**Supplementary Information**

**Whole-brain voxel-based morphometry (VBM) meta-analysis in major depression disorder (MDD)**

Whole-brain VBM meta-analysis was used to determine the pattern of grey matter volume (GMV) changes in MDD relative to healthy controls. Identified studies were published in English before May 2017 from five online public datasets, including PubMed (PubMed Central), Neurosynth, ScienceDirect, Web of Science and the BrainMap database. Keywords included: (1) analysis strategies: ‘voxel based morphometry’ or ‘VBM’ and (2) disorders: ‘depress\*’. Selected studies were restricted to whole-brain structural MRI studies using VBM analysis to compare MDD and healthy control.

Exclusion criteria were:

(1) No healthy control group.

(2) There were only high-risk or sibling groups.

(3) Coordinates not in standard stereotaxic spaces (i.e., the Talairach or Montreal Neurological Institute (MNI) spaces)

(4) Results of the whole-brain analysis did not reach statistical significance.

(5) Peak coordinates were not reported.

(6) Articles were not written in English.

Following the application of these criteria, 68 VBM studies of MDD with 2,737 patients and 3,098 controls were included (Table S1).

**Anisotropic effect-size signed differential mapping (AES-SDM) meta-analysis**

To identify MDD-related GMV changes, the coordinate-based AES-SDM meta-analysis was performed using SDM software (https://www.sdmproject.com/, version 5.141). Compared to other algorithms, such as activation likelihood estimation and multilevel kernel density analysis, AES-SDM uses signed peak coordinates (positive or negative) and effect sizes from included studies to reconstruct on one map, preventing a given voxel from appearing to be positive and negative simultaneously ([Radua & Mataix-Cols, 2009](#_ENREF_51)). Specifically, we first converted the coordinates reported in Talairach space to MNI standard space ([Lancaster et al., 2007](#_ENREF_33)). Then, AES-SDM created an effect-size map and an effect-size variance map from t values and effect-sizes (Hedge’s *d* value) of peak coordinates reported in each study. For the effect-size map, effect-sizes of peaks were calculated based on the t-values and sample sizes. Effect-sizes of neighboring voxels were estimated based on the distance to nearby peaks by means of an unnormalized Gaussian kernel with a FWHM of 20 mm, which is recommended to provide an optimal balance between sensitivity and specificity ([Radua et al., 2012](#_ENREF_52)). For the effect size variance map, the distribution of effect-sizes and sample sizes of each study were used. Next, all maps were combined with a model of random effect by accounting for sample size, intra-study variability and between-study variance ([Radua et al., 2012](#_ENREF_52)). Finally, a null distribution was empirically estimated using permutation statistics with the same number of input coordinates to obtain meta-analytic maps with GMV changes in MDD. This was used to identify transcriptome signatures in the following analysis.

**Investigating the transcriptome signatures of GMV changes in MDD**

In brief, we identified gene expression architectures that associated with MDD-related structural alterations using the Allen Institute for Brain Science (AIBS) dataset and annotated their biological functions through gene ontology (GO) enrichment analysis.

**Allen brain atlas data**

The brain atlas of the transcriptome profiles we used was previously defined by Whitaker et al. ([Whitaker et al., 2016](#_ENREF_78)). The microarray data for six donors (H0351.1009, H0351.1016, H0351.1015, H0351.2002, H0351.1012, H0351.2001) in this atlas are available from the AIBS (<http://human.brain-map.org/static/download>). These subjects did not have history of neuropathological or neuropsychiatric disorders. The whole brain was parcellated in 308 contiguous parcel of approximately equal area (500mm2) across two hemispheres in the MNI standard space ([Whitaker et al., 2016](#_ENREF_78)). In the microarray dataset, each of 3,702 brain tissues was determined the location of anatomical structure based on the MNI coordinates closest to the AIBS sample. Expression data were averaged across all samples from all donors in the matching anatomical structures. Prior to averaging across subjects, two MRI regions were excluded as both the mean and the range of gene expression values in these regions were outliers compared to other regions ([Whitaker et al., 2016](#_ENREF_78)). Expression data for each probe were then normalized by taking the z-score for that probe across the remaining regions, resulting in a regions of interests (ROI)×gene, 306×20737, matrix of the transcriptome profiles. In addition, previous studies used leave-one-donor-out approach and Combining Batches of Gene Expression Microarray Data (ComBat) ([Johnson, Li, & Rabinovic, 2007](#_ENREF_24)) to confirm the robustness of expression profile to the effects of inter-individual differences and artefactual correlation induced by batches and donors ([Romero-Garcia, Warrier, Bullmore, Baron-Cohen, & Bethlehem, 2018](#_ENREF_59)).

