Opposite Molecular Signatures of Depression in Men and Women

Supplemental Information

Supplementary Methods

Gene array data pre-processing

Microarrays were scanned and summarized by manufacturers' defaults. Data from Affymetrix arrays were processed by robust multi-array (RMA) method and data from Illumina arrays by manufacturer's BeadArray software for probe analysis. Batch effects were evaluated and normalized. Oligonucleotide probes (or probesets) were matched to gene symbols using hgu133plus2.db and illuminaHumanv4.db Bioconductor packages.

Individual study analysis

The individual study analysis to detect candidate marker genes involves two major components: random intercept model (RIM) and variable selection. In our previous publication, real data analysis and simulation showed improved statistical power and accuracy when applying the two techniques (1).

Random intercept model (RIM)

To account for the existence of several potential covariates, we applied a random intercept model (RIM). For a given gene *g*, we fit the model:

$$Y_{gik} = \mu_g + \beta_{g0} X_{0ik} + \sum_{l=1}^{L} \beta_{gl} X_{lik} + \alpha_k + \in_{gik}.$$

In the model, Y_{gik} was the gene expression value of gene g (1≤*g*≤*G*) and disease status i(i=1 for control and 2 for MDD) in sample pair k (1≤*k*≤*K*). X_{0ik} was the disease label (1

for MDD, 0 for control). X_{lik} represented values for potential confounding covariate *l* (1≤*l*≤7; 0-1 binary for alcohol dependence, antidepressant drug use and death by suicide, and numerical for age, pH, RIN, and PMI). α_k was the random intercept from a normal distribution with mean zero and variance τ_g^2, which represented the deviation of averaged expression values in the k^{th} pair from the average of the whole population. Finally, ϵ_{gik} were independent random noises that followed a normal distribution with mean zero and variance σ_g^2. Under this model, β_{g0} was the disease effect of gene *g* and represented the parameter of major interest. To obtain an MDD-associated differential expression list in each study, we used the likelihood ratio test to assess the p-values of testing $H_o: \beta_{g0} = 0$ (vs $H_A: \beta_{g0} \neq 0$). The p-values were then corrected for multiple comparisons using Benjamini-Hochberg procedure (2). We previously used simulation and real data to demonstrate that including the random effects α_k improved the statistical power (1).

Variable selection for RIM

We have developed and evaluated a variable selection procedure in the random intercept model (namely, RIM_BIC). At most 2 variables were included as covariates for each gene. Specifically, all possible RIM models that included at most two (i.e. 0, 1 or 2) clinical variables were computed and compared. The model with the smallest Bayesian Information Criterion (BIC) (3) value was selected. Here, different sets of covariates were included for each gene based on which covariates were most relevant. In other words, gene A might be confounded by alcohol and RIN, while gene B is confounded by antidepressant and pH. Similar to RIM model, likelihood ratio tests were used to generate p-values of testing $H_o: \beta_{g0} = 0$ in each gene for the selected model by BIC.

Meta-analysis of gene microarray studies

Random effects model (REM) is a popular method for combining effect sizes in meta-analysis.

$$d_{gk} = \mu_g + \alpha_{gk},$$

where d_{gk} is the standardized mean difference (effect size) for gene g $(1 \le g \le G)$ and study k $(1 \le k \le K)$, where G is total number of genes and K is total number of studies. μ_g is true MDD effect for gene g and $\alpha_{gk} \sim N(0, \tau_g^2)$. The goal is to estimate μ_g. (4) described a procedure to combine effect sizes by inverse variance weighting, where the effect size was defined as the standardized mean difference $d = (\overline{Y}_D - \overline{Y}_C)/S_p$, $\overline{Y}_D$ and $\overline{Y}_C$ were the means of MDD and control groups, respectively and S_p^2 indicated an estimation of the pooled variance. The estimated effect size $\widehat{d_{gk}}$ can be estimated by the coefficient of MDD divided by its standard error (i.e., $\hat{\beta}_{gk}/\hat{\sigma}_{gk}$ from RIM model) from single study analysis. Denote the variance of $\widehat{d_{gk}}$ as S_{gk}^2, which can be estimated using delta method. Denote the between-study variance as τ_g^2 which can be estimated by the method of moments suggested by DerSimonian and Larird (5): $\hat{\tau}_g^2 = \max\left\{0, \frac{Q_g - (K-1)}{S_{g1} - \left(S_{g2}/S_{g1}\right)}\right\}$, where $Q_g = \sum_k w_{gk}(\widehat{d_{gk}} - \mu_g)^2$, $\mu_g = (\sum_k w_{gk}\widehat{d_{gk}}) / \sum w_{gk}$, $w_{gk} = \hat{S}_{gk}^{-2}$, $S_{gr} = \sum_k w_{gk}^r$. μ_g and variance of μ_g could be estimated as $\hat{\mu}(\tau_g) = \frac{\sum(\hat{S}_{gk}^2 + \hat{\tau}_g^2)^{-1}\widehat{d_{gk}}}{\sum(\hat{S}_{gk}^2 + \hat{\tau}_g^2)^{-1}}$ and $\mathrm{Var}\left(\hat{\mu}(\tau_g)\right) = \frac{1}{\sum(\hat{S}_{gk}^2 + \hat{\tau}_g^2)^{-1}}$. Under the assumption that the gene expression levels were normally distributed, a z-score to test for differentially-expressed genes was constructed as, $z_g = \frac{\hat{\mu}(\tau_g)}{\sqrt{\mathrm{Var}\left(\hat{\mu}(\tau_g)\right)}}$, which followed a normal distribution with zero mean and unit variance, under the null. The p-

values of each gene could be calculated and subsequent inferences could be made. We performed Pearson correlation to show the level of statistical agreement across studies. In males, we calculated the Pearson correlation between results from MD2_ACC_M and MD1_ACC_M (both Affy platform), with results represented by scatterplot (**Figure S2A).** In females, we calculated the Pearson correlation between results from MD2_ACC_F and MD3_ACC_F (one Affy platform, one Illumina platform), with results represented by scatterplot (**Figure S2B**).

Meta-regression with variable selection (MetaRG_BIC)

In order to investigate the effect of sex in the random effect model, we adopted a meta-regression model adjusting sex as the only covariate.

$$\mathrm{d_{gk}} = \mu_g + \beta_{gk}\mathrm{X_k} + \alpha_{gk},$$

where μ_g is true MDD effect for gene g and $\alpha_{gk} \sim \mathrm{N}(0, \tau_g^2)$. $\mathrm{X_k}$ is the sex group indicator where $\mathrm{X_k} = 0$ denotes female group and $\mathrm{X_k} = 1$ denotes male group. β_{gk} denotes the sex effect and $\beta_{gk} \neq 0$ indicates the MDD effect in male group and female groups are different. We adopt R package “metaphor” for the estimation procedure.

Sex differences in gene expression in control subjects

We adopted linear models to account for potential confounding covariates (Random Intercept Model). Each gene was fit to linear regression controlling for age, PMI, RIN, and pH. We then used stepwise regression to select the best model, using the covariate with the most significant effect for each gene. Using this model, each gene is tested for the covariate with the most effect on gene expression; that covariate is then used in the model for that gene. This method provides greater statistical power by only accounting for confounding variables that are relevant for each gene. The p-value for significance of the

sex effect is the p-value associated with the t statistic for the coefficient for sex. We then used Benjamini-Hochberg procedure for multiple comparisons within each study to control the false discovery rate (FDR) (2). We then used a q-value cutoff of 0.2 to identify genes that were sexually dimorphic in control subjects. We then asked whether the genes that were sexually dimorphic in controls were present in our meta-regression datasets and calculated the percent overlap.

Confirmation of meta-regression results – replication cohort

We used recently published publicly available RNA-seq data generated using brains from a different brain bank (GEO GSE102556; (6)). Results were confirmed using data from two brain regions (BA11, BA25). We analyzed the effect of MDD separately in men and women. We adopted linear models to account for potential confounding covariates (Random Intercept Model). Each gene was fit to linear regression controlling for RIN, age, medication, and alcohol use (as in the manuscript describing this dataset (6)) In addition, we selected up to two additional covariates using stepwise regression to select the best model. Using this model, each gene is tested for the covariate with the greatest effect on gene expression; that covariate is then used in the model for that gene. This method provides greater statistical power by only accounting for confounding variables that are relevant for each gene. The p-value for significance of the MDD effect is the p-value associated with the t statistic for the coefficient for MDD. We then used a p-value cutoff of 0.05 to identify genes that were DE in MDD subjects (separately in men and women). We then assessed the overlap in DE gene identified in men and women and calculated the percent overlap as well as the percent of overlapping genes that were changed in

opposite directions in men and women with MDD.

Confirmation of meta-regression results – single gene analysis

We confirmed our meta-regression results in two ways. First, since two of the ACC microarray studies (one in men, one in women) were performed at the same time, we could directly compare expression values in men and women. Second, we used qPCR in the AMY of samples obtained from both men and women (controls and MDD). Small qPCR products (80-150 base-pairs) for genes of interest (*ARPP21*, *P2RY12, MTHFR*) were amplified in triplicate on a BioRad CFX96 Touch Real-Time PCR Detection System using standard conditions defined by BioRad (95°C for 2 min followed by 40 cycles: 5s at 95°C, 30s at 60°C). cDNA was amplified in 20µl reactions using SsoAdvanced™ Universal SYBR® Green Supermix according to manufacturer's specifications (450µM primers; BioRad, Hercules, CA, USA). Primer dimers were assessed by amplifying primers without cDNA. Primers were retained if they produced no primer dimers or non-specific signal after 35 cycles and if the product size was as predicted. Results were calculated as the geometric mean of relative intensities compared to two internal control genes (glyceraldehyde-3-phosphate dehydrogenase (*GAPDH*) and cyclophilin G (*CYCLO*)). These housekeeping genes were previously shown not to be altered in MDD (7). qPCR primers are listed in **Table S8**. Both microarray expression and qPCR datasets were analyzed by 2-way ANCOVA using SPSS (SPSS, Inc., Chicago, IL, USA), with main effects of sex and diagnosis, and interaction of sex and diagnosis. The qPCR data were averaged over three replicates and transformed into arbitrary expression levels ($2^{-\Delta Ct}$), with higher values representing greater expression. To determine relevant covariates to

include in the ANCOVA, Pearson correlation was used to assess the effect of age, postmortem interval, brain pH, RNA ratio, and RIN on gene expression. To determine relevant categorical covariates (alcohol abuse, antidepressant use, death by suicide), gene expression measurements were tested by ANOVA on only MDD subjects. For *ARPP21* array, age was used as a covariate in the ANCOVA. For *ARPP21* qPCR, RNA ratio was used as a covariate in the ANCOVA. For *P2RY12*, *MTHFR*, *SLCO1A2*, *ARHGEF3*, *GABRD*, *CAMK2B*, *CACNA1I*, *NOL1*, *NUB1*, and *PSMA3* array, no covariates were used in the ANCOVA. For *P2RY12* qPCR, RNA ratio, age, and PMI were used as covariates in the ANCOVA. For *MTHFR* qPCR, no covariates were used in the ANCOVA. Statistical significance was set at $p < 0.05$.

