doi.org/10.1371/journal.pone.0200003.

[107] Wang Q-S, Yan K, Li K-D, Gao L-N, Wang X, Liu H, et al. Targeting hippocampal phospholipid and tryptophan metabolism for antidepressant-like effects of albiflorin. Phytomedicine 2021;92:153735. https://doi.org/10.1016/j.phymed.2021.153735.

[108] Demin KA, Krotova NA, Ilyin NP, Galstyan DS, Kolesnikova TO, Strekalova T, et al. Evolutionarily conserved gene expression patterns for affective disorders revealed using cross-species brain transcriptomic analyses in humans, rats and zebrafish. Sci Rep 2022;12:20836. https://doi.org/10.1038/s41598-022-22688-x.

Tables

Number	ExperimentID	n	Species	Sex	Author	Year	Platform	Tissue	Treatment
1	GSE109445	12(12)	Rattus norvegicus	Male	Q.-S Wang *et al.,*	2018	Illumina (RNA-Seq)	Ammon's Horn	Fluoxetine
2	GSE123027	24(24)	Mus musculus	Male	Rimmerman *et al*.,	2021	Illumina (RNA-Seq)	Ammon's Horn	Electroconvulsive therapy
3	GSE205325	21(21)	Rattus norvegicus	Male	Demin, Konstantin A *et al*.,	2022	Illumina (RNA-Seq)	Ammon's Horn	Fluoxetine
4	GSE230148	40 (40)	Rattus norvegicus	Male	Weiler, Marina *et al*.,	2023	Agilent (microarray)	Ammon's horn	TMS (modifier intermittent theta burst stimulation), TMS (1 Hz)
5	GSE230149	56(28)	Rattus norvegicus	Male	Weiler, Marina *et al*.,	2023	Agilent (microarray)	Ammon's horn	TMS
6	GSE27532	16(16)	Mus musculus	Male	Lisowski, Pawel *et al*.,	2011	Illumina (microarray)	Dentate gyrus	Desipramine
7	GSE56028	21(21)	Rattus norvegicus	Male	Patrício, Patrícia *et al*.,	2015	Agilent (microarray)	Dentate gyrus	Imipramine, fluoxetine, agomelatine, tianeptine
8	GSE61301	8(8)	Rattus norvegicus	Male	Husain, Basma Fatima Anwar *et al*.,	2015	Agilent (microarray)	Ammon's horn	Imipramine and yohimbine
9	GSE63469	6(6)	Mus musculus	Male	Florian Proft *et al*.,	2019	Affymetrix (microarray)	Ammon's horn	Venlafaxine (high dose), venlafaxine (low dose)
10	GSE73798	60(60)	Mus musculus	Male	Ficek, Joanna *et al*.,	2019	Illumina (microarray)	Ammon's horn	Ketamine
11	GSE81672	99(24)	Mus musculus	Male	Bagot, Rosemary C *et al*.,	2018	Agilent (microarray)	Ammon's horn	Ketamine, imipramine
12	GSE43261	38(38)	Mus musculus	Male	Samuels, Benjamin A *et al*.,	2014	Affymetrix (microarray)	Dentate gyrus	Fluoxetine (ventral), fluoxetine (dorsal)
13	GSE84183	64 (32)	Mus musculus	Male	Hervé, Mylène *et al*.,	2017	Agilent (microarray)	Dentate gyrus	Fluoxetine
14	GSE118670	44 (16)	Mus musculus	Male	Hagihara, Hideo *et al*.,	2019	Affymetrix (microarray)	Dentate gyrus	Fluoxetine
15	GSE26836	12(6)	Mus musculus	Male	Chadwick, Wayne *et al*.,	2015	Illumina (microarray)	Ammon's horn	Amitriptyline

Table 1. Overview of Datasets Included. *Experiment ID refers to the Gene Expression Omnibus (GEO) accession number for each dataset. The sample size n is for the full dataset, with parentheses indicating the sample size of hippocampal samples included in our statistical model for results output. The Species column refers to what species was used in each dataset. The sex column indicates the gender of species. The Author column refers to the first author of publication where available [59–69,107,108]. The Year column refers to the latest update of dataset on Gemma. The Platform column indicates the technology used. The Treatment column indicates each comparison used in the meta-analysis, with multiple comparisons separated by comma. All experimental details indicate the samples used in the transcriptional profiling experiment.*