**The spatial patterns of transcriptome signatures and their relations to the structural changes**

To show the spatial characterization of each significant partial least squares (PLS) component, we multiplied the PLS weights in each component and gene predictor matrix to assign the weights to 306 brain regions. To test the relationship between spatial patterns of significant PLS components and GMV changes, we aligned the VBM meta-analytic map with 306 ROIs in the transcriptome atlas to obtain mean GMV values in each ROI, and separately performed cross-region Pearson correlation analysis with the regional PLS scores in each PLS component.

**Analysis of the gene co-expression network**

 Giventhe relevance of our identified transcriptome architectures to the global structural changes in MDD, we next applied graph-based weighted correlation network analysis (WGCNA), which groups a series of co-varying genes into specialized gene clusters across the whole brain ([Langfelder & Horvath, 2008](#_ENREF_35)). Furthermore, we explored specific biological characterizations in these gene modules that could capture regional GMV variations through the integration of multidimensional information ranging from spatial structures, molecular pathways and cell types.

**Construction of gene co-expression networks**

WGCNA is a graph-based approach to identify groups of densely interconnected genes at a network level, available in R library ([Langfelder & Horvath, 2008](#_ENREF_35)). Groups are characterized by the genes with similar expression patterns of connection strengths to other genes ([Ravasz, Somera, Mongru, Oltvai, & Barabasi, 2002](#_ENREF_53)). WGCNA constructs undirected co-expression networks, comprised of nodes corresponding to genes, and edges corresponding to the pairwise correlations between the gene expression levels. In our analysis, nodes were defined as overlap genes with positive or negative weights among significant PLS components. Edges were derived from a signed similarity parameter (*Sij*) described as follows:

$$S\_{ij}=\left[1+cor\left(x\_{i},x\_{j}\right)\right]/2$$

where gene expression profiles xi and xj consist of the expression of genes i and j across multiple brain regions. Such signed network represents similar expression profiles between paired genes.

 The signed similarity (*Sij*) is then transformed into the connection strength (adjacency matrix, *aij*) through power β, the soft threshold:

$$a\_{ij}=S\_{ij}^{β}$$

 Power preserves the connection strength of highly correlated genes and reduces the emphasis of weak connections on an exponential scale. Thus, higher power values increase the specificity of genes interactions, however, lower power values increase sensitivity of gene connections. The power value was chosen to optimize the scale free property of genes co-expression networks. Here, we selected soft thresholding power 5 based on the scale-free topology criterion.

 Such adjacency matrix is used to calculate the topological overlap matrix (TOM), which measures to what extent each pair of genes has common expression patterns related to other genes in the network:

$$TOM\_{ij}=\left(\sum\_{u}^{}a\_{iu}a\_{uj}+a\_{ij}\right)/\left(min\left(k\_{i},k\_{j}\right)+1-a\_{ij}\right)$$

where $K\_{i}=\sum\_{u}^{}a\_{iu}$ and $K\_{j}=\sum\_{u}^{}a\_{uj}$ separately represents the total connectivity of gene i and gene j with the other genes u.

 Dissimilarity of gene connectivity, defined as 1-TOM, was used to further hierarchical clustering. Finally, we built a large-scale coordinated network to identify common gene co-expression patterns across 306 brain regions.

**Gene modules identification and annotation**

Genes were initially module assignments determined by a hybrid dynamic tree-cutting algorithm with default parameters except deepSplit=2, cutHeight=0.999 ([Langfelder, Zhang, & Horvath, 2008](#_ENREF_36)). Then, gene modules were iteratively merged until all pairs of module eigengenes (ME; the first principle component of the module) were correlated with *r*<0.8 ([Hawrylycz et al., 2015](#_ENREF_21); [Langfelder & Horvath, 2007](#_ENREF_34)). Specifically, it first calculated the MEs to identify highly correlated pairs of modules. If the correlation coefficients between pairs of modules were >0.8, the modules were merged and retested. MEs are considered the most representative gene expression in a module and used to describe the spatial distribution of modules across the whole brain ([Langfelder & Horvath, 2007](#_ENREF_34)).

The ToppGene (<https://toppgene.cchmc.org/>) portal ([Chen, Bardes, Aronow, & Jegga, 2009](#_ENREF_10)) was used to calculate statistical value from hypergeometric test to correct the multiple comparisons (Benjamini and Hochberg FDR q<0.05) and functionally annotated the gene lists in these identified modules. Those annotations included GO annotations (biological process, cellular component and molecular function) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway annotation.