Rank-rank hypergeometric overlap (RRHO)

RRHO is a threshold-free algorithm aiming to identify trends of overlap between two biological signatures defined as ranked lists of differential gene expression. We used RRHO to assess overlap in gene lists generated in men with MDD to gene lists generated in women with MDD. RRHO first ranks all genes based on DE p-values and effect size direction. Then, RRHO iterates through different thresholds of the ranked gene list for each dataset and defines “a candidate gene list” to be the amount of genes that are as extreme or more extreme than the current threshold of the same effect size direction. These procedures result in a matrix of hypergeometric p-values whose dimensions are the length of the ranked lists. The hypergeometric p-values are then (1) corrected for multiple comparisons by Benjamini and Yekutieli correction (8), (2) –log10 transformed, and (3) visualized in the heatmap, with each pixel of the heatmap representing an overlap

between two candidate gene lists. Note that in the method described above, we count the candidate gene list to be as extreme or more extreme of the same effect size direction (either top to middle or bottom to middle for a ranked gene list), which is slightly different from the original algorithm (9), where they always count the candidate gene list in the same direction (i.e., overlap in genes changed in the same direction). This approach was particularly relevant for our investigations, as we were interested in overlap in genes that were changed in opposite directions in men and women with MDD. We further split the heatmap into four quadrants using inner boundaries where the effect size direction of the ranked gene list alters. Under this scenario, all four quadrants of the hypergeometric heatmap are biologically meaningful.

Cell-type specific analysis using a mouse dataset

A secondary source of single cell expression data assayed neural cells from mice of both sexes (10). Expression data (number of molecules per cell) was obtained from the Linnarson lab website (https://storage.googleapis.com/linnarsson-lab-www-blobs/blobs/cortex/expression_mRNA_17-Aug-2014.txt). This dataset assayed 3005 cells from the somatosensory (S1) cortex and hippocampus. We used the provided BackSPIN clustering that marked cells as one of 7 major classes ('level1class' in data file) and 47 cell subclasses. We log transformed the provided molecule counts plus one. For each gene, these log scaled values were standardized across all cells. Cells were then grouped by provided 47 subclasses and the average standardized expression value was calculated for each gene. Genes with average standardized expression levels higher than two standard deviations in a given subclass were considered cell-type enriched. The

area under the receiver operating curve (AUROC) statistic was used to measure enrichment of these cell subclass enriched gene lists. The provided cell-type identities or subclasses in the Zeisel dataset was permuted to determine the empirical p-values of the AUROCs (10,000 random assignments of cell subclasses). False discovery rate was used to correct for multiple tests.

Supplementary Figures

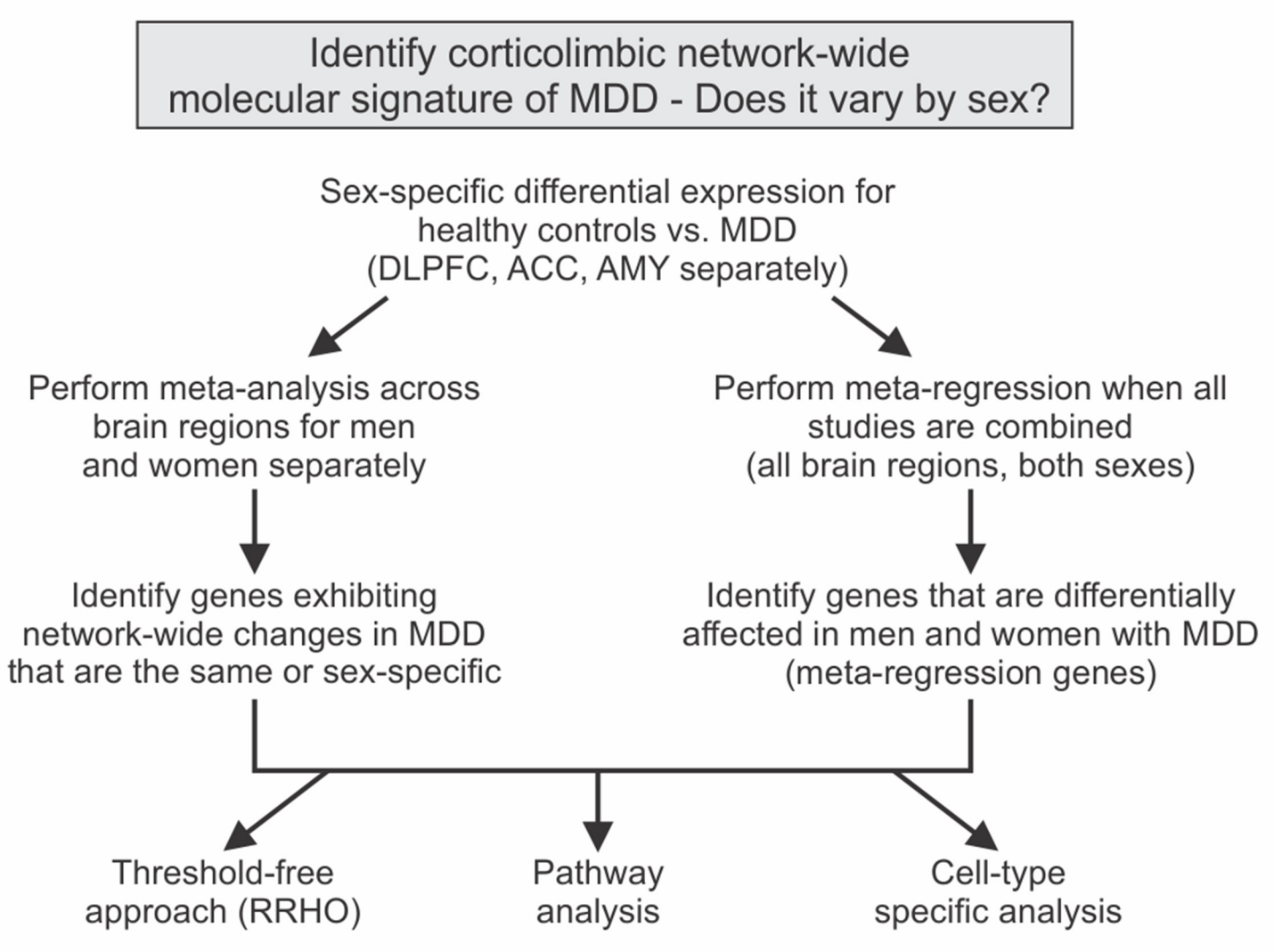

Figure S1. Overview of experimental design for meta-analysis, meta-regression, and downstream analyses.

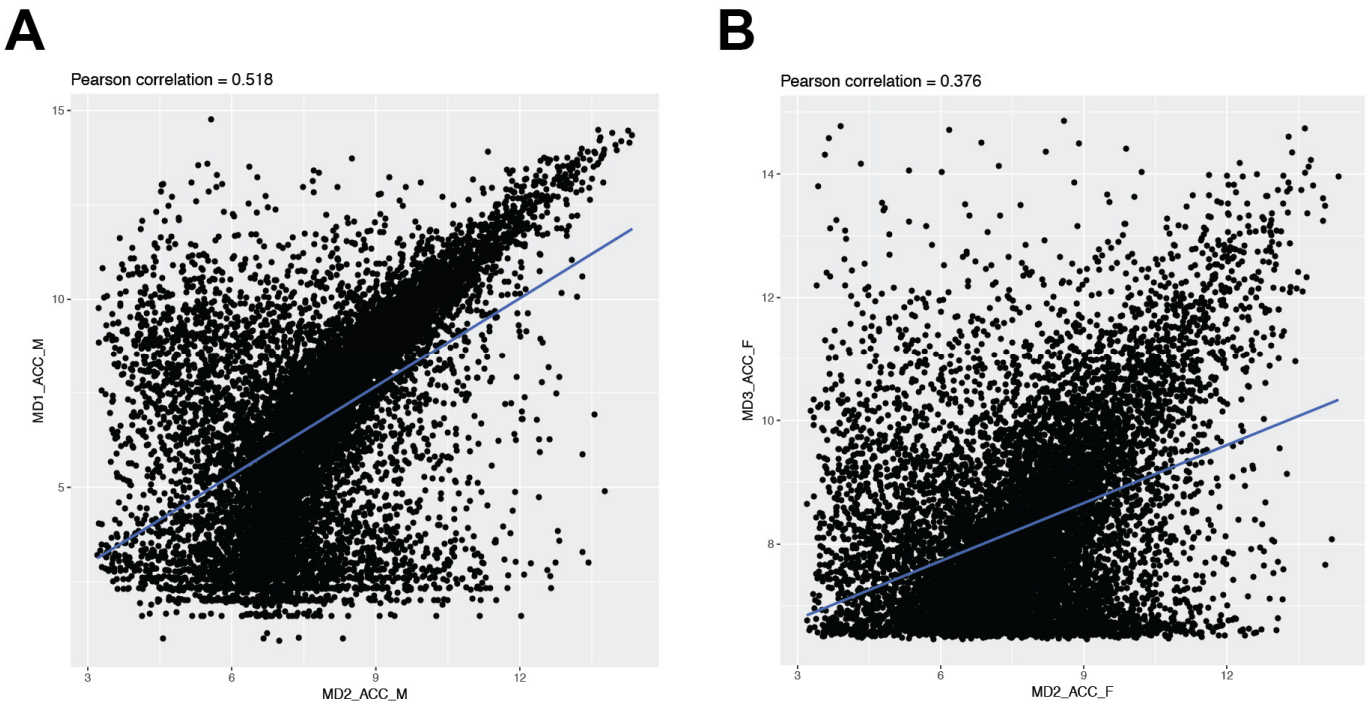

Figure S2. Correlation of gene expression across studies used in meta-analysis. (**A**) In ACC studies performed in males on the same Affymetrix platform, there was a significant correlation of gene expression (Pearson correlation = 0.518). Results are shown by scatterplot. (**B**) In ACC studies performed in females on different platforms (Affymetrix and Illumina), there was a significant correlation of gene expression (Pearson correlation = 0.376). Results are shown by scatterplot.