Gene Symbol	Mouse Entrez Gene ID	Log2FC estimate	SE	pval	CI_lb	CI_ub	#Comparisons	FDR
Plekha2	83436	0.2475899776	6.59E-02	1.72E-04	1.18E-01	3.77E-01	13	4.99E-02
Acan	11595	0.165183483	2.99E-02	3.47E-08	1.06E-01	2.24E-01	12	1.72E-04
Glis1	230587	0.156274248	2.33E-02	2.18E-11	1.11E-01	2.02E-01	14	3.60E-07
Fam135b	70363	0.1560151187	3.33E-02	2.80E-06	9.07E-02	2.21E-01	12	4.20E-03
Tnni1	21952	0.1437095099	3.36E-02	1.90E-05	7.78E-02	2.10E-01	19	1.31E-02
Dmrtb1	56296	0.1348348133	3.43E-02	8.65E-05	6.75E-02	2.02E-01	19	3.48E-02
Gbp2	14469	0.1240126148	3.11E-02	6.72E-05	6.30E-02	1.85E-01	12	2.94E-02
Slc35d2	70484	0.1126670732	2.79E-02	5.55E-05	5.79E-02	1.67E-01	19	2.69E-02
Lefty1	13590	0.1114752119	2.72E-02	4.04E-05	5.83E-02	1.65E-01	15	2.30E-02
Zfp41	22701	0.1072533262	2.79E-02	1.21E-04	5.26E-02	1.62E-01	13	4.23E-02
Iqcg	69707	0.1069414053	2.43E-02	1.08E-05	5.93E-02	1.55E-01	20	9.39E-03
Zfp691	195522	0.1052460925	2.77E-02	1.45E-04	5.10E-02	1.60E-01	22	4.52E-02
Upk1a	109637	0.09881313045	1.90E-02	1.89E-07	6.16E-02	1.36E-01	12	5.29E-04
Tlr9	81897	0.09635245578	1.76E-02	4.17E-08	6.19E-02	1.31E-01	16	1.72E-04
Stxbp5	78808	0.09593981759	2.29E-02	2.74E-05	5.11E-02	1.41E-01	20	1.63E-02
Aff3	16764	0.09577155008	1.84E-02	1.92E-07	5.97E-02	1.32E-01	12	5.29E-04
Cdca7l	217946	0.09425873666	1.97E-02	1.68E-06	5.57E-02	1.33E-01	20	2.77E-03
Zfp324	243834	0.09117376479	1.89E-02	1.43E-06	5.41E-02	1.28E-01	14	2.63E-03
Slc25a45	107375	0.08563147023	1.93E-02	9.34E-06	4.78E-02	1.24E-01	22	8.55E-03
Ccrl2	54199	0.0844801383	1.89E-02	8.05E-06	4.74E-02	1.22E-01	21	8.30E-03
Krt82	114566	0.08432467613	2.00E-02	2.49E-05	4.51E-02	1.24E-01	16	1.58E-02
Insrr	23920	0.08406324486	2.22E-02	1.48E-04	4.06E-02	1.27E-01	17	4.52E-02
Tbx19	83993	0.08250908008	2.16E-02	1.30E-04	4.02E-02	1.25E-01	18	4.38E-02
Gpr160	71862	0.07922014888	2.11E-02	1.75E-04	3.78E-02	1.21E-01	20	4.99E-02
Zc3h15	69082	0.07910430148	1.76E-02	7.21E-06	4.46E-02	1.14E-01	12	8.30E-03
Hid1	217310	0.07788289799	2.05E-02	1.44E-04	3.77E-02	1.18E-01	22	4.52E-02
Dusp9	75590	0.07740942562	1.92E-02	5.42E-05	3.98E-02	1.15E-01	21	2.69E-02
Zfp773	76373	0.07734577945	2.01E-02	1.15E-04	3.80E-02	1.17E-01	11	4.22E-02
Hgsnat	52120	0.07356159795	1.66E-02	9.24E-06	4.10E-02	1.06E-01	12	8.55E-03
Dcaf10	242418	0.07240776452	1.80E-02	5.85E-05	3.71E-02	1.08E-01	22	2.76E-02
Relch	227446	0.0628587036	1.59E-02	7.42E-05	3.18E-02	9.40E-02	22	3.06E-02
Cdkn2d	12581	0.062169905	1.43E-02	1.31E-05	3.42E-02	9.01E-02	12	1.08E-02
Sdhaf3	71238	0.06024045375	1.42E-02	2.24E-05	3.24E-02	8.81E-02	21	1.48E-02
Fen1	14156	0.05952442025	1.58E-02	1.60E-04	2.86E-02	9.04E-02	22	4.80E-02
Naa50	72117	0.05478705597	1.44E-02	1.46E-04	2.65E-02	8.31E-02	21	4.52E-02

Table 2. Meta-Analysis Results: Top Differentially Upregulated Genes (FDR<0.05) in hippocampal tissue following antidepressant treatment. *The rows are ordered by decreasing Log2FC (highest to lowest). Positive Log2FC value denotes that a gene's expression is higher in the experimental group compared to the control group with increasingly positive values signifying stronger effect. Definitions: Log2FC = Log2 Fold Change (Antidepressant treatment vs. Control), SE = Standard Error, CI_lb=confidence interval lower bound, CI_ub=confidence interval upper bound, p-value = nominal p-value, FDR = False Discovery Rate (q-value). The #Comparisons represents the number of treatments that included measurements for the gene following quality control.*