**Cell types characterization of genes within the modules**

 Mouse models have shown the enrichment of genes in different cell types, such as neurons, astrocytes and oligodendrocytes ([Y. Zhang et al., 2014](#_ENREF_83)). Based on the gene symbols within modules, we used this dataset to give an initial description of cell types which were enriched in individual gene clusters. We converted human genes to mouse orthologs using HGNC Comparison of Orthology Predictions (HCOP) tool (<http://www.genenames.org/help/hcop>) ([Eyre, Wright, Lush, & Bruford, 2007](#_ENREF_16)). If more than one ortholog was found, we selected the gene supported by the most databases (the ‘15-column’ format of the HCOP bulk downloads tool). Then, for genes within each module, we compared them with the cell type dataset and separately counted genes that had a significant enrichment (at least 10 fragments per kilobase of transcript sequence per million mapped fragments [FPKM]) in neurons, astrocytes and oligodendrocytes. Then, we calculated the proportion of each cell type in individual gene modules.

**Table S1. Datasets included in this study.**

|  |  |  |
| --- | --- | --- |
| Datasets | Subjects (patients/controls) | Source |
| Major depressive disorder neuroimaging dataset | 2737/3098 | Meta-dataset |
| Human brain transcriptome dataset | 0/6 | Allen Institute |
| Major depressive disorder brain transcriptome datasets | 16/16 | GSE54565 |
| 10/10 | GSE54562 |
| 29/56 | GSE92538 |
| 14/14 | Shelton et al. ([Shelton et al., 2011](#_ENREF_65)) |
| Cell type dataset | 0/3-12 | Zhang et al. ([Y. Zhang et al., 2014](#_ENREF_83)) |
| Human brain proteome dataset | 0/6 | Carlyle et al., ([Carlyle et al., 2017](#_ENREF_8)) |