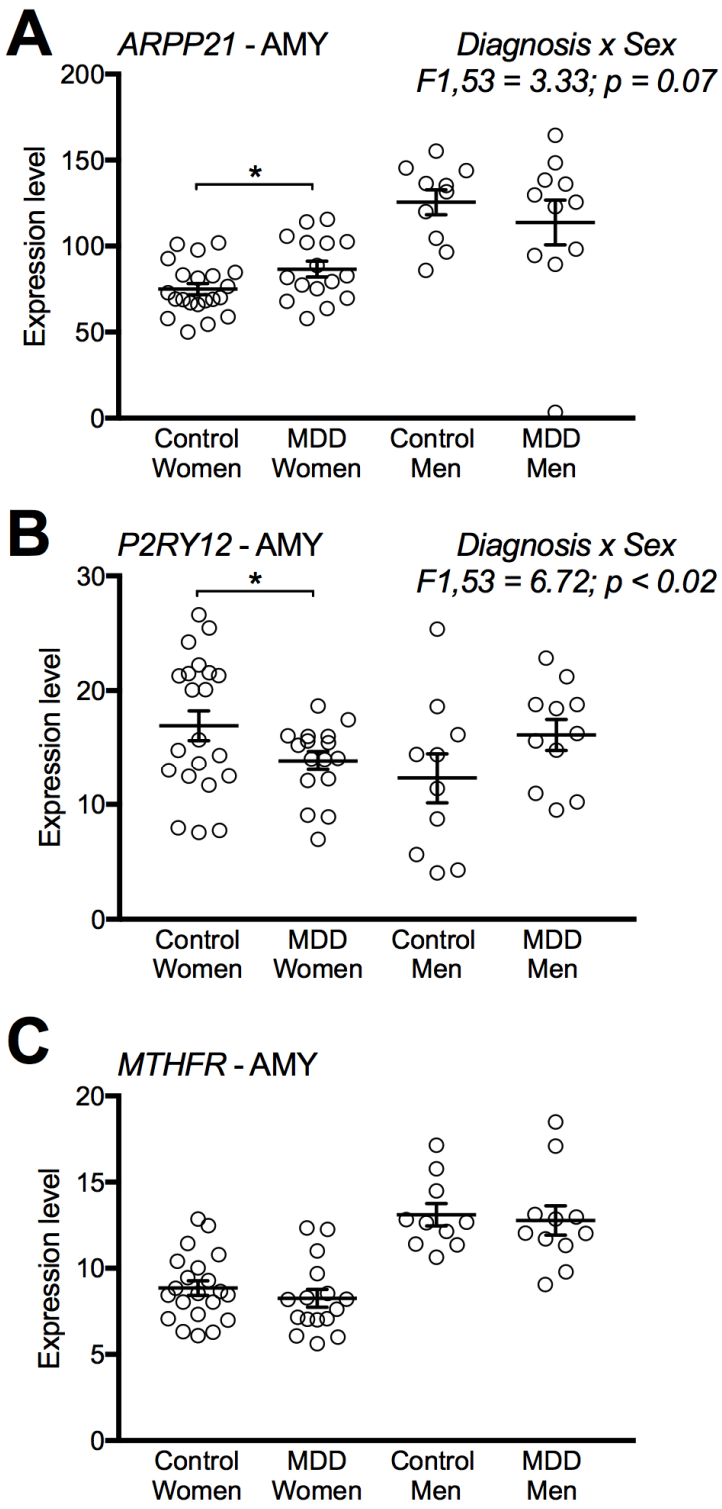

Figure S3. Verification of meta-regression results using qPCR in AMY. There were sex x diagnosis interactions for *ARPP21* (**A**) and *P2RY12* (**B**), but not for MTHFR (C). For *ARPP21* (**A**), there was a significant increase in expression in only women with MDD. For *P2RY12* (**B**), there was a significant decrease in expression in only women with MDD. *, $p < 0.05$.

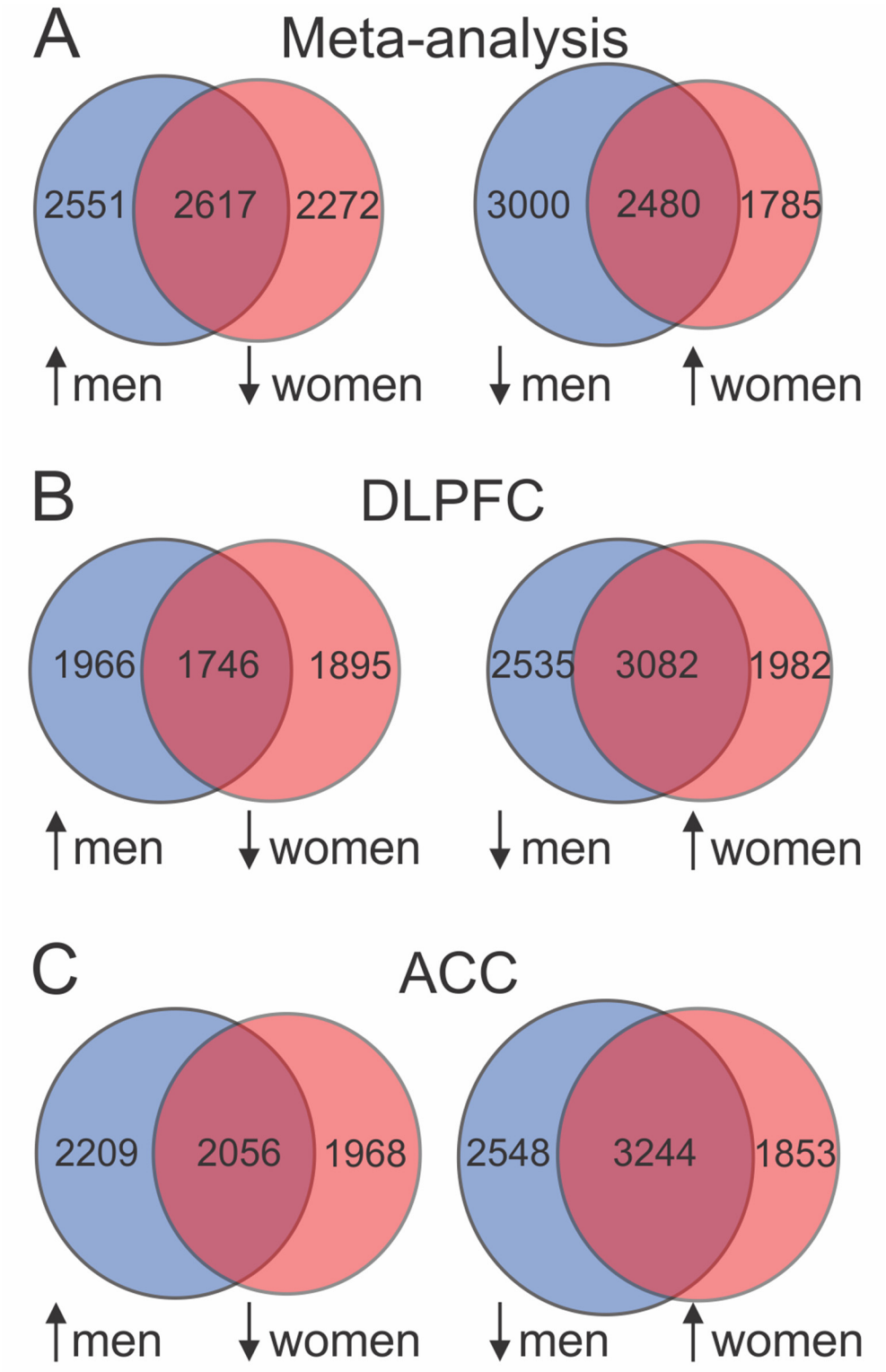

Figure S4. Overlap in opposite molecular profiles in men and women with MDD. (A) Venn diagrams indicating overlap in RRHO-identified genes from the full meta-analysis. **(B)** Venn diagrams indicating overlap in RRHO-identified genes from the DLPFC. **(C)** Venn diagrams indicating overlap in RRHO-identified genes from the ACC.