Gene Symbol	Mouse Entrez Gene ID	Log2FC estimate	SE	pval	CI_lb	CI_ub	#Comparisons	FDR
Fbxw10	213980	-0.2059017947	3.98E-02	2.27E-07	-2.84E-01	-1.28E-01	12	5.35E-04
Unc13c	208898	-0.1905134988	4.45E-02	1.85E-05	-2.78E-01	-1.03E-01	22	1.31E-02
Or13a28	18362	-0.1598585943	4.01E-02	6.78E-05	-2.39E-01	-8.12E-02	11	2.94E-02
Ccdc160	434778	-0.1538528494	3.06E-02	5.01E-07	-2.14E-01	-9.39E-02	14	1.03E-03
Mertk	17289	-0.1380934592	3.19E-02	1.52E-05	-2.01E-01	-7.55E-02	21	1.19E-02
Kcnk10	72258	-0.1377280699	3.62E-02	1.42E-04	-2.09E-01	-6.68E-02	22	4.52E-02
C1qtnf7	109323	-0.1361763373	2.15E-02	2.19E-10	-1.78E-01	-9.41E-02	19	1.80E-06
Cables1	63955	-0.1157776543	2.59E-02	7.52E-06	-1.66E-01	-6.51E-02	20	8.30E-03
Gpr182	11536	-0.1155951033	2.96E-02	9.27E-05	-1.74E-01	-5.76E-02	22	3.55E-02
Ankrd7	75196	-0.1072717285	2.79E-02	1.18E-04	-1.62E-01	-5.27E-02	20	4.23E-02
Ccl20	20297	-0.1065415508	2.35E-02	5.64E-06	-1.53E-01	-6.05E-02	15	7.75E-03
Lrrc1	214345	-0.09097564246	2.04E-02	8.00E-06	-1.31E-01	-5.10E-02	22	8.30E-03
Nrsn1	22360	-0.08859839354	2.05E-02	1.59E-05	-1.29E-01	-4.84E-02	20	1.19E-02
Pea15a	18611	-0.08653463666	2.17E-02	6.55E-05	-1.29E-01	-4.40E-02	22	2.94E-02
Hexd	238023	-0.07826450113	1.87E-02	2.77E-05	-1.15E-01	-4.17E-02	20	1.63E-02
Sim2	20465	-0.07685815897	1.93E-02	6.99E-05	-1.15E-01	-3.90E-02	21	2.96E-02
Csad	246277	-0.07527284625	2.00E-02	1.73E-04	-1.15E-01	-3.60E-02	22	4.99E-02
Clcn2	12724	-0.07227224327	1.77E-02	4.54E-05	-1.07E-01	-3.75E-02	21	2.50E-02
Map3k1	26401	-0.0720827975	1.78E-02	4.89E-05	-1.07E-01	-3.73E-02	22	2.60E-02
C2cd2	207781	-0.06952710981	1.78E-02	8.99E-05	-1.04E-01	-3.47E-02	21	3.53E-02
Krt27	16675	-0.06874582022	1.79E-02	1.28E-04	-1.04E-01	-3.36E-02	18	4.38E-02
Xrcc6	14375	-0.06117879643	1.58E-02	1.09E-04	-9.22E-02	-3.02E-02	22	4.08E-02
Rpp25l	69961	-0.0602812121	1.49E-02	5.23E-05	-8.95E-02	-3.11E-02	22	2.69E-02

Table 3. Meta-Analysis Results: Top Differentially Downregulated Genes (FDR<0.05) in the hippocampus following antidepressant treatment. *The rows are ordered by increasing Log2FC value (lowest to highest). Negative Log2FC value denotes that a gene's expression is higher in the experimental group compared to the control group, with increasingly negative values signifying stronger effect.*