**Table S2. Summary of the studies included in the VBM meta-analysis.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| First author | No. of MDD (male) | No. of controls (male) | Age (year):MDD/controls | Subtype | Effect size | Regions of volumetric changes |
| Treadway et al. ([Treadway et al., 2009](#_ENREF_69)) | 10 (0) | 10 (0) | 19.0/19.0 | MDD | 1.23 | Lower: bilateral rostral anterior cingulate |
| Van Tol et al. ([van Tol et al., 2010](#_ENREF_71)) | 68 (24) | 24 (24) | 37.2/40.5 | MDD | NA | Lower: right Inferior frontal, |
| Vasic et al. ([N. Vasic, Walter, Hose, & Wolf, 2008](#_ENREF_72)) | 15 (9) | 14 (8) | 37.4/31.4 | UD | NA | Lower: thalamus, left hippocampus, cingulate |
| Wagner et al. ([Wagner et al., 2008](#_ENREF_74)) | 15 (0) | 16 (0) | 41.4/38.8 | UD | 1.58 | Lower: right amygdala, right orbitofrontal, left middle frontal, subgenual cortex |
| Zhang et al. ([T. J. Zhang et al., 2009](#_ENREF_81)) | 15 (10) | 15 (10) | 33.5/33.4 | TRD | 1.39 | Lower: cingulate, right parahippocampus, right insula, right uncus, right transverse temporal, right caudate |
| Zou et al. ([Zou et al., 2010](#_ENREF_84)) | 23 (10) | 23 (10) | 31.1/36.6 | MDD | NA | Lower: bilateral hippocampus |
| Abe et al. ([Abe et al., 2010](#_ENREF_1)) | 21 (11) | 42 (22) | 48.1/48.0 | MDD | 1.24 | Lower: right parahippocampus, bilateral middle frontal, left inferior occipital, left supramarginal, right superior temporal, left parietal, bilateral anterior cingulate |
| Amico et al. ([Amico et al., 2011](#_ENREF_3)) | 33 (19) | 64 (36) | 32.0/30.4 | MDD | 0.72 | Lower: bilateral dorsomedial prefrontal, bilateral anterior cingulate, bilateral caudateGreater: right hippocampus |
| Arnone et al. ([Arnone et al., 2009](#_ENREF_5)) | 25 (9) | 35 (12) | 33.2/31.4 | MDD | NA | Lower: posterior cingulate, left orbitofrontal, right inferior frontalGreater: left caudate |
| Bergouignan et al. ([Bergouignan et al., 2009](#_ENREF_6)) | 21 (4) | 21 (7) | 33.2/28.2 | UD | NA | Lower: right cingulate, right middle temporal, right posterior lobe, right superior parietal, right parahippocampus, left inferior semi-lunar lobule |
| Cheng et al. ([Cheng et al., 2010](#_ENREF_11)) | 68 (NA) | 68 (NA) | 29.9/28.9 | MDD | NA | Lower: right supplementary motor area |
| Frodl et al. ([Frodl et al., 2008](#_ENREF_18)) | 77 (42) | 77 (42) | 42.6/40.5 | MDD | 0.6 | Lower: bilateral anterior cingulate, bilateral dorsolateral prefrontal, bilateral dorsolmedial prefrontal, left amygdala, bilateral hippocampus |
| Inkster et al. ([Inkster et al., 2011](#_ENREF_23)) | 145 (16) | 183 (35) | 47.6/50.4 | RDD | NA | Lower: right superior parietal |
| Kim et al. ([Kim, Hamilton, & Gotlib, 2008](#_ENREF_26)) | 22 (NA) | 25 (6) | 38.5/35.3 | MDD | 1.46 | Lower: bilateral thalamus, bilateral caudate |
| Lai et al. ([Lai, Hsu, & Wu, 2010](#_ENREF_30)) | 16 (5) | 15 (11) | 37.9/34.3 | MDD | NA | Lower: bilateral medial frontal, bilateral rectus, bilateral subcallosal, right middle frontal, right parahippocampus, bilateral thalamus, bilateral striatum, bilateral superior temporal, bilateral occipital lingual, bilateral cerebellum |
| Lee et al. ([Lee et al., 2011](#_ENREF_37)) | 47 (5) | 51 (5) | 46.0/45.7 | MDD | 0.72 | Lower: midbrain, anterior cingulate, right thalamus, bilateral insula, bilateral accumbens, bilateral amygdala, bilateral hippocampus, bilateral fusiform, bilateral lingual, bilateral middle temporal, bilateral superior temporal, cerebellum |
| Leung et al. ([Leung et al., 2009](#_ENREF_38)) | 17 (0) | 17 (0) | 45.5/45.8 | MDD | 1.4 | Lower: right middle frontal, left angular, right superior temporal, right precentral, left precuneus, left middle temporal, cingulateGreater: left posterior cingulate |
| Li et al. ([Li et al., 2010](#_ENREF_39)) | 44 (11) | 25 (6) | 44.6/40.6 | RDD | NA | Lower: left thalamus, left dorsolateral prefrontal, left precentral, right superior prefrontal, left superior frontal, left postcentral |
| Peng et al. ([J. Peng et al., 2011](#_ENREF_49)) | 22 (8) | 30 (11) | 46.7/45.9 | MDD | 1.12 | Lower: bilateral superior temporal, bilateral insula, bilateral inferior frontal, right middle temporal, bilateral middle frontal, right orbitofrontal, bilateral middle frontal, left parahippocampus, left cerebellum |
| Salvadore et al. ([Salvadore et al., 2011](#_ENREF_60)) | 58 (21) | 107 (47) | 38.8/36.2 | MDD | 0.63 | Lower: left inferior frontal, right superior frontal, right middle frontalGreater: right anterior cingulate |