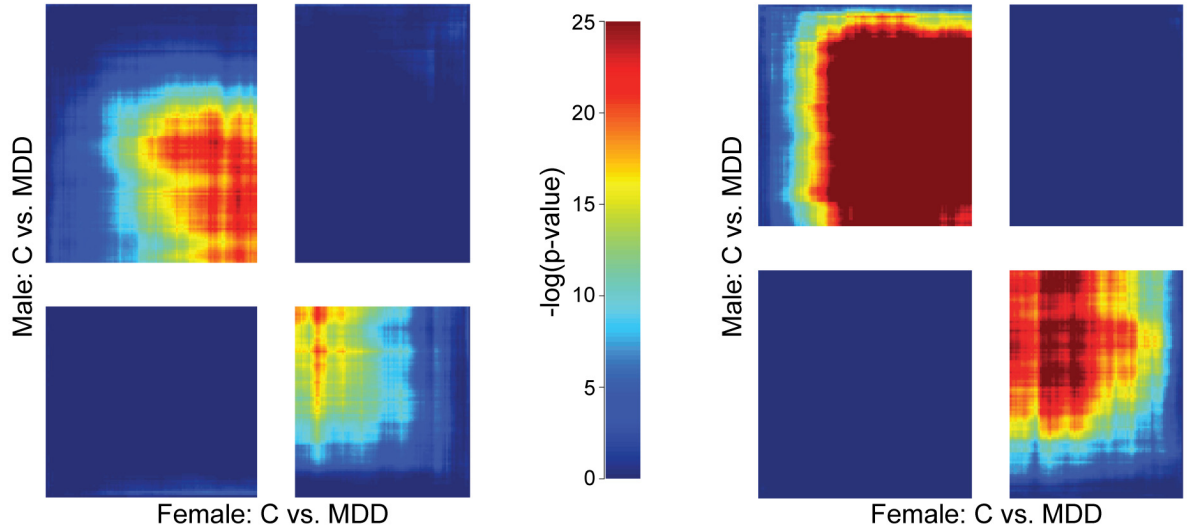

Figure S5. RRHO analysis of replication dataset from Labonte et al. (6) confirmed the opposite transcriptional profile of male and female depression in BA25 (**left**) and BA11 (**right**).

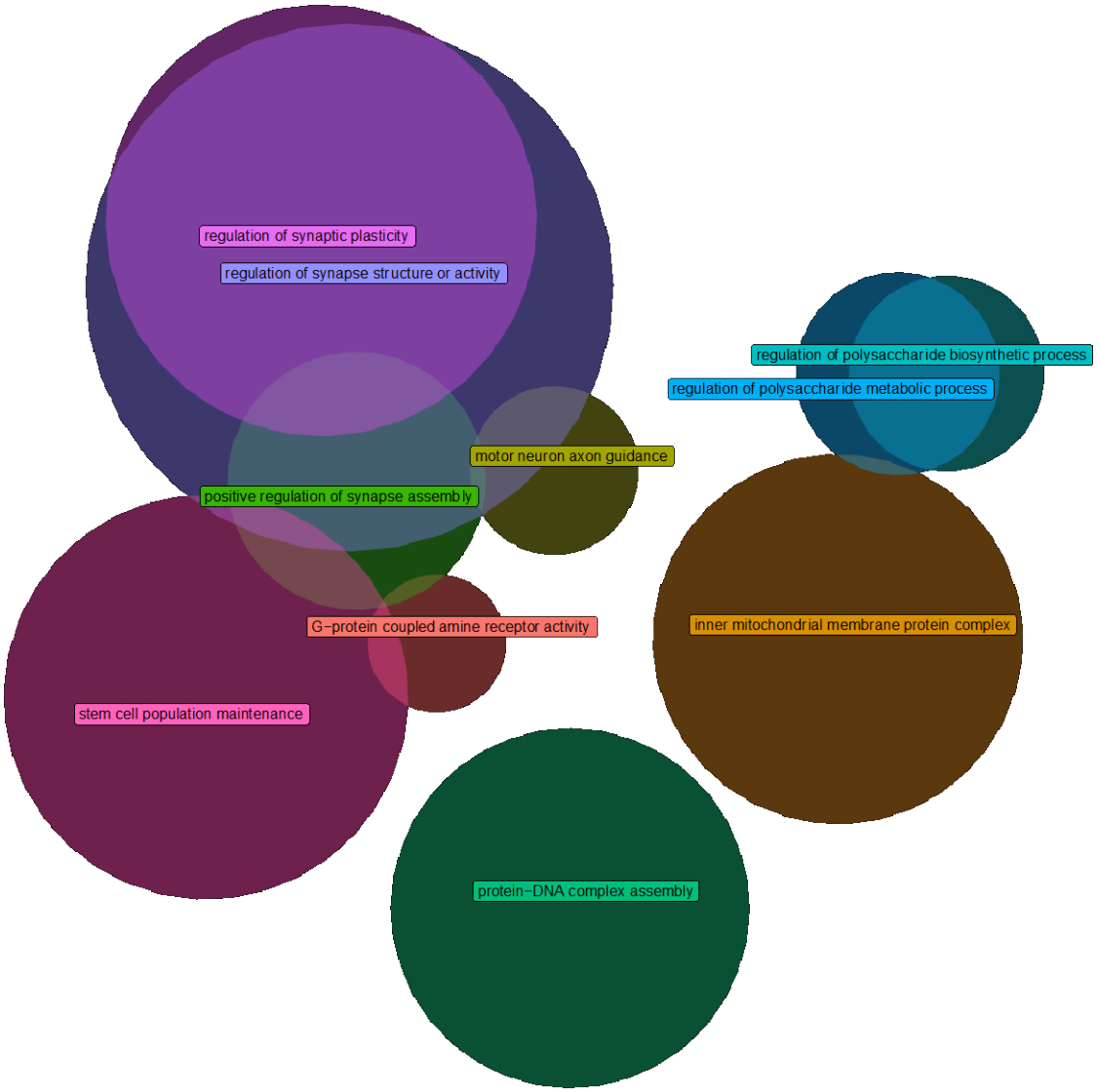

Figure S6. Overlap of top 10 biological pathways identified in men with MDD. Note the high level of overlap in the synapse-related pathways.

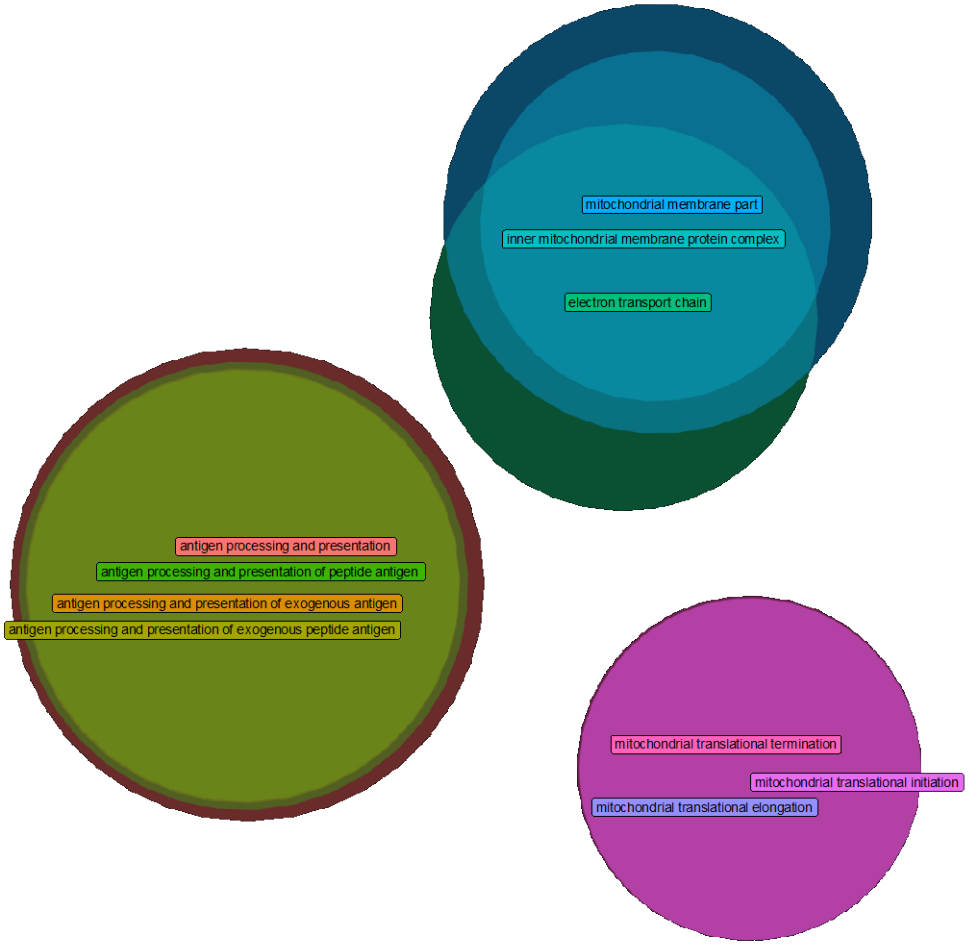

Figure S7. Overlap of top 10 biological pathways identified in women with MDD. Note the high level of overlap in the antigen-related pathways. Additionally, the mitochondrial translation-related pathways overlapped with each other, but not with the mitochondrial membrane-related pathways.