Figures

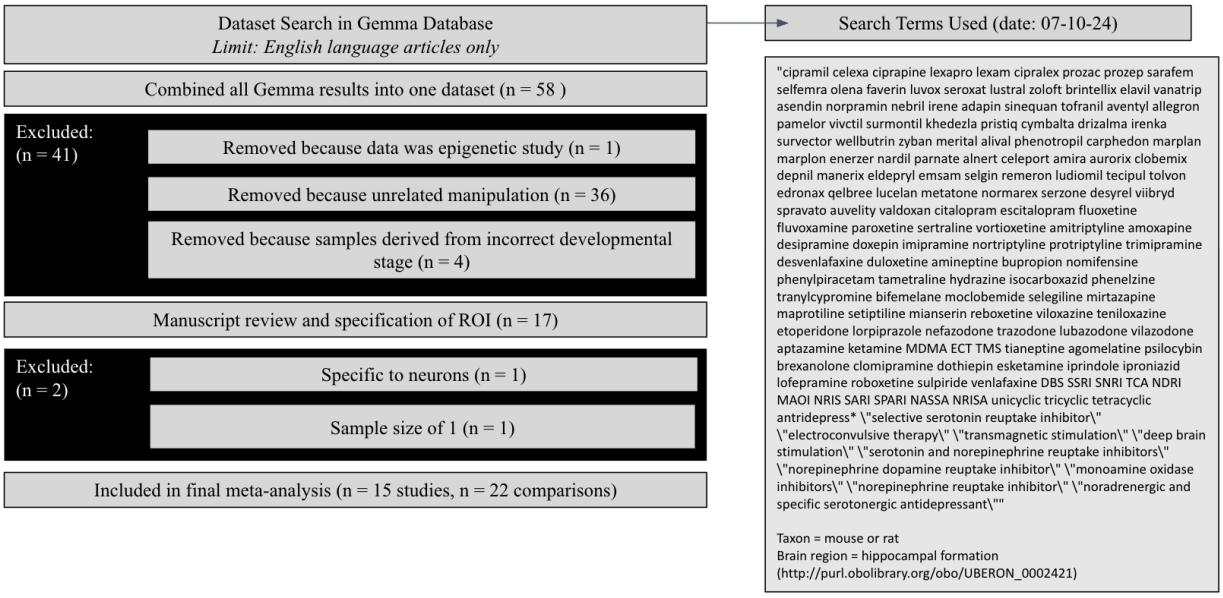


Figure 1. Diagram Overviewing Dataset Search and Selection. *We identified transcriptional profiling datasets of laboratory rodents treated with antidepressants within the Gemma database using pre-specified keywords. The search encompassed tissue from the hippocampal formation. The titles, abstracts, and metadata for the datasets were initially scanned and filtered using pre-specified inclusion/exclusion criteria, including indications that the dataset was an epigenetic study, a manipulation unrelated to antidepressants or samples originated from the incorrect developmental stage. The secondary screening step included a detailed review of the metadata on Gemma and published methodology, followed by a final specification of the region of interest (ROI: Hippocampus). Datasets were excluded in the secondary dataset filtering if they did not include a sufficient sample size or were cell specific.*