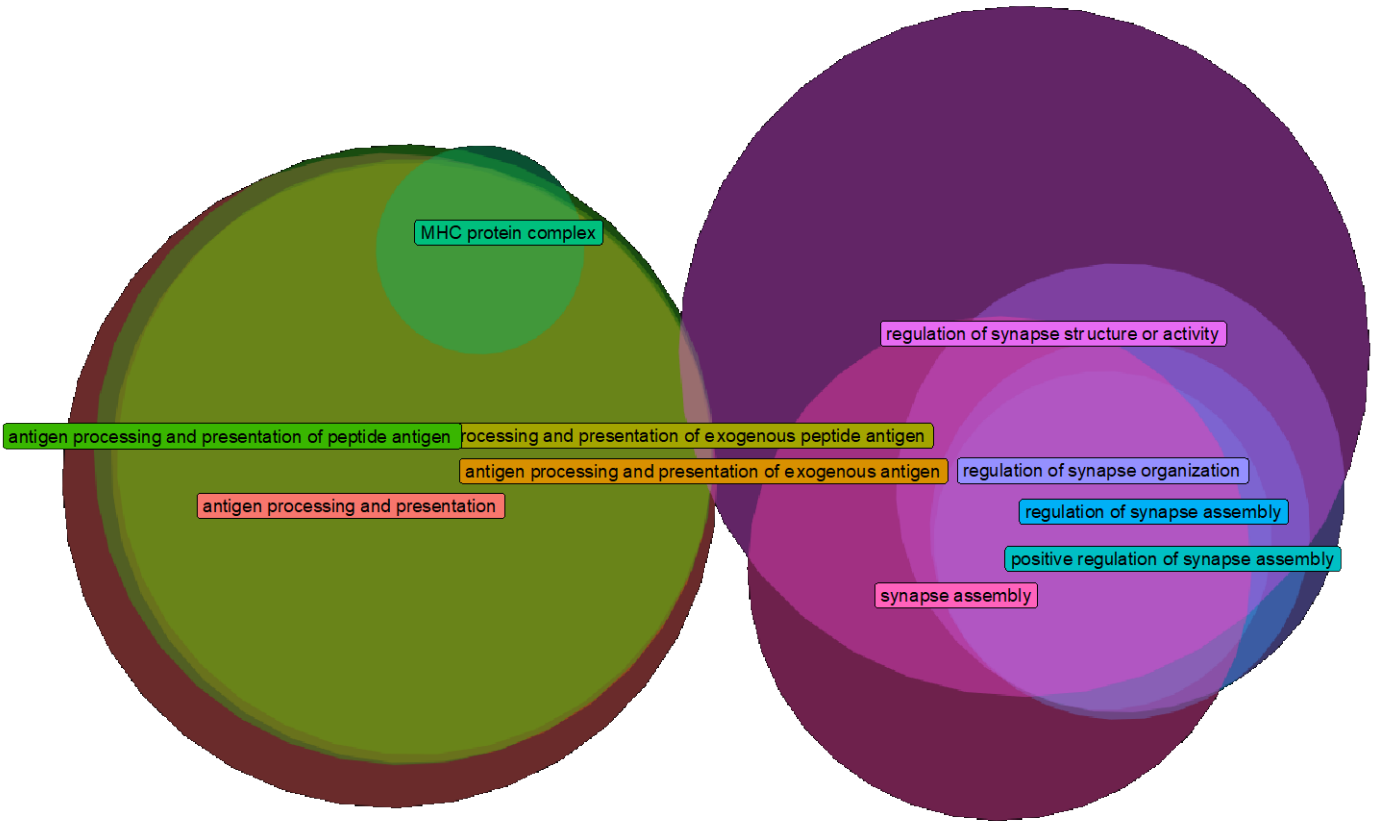

Figure S8. Overlap of top 10 biological pathways identified in the meta-regression dataset. Note the high level of overlap in the antigen-related and MHC pathways. Additionally, the synapse-related pathways are also highly overlapping.

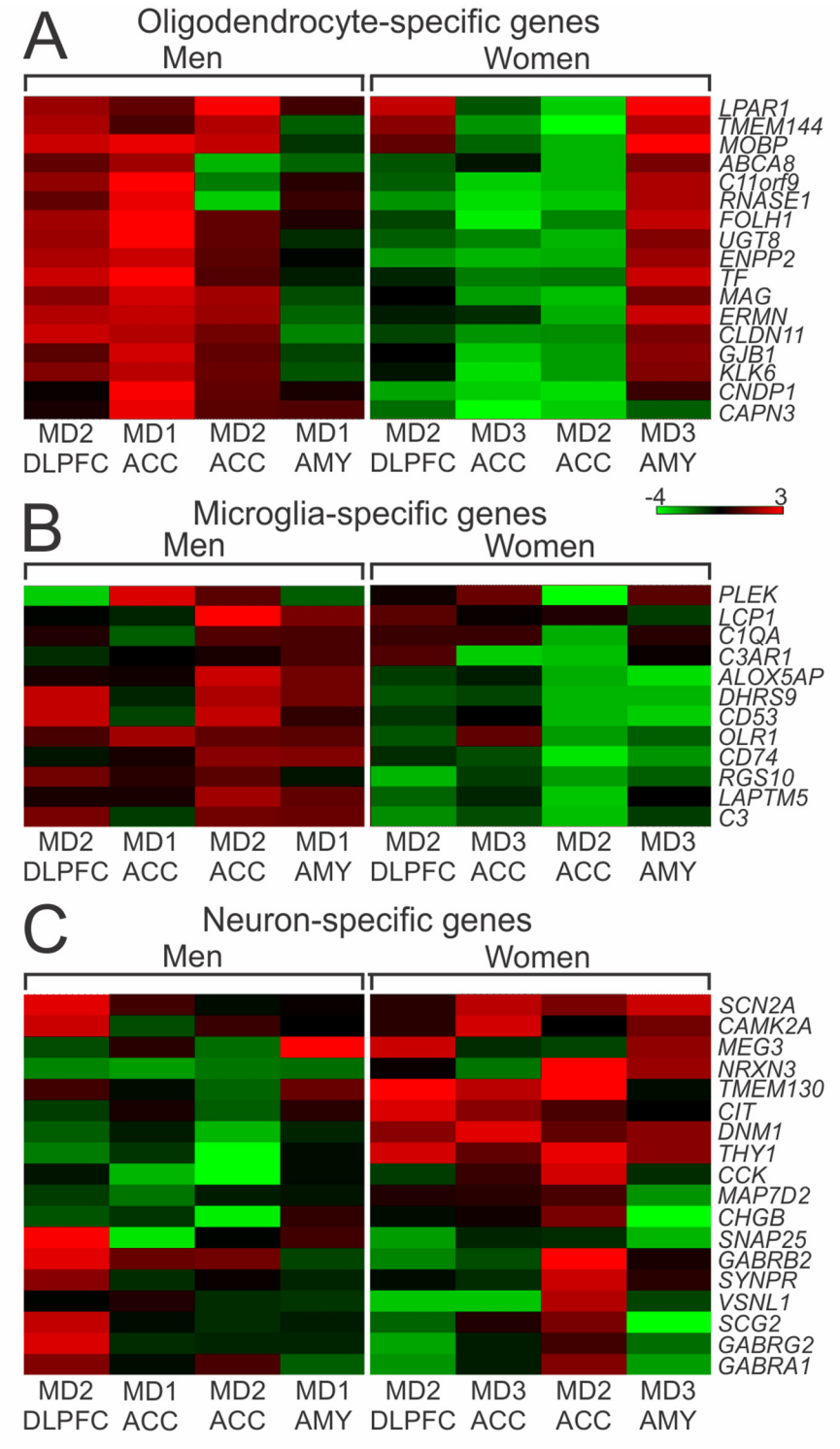

Figure S9. Cell type-specific changes in MDD. (A) There were sex-specific and brain region-specific changes in oligodendrocyte genes. The overall cell type-specific signal when all three brain regions were combined indicated upregulation of oligodendrocyte-specific genes in men with MDD and downregulation of these same genes in women with MDD. This finding was driven by the DLPFC and ACC, with opposite direction of effects

in AMY. **(B)** Across all three brain regions, there were increases in microglia-specific genes in men with MDD, but decreases in these same genes in women with MDD. **(C)** Across brain regions, there were consistent decreases in neuron-specific genes in men with MDD. There were nonsignificant increases in these same neuron-specific genes in women with MDD.

Table S1. Description of eight MDD microarray studies, including data pre-processing and number of genes investigated. See also previous reports on the cohorts and datasets (11-14).

Study name	Sex	Brain region	Sample size	Array platform	# genes before matching	# genes after matching	# genes in common	# genes after filtering
1-MD_ACC_M	Male	ACC	32 (16 pairs)	Affy. HG-U133 Plus 2	40610	19621	16689	10680 genes (20%MV; 20%SD) = 16689 x 0.8 x 0.8
2-MD_ACC_M	Male	ACC	18 (9 pairs)	Affy. HG-U133 Plus 2	53596	19572		
3-MD_ACC_F	Female	ACC	26 (13 pairs)	Affy. HG-U133 Plus 2	53596	19572		
4-MD_ACC_F	Female	ACC	40 (20 pairs)	IlluminaHumanHT-12	48803	25159		
5-MD_AMY_M	Male	AMY	28 (14 pairs)	Affy. HG-U133 Plus 2	40610	19621		
6-MD_AMY_F	Female	AMY	40 (20 pairs)	IlluminaHumanHT-12	48803	25159		
7-MD_DLPFC_M	Male	DLPFC	28 (14 pairs)	Affy. HG-U133 Plus 2	53596	19572		
8-MD_DLPFC_F	Female	DLPFC	30 (15 pairs)	Affy. HG-U133 Plus 2	53596	19572		

Table S2. Demographic and technical details on individual subjects included in each microarray study.

Hu#	Subject Group	DSM-IV Diagnosis	MOD	COD	Sex	Age	Race	PMI	pH	RNA ratio	RIN	Medication ATOD	Tobacco ATOD	1-MD1-ACC-M	2-MD2-ACC-M	3-MD2-ACC-F	4-MD3-ACC-F	5-MD1-AMY-M	6-MD3-AMY-F	7-MD2-DLPFC-M	8-MD2-DLPFC-F
615	Control	None	Natural	Ruptured abdominal aortic	M	62	W	7.2	6.4	1.35	7.8	N	N	1				1		1	
789	Control	None	Accidental	Asphyxiation	M	22	W	20.1	7.0	2.00	7.8	N	N	1				1		1	
795	Control	None	Natural	Ruptured abdominal aortic	M	68	W	11.8	6.8	1.60	8.2	N	N	1				1		1	
1031	Control	None	Natural	ASCVD	M	53	W	23.2	6.8	1.50	8.9	N	N	1	1			1		1	
604	Control	None	Natural	Hypoplastic coronary	M	39	W	19.3	7.1	2.11	8.6	N	N	1				1			
685	Control	None	Natural	Hypoplastic coronary	M	56	W	14.5	7.1	1.70	8.1	O	U	1				1			
713	Control	None	Natural	ASCVD	M	58	W	37.5	7.0	1.55	8.4	U	Y	1				1			
736	Control	None	Natural	ASCVD	M	54	W	15.5	6.9	1.56	8.3	N	N	1				1			
852	Control	None	Natural	Cardiac tamponade	M	54	W	8.0	6.9	1.79	9.1	N	Y	1				1			
857	Control	None	Natural	ASCVD	M	48	W	16.6	6.7	2.03	8.9	N	Y	1				1			
1047	Control	None	Natural	ASCVD	M	43	W	13.8	6.6	1.83	9.0	O	N	1				1			
1067	Control	None	Natural	Hypertensive heart	M	49	W	6.0	6.6	1.44	8.2	O	N	1				1			
1086	Control	None	Natural	ASCVD	M	51	W	24.2	6.8	1.36	8.1	N	Y	1				1			
1122	Control	None	Natural	Cardiac tamponade	M	55	W	15.4	6.7	1.40	7.9	O	Y	1				1			
546	Control	None	Natural	ASCVD	F	37	W	23.5	6.7	2.00	8.6	U	U			1			1		1
567	Control	None	Natural	Mitral valve prolapse	F	46	W	15.0	6.8	2.30	8.9	N	U			1			1		1
575	Control	None	Natural	ASCVD	F	55	B	11.3	6.8	1.80	9.6	U	U			1			1		1
1034	Control	None	Natural	Endocardial fibroelastosis	F	23	W	8.5	7.0	2.00	7.8	N	N			1			1		1
1092	Control	None	Natural	Mitral valve prolapse	F	40	B	16.6	6.8	1.70	8.0	O	N			1			1		1
1247	Control	None	Natural	ASCVD	F	58	W	22.7	6.4	1.30	8.4	O	N			1			1		1

Hu#	Subject Group	DSM-IV Diagnosis	MOD	COD	Sex	Age	Race	PMI	pH	RNA ratio	RIN	Medication ATOD	Tobacco ATOD	1-MD1-ACC-M	2-MD2-ACC-M	3-MD2-ACC-F	4-MD3-ACC-F	5-MD1-AMY-M	6-MD3-AMY-F	7-MD2-DLPFC-M	8-MD2-DLPFC-F
1282	Control	None	Natural	ASCVD	F	39	W	24.5	6.8	1.30	7.5	N	N			1			1		1
1391	Control	None	Natural	ASCVD	F	51	W	7.80	6.6	1.60	7.1	O	Y			1			1		1
1403	Control	Adjustment disorder with mixed anxiety & depressed mood, in remission (8 months)	Natural	ASCVD	F	45	W	12.3	6.7	1.80	8.2	O	Y			1			1		1
1466	Control	None	Accidental	Trauma	F	64	B	20.0	6.7	2.00	8.8	O	N			1			1		1
1196	Control	None	Accidental	Asphyxiation	F	36	W	14.5	6.4	1.80	8.2	O	N				1		1		1
568	Control	None	Natural	ASCVD	F	60	W	9.5	6.9	1.90	8.7	N	U				1		1		1
627	Control	None	Natural	COPD	F	43	B	14.1	7.1	1.00	7.0	O	N				1		1		
818	Control	None	Accidental	Anaphylactic reaction	F	67	W	24.0	7.1	1.50	8.4	O	N				1		1		
840	Control	Adjustment disorder with depressed mood, current; AAR (20 years remission)	Natural	ASCVD	F	41	W	15.4	6.8	2.00	9.1	N	Y				1		1		
1081	Control	AAR (20 years remission)	Natural	COPD	F	57	W	14.9	6.8	1.80	9.0	B O	N				1		1		
1099	Control	None	Natural	Cardiomyopathy	F	24	W	9.1	6.5	1.90	8.6	O	Y				1		1		
1280	Control	None	Natural	Pulmonary	F	50	W	23.5	6.7	1.30	7.7	U	U				1		1		
1355	Control	None	Natural	Subarachnoid hemorrhage	F	74	W	24.9	6.6	1.90	7.0	O	N				1		1		
10013	Control	None	Accidental	Trauma	F	16	W	9.3	6.7	1.80	9.0	O	N				1		1		
1129	Control	None	Natural	ASCVD	M	54	W	21.0	6.8	1.50	9.0	N	N		1					1	
1317	Control	None	Natural	ASCVD	M	56	W	22.9	6.5	1.20	8.8	O	Y		1					1	
1372	Control	None	Accidental	Asphyxiation	M	37	W	20.5	6.6	1.60	9.0	O	U		1					1	

Hu#	Subject Group	DSM-IV Diagnosis	MOD	COD	Sex	Age	Race	PMI	pH	RNA ratio	RIN	Medication ATOD	Tobacco ATOD	1-MD1-ACC-M	2-MD2-ACC-M	3-MD2-ACC-F	4-MD3-ACC-F	5-MD1-AMY-M	6-MD3-AMY-F	7-MD2-DLPFC-M	8-MD2-DLPFC-F
1394	Control	None	Natural	ASCVD	M	45	W	17.3	6.6	1.90	7.3	N	N		1					1	
1439	Control	None	Natural	Subarachnoid hemorrhage	M	56	W	16.1	6.8	2.10	7.7	O	Y		1					1	
1444	Control	None	Natural	Pulmonary	M	46	W	22.0	6.5	2.10	8.4	N	N		1					1	
1462	Control	None	Natural	ASCVD	M	47	W	17.2	6.6	2.00	8.5	N	N		1					1	
612	Control	None	Accidental	Aspiration	M	60	W	9.6	6.8	1.50	9.0	N	U							1	
1214	Control	None	Natural	ASCVD	M	57	W	16.4	6.4	1.70	7.5	O	N							1	
1447	Control	None	Natural	ASCVD	M	51	W	16.2	6.5	1.80	8.5	N	N							1	
686	Control	None	Natural	ASCVD	F	52	W	22.6	7.1	1.90	8.5	O	Y			1					1
731	Control	None	Natural	ASCVD	F	63	W	10.5	6.8	1.60	8.2	N	Y			1					1
1293	Control	None	Accidental	Trauma	F	65	W	18.5	6.6	1.30	7.0	N	N			1					1
1270	Control	None	Accidental	Trauma	F	73	W	19.7	6.7	1.40	7.7	O	N			1					1
634	Control	None	Natural	ASCVD	M	52	W	16.2	7.0	1.90	8.5	N	U	1							
1374	Control	None	Natural	ASCVD	M	43	W	21.7	6.6	1.80	7.2	O	Y		1						
505	MDD	MDD, recurrent, severe without psychotic features; ADC	Suicide	Gunshot	M	57	W	12.8	7.1	1.80	8.9	N	Y	1				1		1	
513	MDD	MDD, recurrent, severe with psychotic features; ODC	Suicide	Hanging	M	24	W	13.1	6.9	1.90	9.0	N	Y	1				1		1	
868	MDD	MDD, recurrent, severe without psychotic features; ADC; OAC	Accidental	Trauma	M	47	W	10.5	6.8	1.50	9.3	N	N	1				1		1	
598	MDD	MDD, single episode, severe without psychotic features; OAR	Suicide	Gunshot	M	69	W	5.9	7.3	1.61	8.8	D O	Y	1				1			

Hu#	Subject Group	DSM-IV Diagnosis	MOD	COD	Sex	Age	Race	PMI	pH	RNA ratio	RIN	Medication ATOD	Tobacco ATOD	1-MD1-ACC-M	2-MD2-ACC-M	3-MD2-ACC-F	4-MD3-ACC-F	5-MD1-AMY-M	6-MD3-AMY-F	7-MD2-DLPFC-M	8-MD2-DLPFC-F
600	MDD	MDD, single episode, severe without psychotic features	Suicide	Hanging	M	63	W	9.9	6.7	1.71	7.1	O	N	1				1			
698	MDD	MDD, single episode, severe with psychotic features	Suicide	Hanging	M	59	W	13.0	6.8	1.50	9.0	D O P	N	1				1			
783	MDD	MDD, recurrent, in full remission	Natural	Dissection of the aorta	M	63	W	11.5	6.5	1.36	8.8	O	N	1				1			
809	MDD	MDD, single episode, in full remission	Natural	ASCVD	M	50	W	20.0	6.9	1.52	8.5	D O	Y	1				1			
863	MDD	MDD, single episode, severe without psychotic features	Natural	ASCVD	M	51	W	28.3	7.3	1.52	8.4	N	N	1				1			
926	MDD	MDD, single episode, severe without psychotic features; AAR	Natural	Arteriosclerotic and hypertensive heart	M	56	W	19.0	7.0	1.38	7.3	D O	Y	1				1			
943	MDD	MDD, recurrent, in partial remission; ADC; OAC; ODR	Suicide	Gunshot	M	56	W	15.4	6.6	1.49	8.2	O	Y	1				1			
1001	MDD	MDD, single episode, in full remission	Natural	Arteriosclerotic and hypertensive heart	M	53	W	7.3	6.6	1.38	7.6	O	Y	1				1			
1060	MDD	MDD, single episode, in full remission; AAC	Suicide	Hanging	M	30	W	11.1	6.6	1.32	8.3	O	N	1				1			