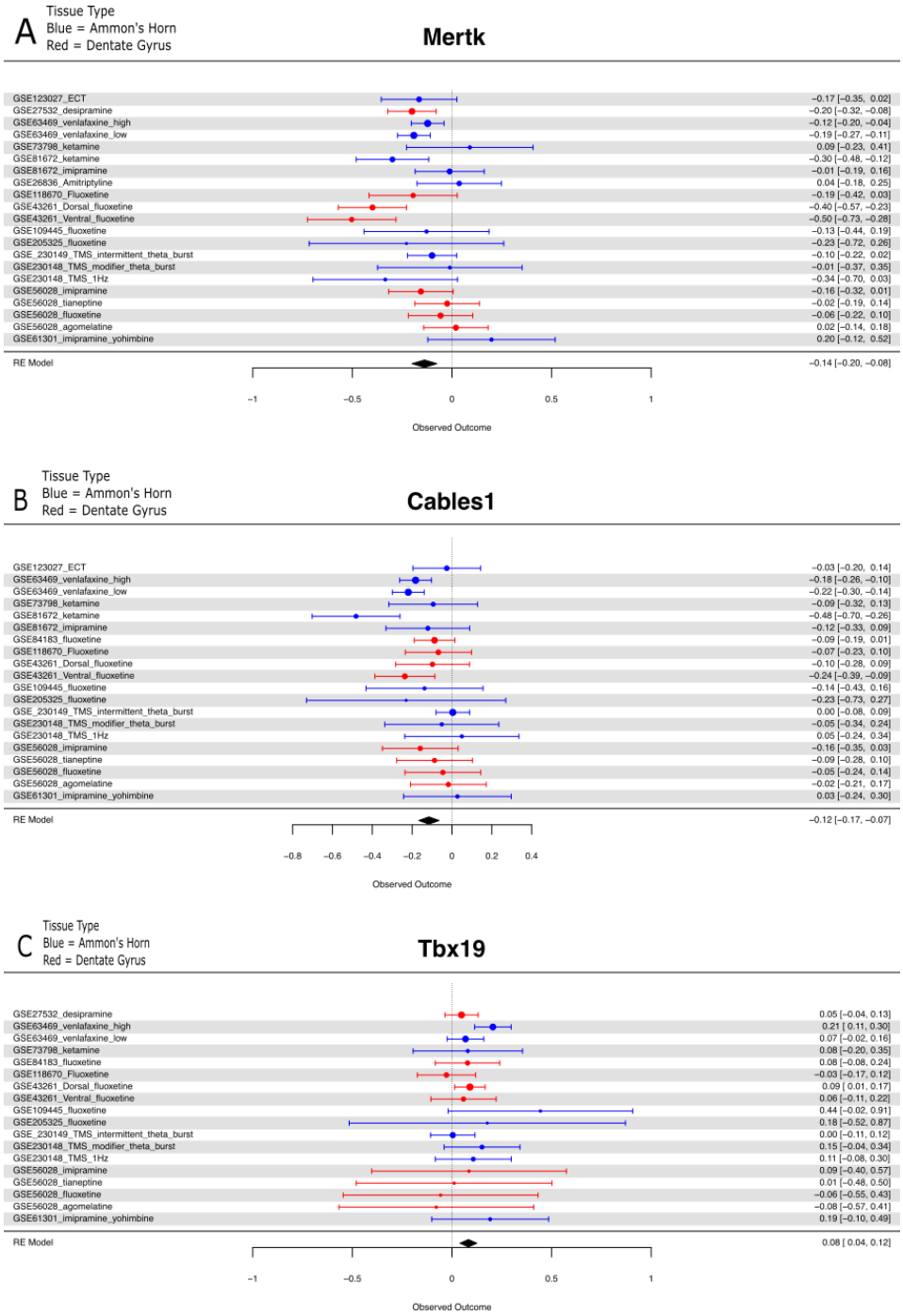


Figure 2. Forest plots for three differentially expressed genes (FDR<0.05) with prior research on stress response functions. *Rows illustrate Log2FC (circles) with 95% confidence intervals (whiskers) for each of the datasets and the meta-analysis random effects model ("RE Model"). Forest plots allow for visual inspection of the consistency and magnitude of effects across all comparisons.* ***A.*** *MER proto-oncogene tyrosine kinase. Significantly differentially expressed across 21 datasets, downregulated.* ***B.*** *Cdk5 And Abl Enzyme Substrate. Significantly differentially expressed across 20 datasets, downregulated.* ***C.*** *T-box*

Transcription Factor 19. Significantly differentially expressed across 18 datasets, upregulated. Definitions: Log2FC = Log2 Fold Change (Antidepressant treatment vs. Control), SE = Standard Error, CI_lb=confidence interval lower bound, CI_ub=confidence interval upper bound, p-value = nominal p-value, FDR = False Discovery Rate (q-value). The #Comparisons represents the number of treatments that included measurements for the gene following quality control.

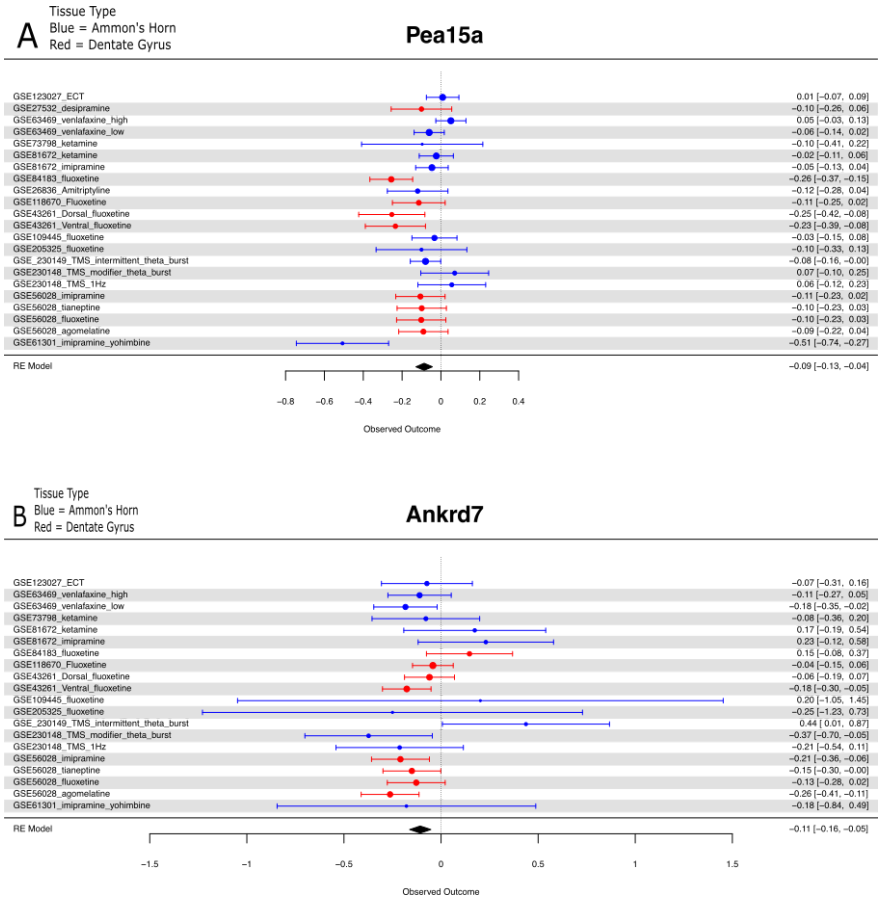


Figure 3. Forest plots for three differentially expressed genes (FDR<0.05) with prior research on morphological changes in the hippocampus. *Rows illustrate Log2FC (circles) with 95% confidence intervals (whiskers) for each of the datasets and the meta-analysis random effects model ("RE Model"). Forest plots allow for visual inspection of the consistency and magnitude of effects across all comparisons.* ***A.*** *Proliferation and apoptosis adaptor protein 15A. Significantly differentially expressed across 22 datasets, downregulated* ***B.*** *Ankyrin repeat domain 7. Significantly differentially expressed across 20 datasets, downregulated.*