Hu#	Subject Group	DSM-IV Diagnosis	MOD	COD	Sex	Age	Race	PMI	pH	RNA ratio	RIN	Medication ATOD	Tobacco ATOD	1-MD1-ACC-M	2-MD2-ACC-M	3-MD2-ACC-F	4-MD3-ACC-F	5-MD1-AMY-M	6-MD3-AMY-F	7-MD2-DLPFC-M	8-MD2-DLPFC-F
1049	MDD	MDD, single episode, severe without psychotic features	Natural	Cardiomyopathy	M	48	W	5.4	6.6	1.45	8.4	D O	N					1			
803	MDD	MDD, recurrent, in partial remission	Accidental	Trauma	F	65	W	18.0	7.0	1.90	9.0	D O	N			1			1		1
934	MDD	MDD, recurrent, severe with psychotic features	Natural	ASCVD	F	54	W	17.9	6.5	1.20	8.2	D O	N			1			1		1
967	MDD	MDD, recurrent, moderate; ADC	Natural	ASCVD	F	40	W	22.2	6.6	1.6	7.4	N	Y			1			1		1
986	MDD	MDD, recurrent, severe without psychotic features	Natural	Bronchial asthma	F	53	W	11.9	6.7	1.80	8.8	D O	N			1			1		1
1041	MDD	MDD, recurrent, severe with psychotic features; AAC; ODC	Accidental	Combined drug overdose	F	52	W	10.3	6.5	1.50	8.4	B D O P	Y			1			1		1
1157	MDD	MDD, recurrent, severe without psychotic features	Suicide	Hanging	F	26	W	13.4	6.4	1.50	7.8	D	N			1			1		1
1190	MDD	MDD, recurrent, severe without psychotic features; ADC	Suicide	Asphyxiation	F	47	W	22.3	6.6	1.6	8.0	N	Y			1			1		1
1221	MDD	MDD, recurrent, severe without psychotic features	Natural	Pulmonary thrombosis	F	28	B	24.8	6.6	1.8	7.2	N	N			1			1		1

Hu#	Subject Group	DSM-IV Diagnosis	MOD	COD	Sex	Age	Race	PMI	pH	RNA ratio	RIN	Medication ATOD	Tobacco ATOD	1-MD1-ACC-M	2-MD2-ACC-M	3-MD2-ACC-F	4-MD3-ACC-F	5-MD1-AMY-M	6-MD3-AMY-F	7-MD2-DLPFC-M	8-MD2-DLPFC-F
1249	MDD	MDD, recurrent, moderate; ODR	Accidental	Combined drug overdose	F	40	W	11.2	6.5	2.00	9.0	B C D O	Y			1			1		1
1254	MDD	MDD, recurrent, severe without psychotic features	Suicide	Incised wounds	F	39	W	12.8	6.4	1.90	9.0	D	N			1			1		1
1408	MDD	MDD, recurrent, severe without psychotic features; ADC	Accidental	Trauma	F	37	W	15.5	6.6	1.6	7.0	B D O	N				1		1		1
564	MDD	MDD, single episode, severe with psychotic features	Suicide	Hanging	F	56	W	16.8	7.0	1.90	9.2	B D O	Y				1		1		
666	MDD	MDD, single episode, in partial remission	Accidental	Trauma	F	16	W	10.0	7.3	2.00	9.4	D	N				1		1		
1202	MDD	MDD, recurrent, in partial remission	Natural	Pulmonary embolism	F	39	W	11.2	6.4	1.80	8.0	D O	Y				1		1		
1289	MDD	MDD, single episode, mild	Natural	ASCVD	F	46	W	25.0	6.3	1.40	7.3	U	N				1		1		
1315	MDD	MDD, single episode, severe without psychotic features; AAC	Suicide	Hanging	F	28	W	12.4	7.0	1.50	7.9	N	Y				1		1		
1332	MDD	MDD, recurrent, in partial remission; ADR; ODC	Natural	ASCVD	F	46	W	17.5	6.7	1.60	8.9	B D O	Y				1		1		

Hu#	Subject Group	DSM-IV Diagnosis	MOD	COD	Sex	Age	Race	PMI	pH	RNA ratio	RIN	Medication ATOD	Tobacco ATOD	1-MD1-ACC-M	2-MD2-ACC-M	3-MD2-ACC-F	4-MD3-ACC-F	5-MD1-AMY-M	6-MD3-AMY-F	7-MD2-DLPFC-M	8-MD2-DLPFC-F
1356	MDD	MDD, recurrent, in partial remission, AAC	Accidental	Intraperitoneal hemorrhage	F	60	W	20.6	6.1	1.80	8.5	D O	N				1		1		
1360	MDD	MDD, single episode, severe without psychotic features; ODC	Suicide	Drowning	F	59	W	18.1	6.4	1.40	7.6	D	Y				1		1		
10028	MDD	MDD, single episode, severe without psychotic features	Suicide	Gunshot	F	72	W	23.1	6.7	1.40	7.0	O	N				1		1		
613	MDD	MDD, recurrent, severe with psychotic features; AAR	Suicide	Gunshot	M	59	W	15.6	7.0	1.90	9.1	O	N	1						1	
1013	MDD	MDD, recurrent, severe without psychotic features	Suicide	Nail gun wound	M	46	W	16.1	6.3	1.50	8.0	N	N		1					1	
1161	MDD	MDD, recurrent, in partial remission, ADR	Natural	ASCVD	M	57	W	15.9	6.6	2.00	7.6	D O	Y		1					1	
1253	MDD	MDD, recurrent, in partial remission; ADC; ODC	Natural	ASCVD	M	58	W	12.5	6.8	1.90	8.1	C D O	Y		1					1	
1261	MDD	MDD, recurrent, moderate; ADC; ODC; OAR	Accidental	Electrocution	M	46	W	22.8	6.6	1.90	8.8	D O	N		1					1	
1312	MDD	MDD, recurrent, severe without psychotic features; ADR; ODC	Accidental	Combined drug overdose	M	51	W	24.6	6.5	1.60	8.5	O	N		1					1	

Hu#	Subject Group	DSM-IV Diagnosis	MOD	COD	Sex	Age	Race	PMI	pH	RNA ratio	RIN	Medication ATOD	Tobacco ATOD	1-MD1-ACC-M	2-MD2-ACC-M	3-MD2-ACC-F	4-MD3-ACC-F	5-MD1-AMY-M	6-MD3-AMY-F	7-MD2-DLPFC-M	8-MD2-DLPFC-F
1320	MDD	MDD, recurrent, moderate; ADC	Natural	ASCVD	M	55	W	24.4	6.5	1.30	7.2	N	Y		1					1	
10010	MDD	MDD, recurrent, severe with psychotic features; AAR	Suicide	Amitriptyline overdose	M	42	W	14.3	6.4	1.80	7.6	C D O	N		1					1	
10031	MDD	MDD, recurrent, severe without psychotic features; ADC; OAR	Accidental	Combined drug overdose	M	36	W	20.0	6.8	2.00	8.9	C D P	Y		1					1	
1389	MDD	MDD, recurrent, severe without psychotic features; ADC	Natural	ASCVD	M	61	W	16.0	6.6	1.90	8.4	N	N							1	
10012	MDD	MDD, recurrent, severe without psychotic features; ODC	Suicide	Hanging	M	49	W	24.2	6.4	1.50	8.8	O	Y							1	
1143	MDD	MDD, recurrent, severe without psychotic features; ADR; ODC	Accidental	Combined drug overdose	F	49	W	23.4	6.4	1.80	8.1	B D O	Y			1					1
565	MDD	MDD, recurrent, severe without psychotic features; AAC; ODR	Suicide	Gunshot	F	62	W	12.5	6.9	2.00	9.2	D	N			1					1
1272	MDD	MDD, recurrent, unspecified; ADC; ODC	Accidental	Asphyxiation	F	64	W	12.1	6.6	1.40	7.8	B C D O	Y			1					1

Hu#	Subject Group	DSM-IV Diagnosis	MOD	COD	Sex	Age	Race	PMI	pH	RNA ratio	RIN	Medication ATOD	Tobacco ATOD	1-MD1-ACC-M	2-MD2-ACC-M	3-MD2-ACC-F	4-MD3-ACC-F	5-MD1-AMY-M	6-MD3-AMY-F	7-MD2-DLPFC-M	8-MD2-DLPFC-F
860	MDD	MDD, recurrent; severe with psychotic features	Natural	ASCVD	F	74	W	22.8	7.0	1.20	8.1	B D O P	Y			1					1
619	MDD	MDD, severe without psychotic features; ODR	Suicide	Gunshot	M	55	W	18.8	6.9	1.33	7.9	B D	Y	1							
1226	MDD	MDD, recurrent, severe without psychotic features; ODC; ODR; OAC; OAR	Natural	ASCVD	M	44	W	19.3	6.5	1.70	7.5	N	Y		1						

Abbreviations: AAC, alcohol abuse current; AAR, alcohol abuse remission; ADC, alcohol dependence current; ADR, alcohol dependence remission; ASCVD, arteriosclerotic cardiovascular disease; ATOD, at time of death; B, benzodiazepines; B, black subject; C, anticonvulsants; COD, cause of death; COPD, chronic obstructive pulmonary disease; D, antidepressants; F, female; M, male; MDD, major depressive disorder; MOD, mode of death; N, no medications or no tobacco at time of death; O, other medication(s); OAC, other substance abuse current; OAR, other substance abuse remission; ODC, other substance dependence current; ODR, other substance dependence remission; P, antipsychotics; PMI, postmortem interval in hours; RIN, RNA integrity number; W, white subject; Y, yes.

Table S3. Genes identified via meta-regression which are changed in opposite directions in men and women with MDD.