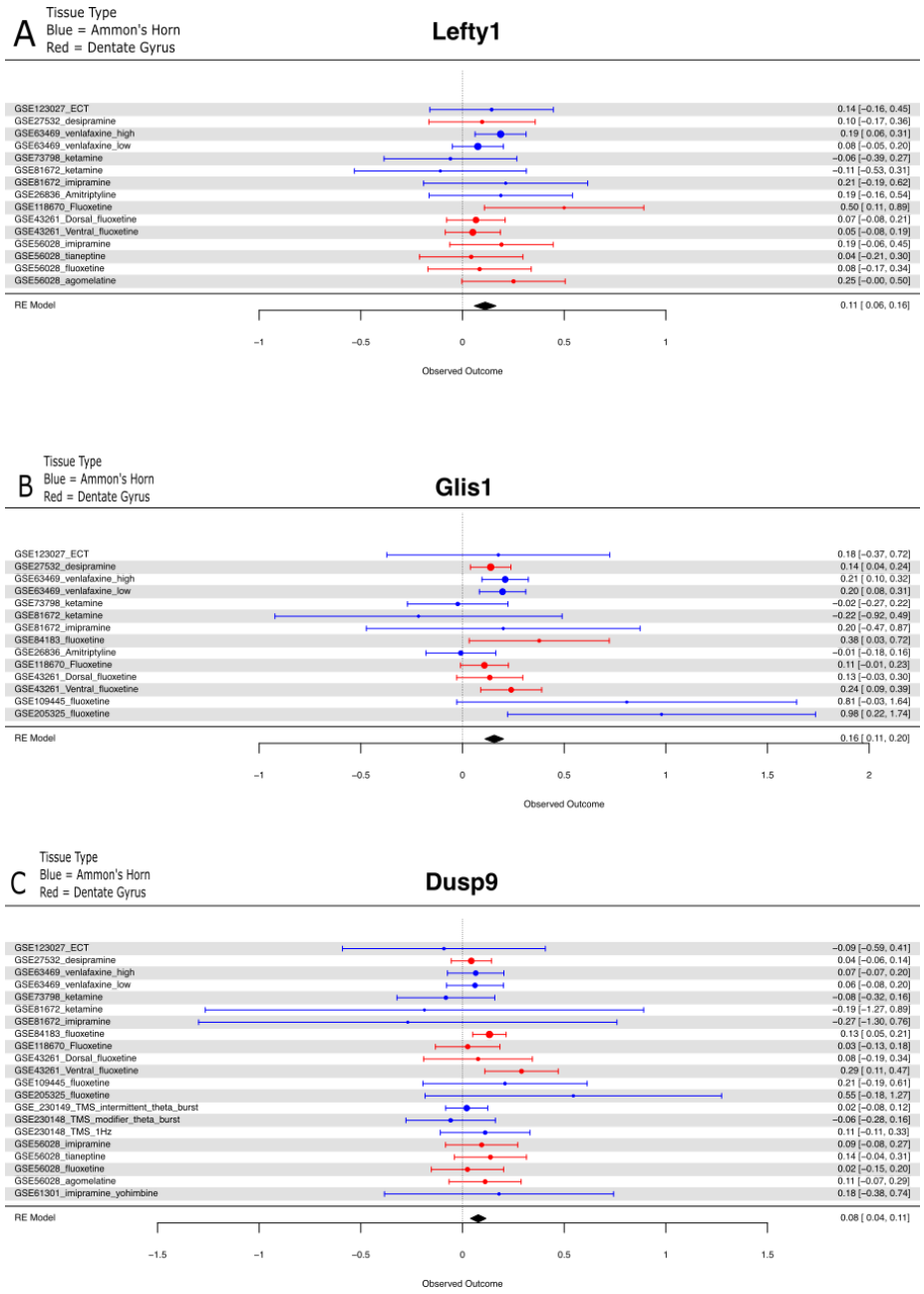


Figure 4. Forest plots for three differentially expressed genes (FDR<0.05) with prior research on neurodevelopment and neuroplasticity in the hippocampus. *Rows illustrate Log2FC (circles) with 95% confidence intervals (whiskers) for each of the datasets and the meta-analysis random effects model ("RE Model"). Forest plots allow for visual inspection of the consistency and magnitude of effects across all comparisons.* ***A****. Left-right determination factor 1. Significantly differentially expressed across 15 datasets, upregulated.* ***B.*** *GLIS family zinc finger 1. Significantly differentially expressed across 14 datasets, upregulated.* ***C.*** *Dual Specificity Protein Phosphatase 9. Significantly differentially expressed across 21 datasets, upregulated.*

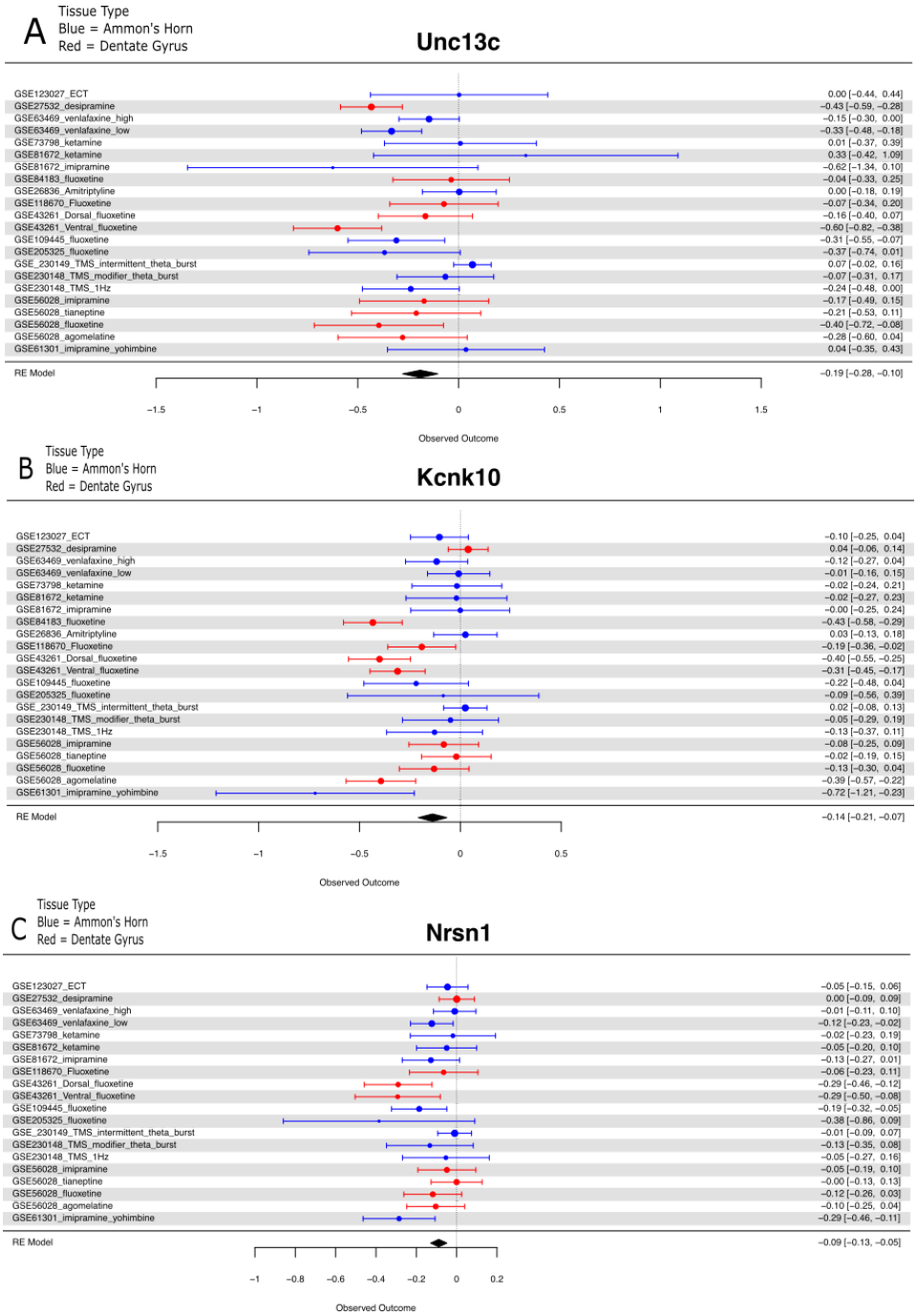


Figure 5. Forest plots for three differentially expressed genes (FDR<0.05) with prior research on neuronal signaling in the hippocampus. *Rows illustrate Log2FC (circles) with 95% confidence intervals (whiskers) for each of the datasets and the meta-analysis random effects model ("RE Model"). Forest plots allow for visual inspection of the consistency and magnitude of effects across all comparisons.* ***A.*** *Unc-13 homolog C. Significantly differentially expressed across 22 datasets, downregulated* ***B.*** *Potassium Two Pore Domain Channel Subfamily K Member 10. Significantly differentially expressed across 22*

datasets, downregulated. ***C.*** *Neurensin 1. Significantly differentially expressed across 20 datasets, downregulated.*