Gene symbol	*MetaR*	*Men*		*Women*	
	q-value	*Effect Size*	*q-value*	*Effect Size*	*q-value*
C2CD2L	$< 10^{-29}$	- 1.68	$< 10^{-10}$	1.90	$< 10^{-16}$
P2RY12	$< 10^{-24}$	0.92	$< 10^{-4}$	- 2.73	$< 10^{-20}$
PTPRF	$< 10^{-22}$	- 1.56	$< 10^{-7}$	1.68	$< 10^{-15}$
GALC	$< 10^{-22}$	1.28	$< 10^{-6}$	- 1.41	$< 10^{-13}$
PCDHB4	$< 10^{-20}$	1.79	$< 10^{-10}$	- 1.26	$< 10^{-11}$
KLF3	$< 10^{-20}$	1.65	$< 10^{-8}$	- 2.37	$< 10^{-18}$
OGFR	$< 10^{-20}$	- 1.89	$< 10^{-8}$	1.69	$< 10^{-15}$
PHLDA1	$< 10^{-20}$	1.48	$< 10^{-9}$	- 1.50	$< 10^{-12}$
TMEM168	$< 10^{-20}$	0.86	$< 10^{-3}$	- 1.54	$< 10^{-14}$
UNC84A	$< 10^{-18}$	- 1.63	$< 10^{-9}$	0.87	$< 10^{-6}$
ADCY3	$< 10^{-17}$	- 1.83	$< 10^{-11}$	0.64	< 0.05
ZMYND8	$< 10^{-16}$	- 2.42	$< 10^{-13}$	1.74	$< 10^{-6}$
RCCD1	$< 10^{-15}$	- 1.27	$< 10^{-6}$	1.56	$< 10^{-13}$
CDH3	$< 10^{-13}$	- 1.13	$< 10^{-4}$	1.41	$< 10^{-12}$
ARPP21	$< 10^{-13}$	- 2.08	$< 10^{-8}$	3.19	$< 10^{-6}$
GLIPR1	$< 10^{-13}$	2.04	$< 10^{-11}$	- 2.29	$< 10^{-6}$
SMAD3	$< 10^{-12}$	- 2.32	$< 10^{-6}$	1.19	$< 10^{-9}$
CCDC86	$< 10^{-12}$	- 0.89	$< 10^{-4}$	1.08	$< 10^{-8}$
IER5L	$< 10^{-12}$	- 2.03	$< 10^{-7}$	1.26	$< 10^{-9}$
MTHFR	$< 10^{-12}$	- 2.01	$< 10^{-4}$	1.70	$< 10^{-13}$
SPTBN4	$< 10^{-12}$	- 2.17	$< 10^{-8}$	2.05	$< 10^{-7}$
ADCY9	$< 10^{-11}$	- 1.49	$< 10^{-9}$	0.89	$< 10^{-4}$
KIAA0774	$< 10^{-10}$	- 1.83	$< 10^{-6}$	1.16	$< 10^{-7}$
ICMT	$< 10^{-10}$	- 2.31	$< 10^{-4}$	1.04	$< 10^{-7}$
NEDD4L	$< 10^{-10}$	- 1.72	$< 10^{-10}$	2.19	$< 10^{-3}$
OGDHL	$< 10^{-10}$	- 1.15	< 0.05	1.54	$< 10^{-14}$
KIAA2013	$< 10^{-10}$	- 2.07	$< 10^{-5}$	1.69	$< 10^{-7}$
RNF34	$< 10^{-10}$	- 1.17	$< 10^{-6}$	1.86	$< 10^{-3}$
CPLX2	$< 10^{-10}$	- 1.94	$< 10^{-11}$	1.79	< 0.05
SCP2	$< 10^{-9}$	2.08	< 0.05	- 1.13	$< 10^{-8}$
ZDHHC8	$< 10^{-9}$	- 1.42	$< 10^{-7}$	1.42	$< 10^{-6}$
RBM15	$< 10^{-9}$	- 1.89	$< 10^{-9}$	1.33	$< 10^{-3}$
BCL7B	$< 10^{-9}$	- 2.09	< 0.05	0.66	$< 10^{-3}$
ABCB9	$< 10^{-9}$	- 1.78	$< 10^{-6}$	1.40	$< 10^{-5}$
MLF2	$< 10^{-9}$	- 1.71	$< 10^{-9}$	0.75	< 0.05
ZBTB46	$< 10^{-9}$	- 1.99	$< 10^{-5}$	2.09	$< 10^{-3}$
GOPC	$< 10^{-9}$	1.53	$< 10^{-8}$	- 1.44	$< 10^{-4}$
ANKRD27	$< 10^{-8}$	- 1.52	$< 10^{-8}$	- 1.33	$< 10^{-3}$
EIF5A2	$< 10^{-8}$	- 1.18	$< 10^{-6}$	1.01	$< 10^{-3}$
DNM1	$< 10^{-8}$	- 1.30	$< 10^{-3}$	1.49	$< 10^{-7}$
DARC	$< 10^{-7}$	- 0.82	< 0.05	0.97	$< 10^{-6}$
NR2C2	$< 10^{-7}$	- 1.65	$< 10^{-5}$	1.01	$< 10^{-4}$
ADRM1	$< 10^{-7}$	- 1.07	$< 10^{-5}$	0.90	$< 10^{-3}$
DCTN1	$< 10^{-7}$	- 1.50	$< 10^{-3}$	1.16	$< 10^{-6}$
PQLC2	$< 10^{-7}$	- 0.84	$< 10^{-3}$	1.71	< 0.05
CYP2B7P1	$< 10^{-6}$	- 0.99	$< 10^{-5}$	1.16	$< 10^{-3}$
PRR7	$< 10^{-6}$	- 1.23	$< 10^{-3}$	0.64	< 0.05
DLGAP2	$< 10^{-6}$	- 1.60	< 0.05	1.19	$< 10^{-3}$
ELP2	$< 10^{-5}$	- 1.19	< 0.05	0.94	$< 10^{-3}$
NUDT17	$< 10^{-5}$	- 0.88	< 0.05	1.07	$< 10^{-3}$
SGPP1	$< 10^{-5}$	1.19	< 0.05	- 0.97	$< 10^{-3}$
SULT4A1	$< 10^{-5}$	- 0.88	$< 10^{-3}$	0.82	$< 10^{-3}$

Table S4. Overlap in DE genes from male MDD and female MDD with genes that are DE between male and female healthy controls.[a]

	DE genes for meta-regression that are also DE at baseline	DE genes in males with MDD that are also DE at baseline	DE genes in females with MDD that are also DE at baseline	DE genes in opposite directions in male and female MDD that are also DE at baseline
ACC	10/1027	6/706	10/882	1/52
DLPFC	9/1027	3/706	9/882	1/52

[a]For baseline sex difference analysis, a cutoff of q < 0.2 was used to identify genes that were sexually dimorphic in control subjects.

Table S5. Sex-specific depression changes confirmed using a different brain bank cohort.[a]

	DE genes in women with MDD	DE genes in men with MDD	Overlap of DE genes in men and women with MDD	% genes changed in opposite directions in men and women with MDD
BA11	3798	3237	299	61%
BA25	4331	4776	476	48%

[a]We used recently published publically available RNA-seq data generated using brains from a different brain bank (GEO GSE102556; (6)). p < 0.05 was used as a DE cutoff.

Table S6. Replication cohort: top 10 transcripts significantly changed in opposite directions in men and women with MDD.

BA11					BA25				
Gene symbol	*Men*		*Women*		*Gene symbol*	*Men*		*Women*	
	Effect size	*p-value*	*Effect size*	*p-value*		*Effect size*	*p-value*	*Effect size*	*p-value*
FCGR1C	-1.840	$>10^{-4}$	1.81	$>10^{-4}$	*EDAR*	-1.45	>0.05	1.48	>0.05
RP11-462G2.2	-1.18	$>10^{-3}$	2.15	$>10^{-4}$	*RP11-536O18.2*	-1.43	$>10^{-3}$	1.02	>0.05
MYBPH	-1.14	>0.05	1.78	$>10^{-4}$	*HLA-DOB*	-1.39	>0.05	2.12	$>10^{-3}$
SNORD53_SNORD92	1.27	$>10^{-5}$	-1.64	>0.05	*RP11-370B11.1*	-1.37	$>10^{-3}$	1.12	>0.05
AC097721.1	-1.50	$>10^{-3}$	1.21	>0.05	*KCNE1L*	-1.35	>0.05	1.68	>0.05
RPS3AP25	-0.82	>0.05	1.82	$>10^{-3}$	*AC104088.1*	-1.34	$>10^{-3}$	1.21	$>10^{-3}$
CD69	-0.86	>0.05	1.67	>0.05	*RP4-660H19.1*	-1.32	>0.05	0.80	>0.05
KRT8P13	-1.00	>0.05	1.53	>0.05	*IRX6*	-1.31	>0.05	1.38	>0.05
RP11-307C19.3	0.79	>0.05	-1.73	$>10^{-3}$	*CTD-2623N2.11*	-1.24	>0.05	1.36	$>10^{-3}$
RP11-159C21.4	-1.17	$>10^{-3}$	1.34	>0.05	*AC110754.3*	-1.22	$>10^{-3}$	1.13	>0.05

Table S7. Sex-specific associations of transcriptomic cell-type enriched gene sets using mouse reference dataset.[a]

Cell type	Men		Women	
	p-value	AUC	p-value	AUC
Astro2	< 0.005	0.683 ↑	NS	0495
Astro1	< 0.005	0.681 ↑	NS	0.497
Mgl2	< 0.05	0.594 ↑	$< 10^{-4}$	0.377 ↓
S1PyrL4	< 0.2	0.602 ↑	< 0.005	0.602 ↑
Epend	< 0.01	0.612 ↑	NS	0.518
Oligo5	< 0.01	0.718 ↑	NS	0.408

Abbreviation: AUC, area under the curve. [a]AUC > 0.5 indicates a cell type is enriched in genes that were downregulated in MDD in that sex. AUC < 0.5 indicates a cell type is enriched in genes that were upregulated in MDD in that sex. Bold indicates cell-types affected in opposite directions in men and women with MDD.

Table S8. Primers used in qPCR studies.

Gene	Forward	Reverse
ARPP21	5’ TAC CAC CGG CAC TTA CAA 3’	5’ GGG AAG CGA TAC AAT CCA 3’
P2RY12	5’ GTG TCA AGT TAC CTC CGT CAT A 3’	5’ TAA ATG GCC TGG TGG TCT 3’
MTHFR	5’ TTG TGT TTG GTT TGG TGG T 3’	5’ CAT CGG TCA GTC CCT CTC 3’
GAPDH	5’ TGC ACC ACC AAC TGC TTA GC 3’	5’ GGC ATG GAC TGT GGT CAT G 3’
CYCLO	5’ GCA GAC AAG GTC CCA AAG 3’	5’ GAA GTC ACC ACC CTG ACA C 3’

Supplemental References

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