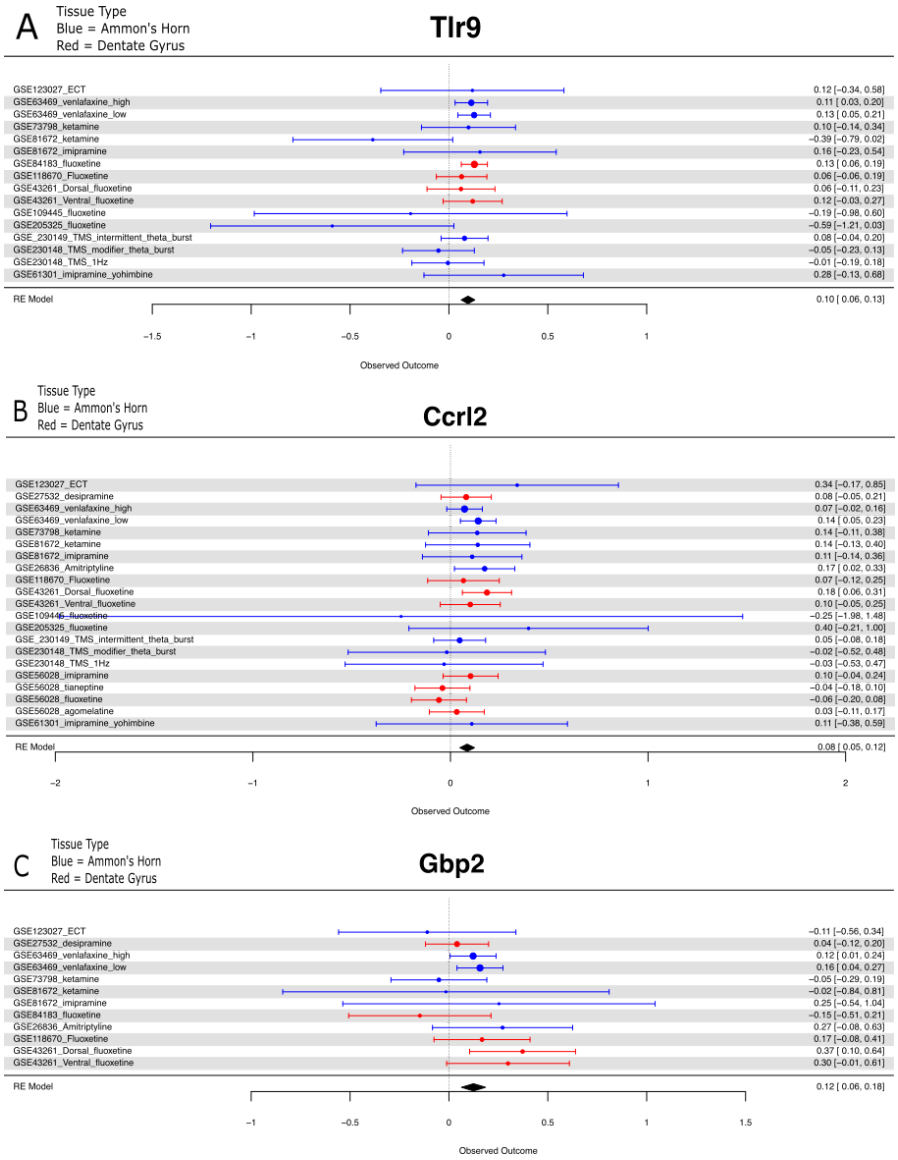


Figure 6. Forest plots for three differentially expressed genes (FDR<0.05) with prior research on immune function in the nervous system. *Rows illustrate Log2FC (circles) with 95% confidence intervals (whiskers) for each of the datasets and the meta-analysis random effects model ("RE Model"). Forest*

plots allow for visual inspection of the consistency and magnitude of effects across all comparisons. ***A.*** *Toll-like receptor 9. Significantly differentially expressed across 16 datasets, upregulated. Downregulation appears to be tissue and depression model specific. Fluoxetine datasets in the dentate gyrus (red) show upregulation, downregulation in Ammon's horn (blue). Ketamine shows upregulation in datasets with no depression model (GSE73798), downregulation in CSDS model (GSE81672).* ***B.*** *C-C motif chemokine receptor-like 2. Significantly differentially expressed across 21 datasets, upregulated.* ***C.*** *Guanylate Binding Protein 2. Significantly differentially expressed across 12 datasets, upregulated.*

Supplemental Table Legends

Table S1. The full meta-analysis results (16,494 genes, 16,439 stable meta-analysis estimates). *This .xlsx file includes two worksheets: 1) The worksheet "metaOutputByPval" 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 "Column Definitions" provides the definitions for the variables present in each column in "metaOutputByPval".*

Table S2: The full fast Gene Set Enrichment Analysis (fGSEA) results (9322 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 "Column Definitions" provides the definitions for the variables present in each column in "fGSEA_Results".*