| Scheuerecker et al. ([Scheuerecker et al., 2010](#_ENREF_61)) | 13 (10) | 15 (10) | 37.9/35.5 | MDD | 1.64 | Lower: left inferior frontal, left middle temporal, bilateral postcentral, left inferior parietal, left superior temporal, left operculum, right inferior occipital, left inferior temporalGreater: right operculum, right superior frontal, right precuneus, left inferior frontal, right amygdala |
| Soriano-Mas et al. ([Soriano-Mas et al., 2011](#_ENREF_66)) | 70 (29) | 40 (17) | 64.6/59.2 | MD | 0.94 | Lower: right middle occipital, right and left insula |
| Tang et al. ([Tang et al., 2007](#_ENREF_68)) | 14 (0) | 13 (0) | 29.5/29.5 | MDD | 1.77 | Lower: bilateral anterior cingulate, right amygdala |
| Shah et al. ([Shah, Ebmeier, Glabus, & Goodwin, 1998](#_ENREF_64)) | 20 (13) | 20 (13) | 48.9/49.3 | UD | NA | Lower: left superior temporal, left inferior frontal, bilateral hippocampus, left inferior temporal |
| de Azevedo-Marques Perico et al. ([de Azevedo-Marques Perico et al., 2011](#_ENREF_13)) | 20 (5) | 94 (55) | 29.9/30.2 | MDD | NA | Lower: bilateral dorsolateral prefrontal  |
| Egger et al. ([Egger et al., 2008](#_ENREF_15)) | 14 (4) | 20 (7) | 71.4/72.3 | GD | NA | Lower: right amygdala, right hippocampus, bilateral orbitofrontal |
| Hwang et al. ([Hwang et al., 2010](#_ENREF_22)) | 70 (70) | 26 (26) | 79.4/79.5 | GD | NA | Lower: right insula, bilateral posterior cingulateGreater: right occipital, right cerebellum |
| Mak et al. ([Mak, Wong, Han, & Lee, 2009](#_ENREF_44)) | 17 (0) | 17 (0) | 45.5/45.8 | MDD | NA | Lower: right anterior cingulate, right superior frontal, right superior medial frontal, left middle frontal, right inferior orbitofrontal, right precentral, right superior temporal, left middle temporal, right fusiform, left precuneus |
| Ries et al. ([Ries, Wichmann, Bendlin, & Johnson, 2009](#_ENREF_57)) | 15 (5) | 32 (14) | 66.3/68.4 | GD | 1.07 | Lower: right lateral parietal, posterior cingulate, bilateral lateral parietal |
| Shad et al. ([Shad, Muddasani, & Rao, 2012](#_ENREF_63)) | 22 (11) | 22 (12) | 15.0/16.0 | MDD | 2.08 | Lower: bilateral inferior frontal, left middle frontal, right superior frontal, right middle frontal, right caudate, right superior temporal, right middle temporal, bilateral thalamus, bilateral cerebellum |
| Wagner et al. ([Wagner et al., 2011](#_ENREF_75)) | 30 (5) | 30 (5) | 37.6/35.1 | MDD | 1.16 | Lower: bilateral caudate, right inferior frontal, right subgenual, bilateral hippocampus, left orbitofrontal, left superior frontal |
| Yuan et al. ([Yuan et al., 2008](#_ENREF_80)) | 19 (9) | 16 (8) | 67.1/67.7 | GD | NA | Lower: right superior, left postcentral, right middle temporalGreater: left cingulate |
| Zhang et al. ([X. Zhang et al., 2012](#_ENREF_82)) | 33 (17) | 32 (17) | 20.5/21.0 | MDD | NA | Lower: left precentralGreater: right thalamus |
| Yang et al. ([Yang et al., 2015](#_ENREF_79)) | 51 (20) | 51 (20) | 31.0/31.1 | MDD | 0.79 | Lower: left medial frontal, left lingual, left superior frontalGreater: left posterior cingulate, left inferior frontal |
| Kong et al. ([Lingtao Kong et al., 2013](#_ENREF_28)) | 29 (16) | 33 (16) | 30.1/29.9 | MDD | 0.97 | Lower: left ventral prefrontal |
| Alemany et al. ([Alemany et al., 2013](#_ENREF_2)) | 12 (2) | 21 (12) | 41.6/34.9 | MDD | 2.01 | Lower: right fusiform, right temporal inferior, right cerebellum, right amygdala, bilateral temporal superior, left fusiform, left amygdala |
| Peng et al. ([H. Peng et al., 2014](#_ENREF_48)) | 38 (13) | 28 (15) | 29.4/28.6 | MDD | NA | Lower: left insula, right middle temporalGreater: right parietal |
| Machino et al. ([Machino et al., 2014](#_ENREF_43)) | 29 (16) | 29 (16) | 39.6/38.7 | MDD | NA | Lower: bilateral anterior cingulate, right superior frontal, right cerebellum |
| Jung et al. ([Jung et al., 2014](#_ENREF_25)) | 50 (14) | 29 (8) | 41.9/43.6 | MDD | NA | Lower: bilateral insula, right superior frontal |
| Klauser et al. ([Klauser et al., 2015](#_ENREF_27)) | 56 (16) | 33 (12) | 34.0/34.7 | MDD | 1.05 | Lower: ventromedial prefrontal |
| Depping et al. ([Depping et al., 2015](#_ENREF_14)) | 22 (0) | 22 (0) | 33.5/31.4 | MDD | NA | Lower: anterior cingulate, medial prefrontal |
| Lai et al. ([Lai & Wu, 2015](#_ENREF_32)) | 53 (25) | 54 (25) | 40.1/40.4 | MDD | 0.91 | Lower: bilateral medial frontal, right superior temporal, right superior frontal, bilateral cerebellum |
| Nakano et al. ([Nakano et al., 2014](#_ENREF_45)) | 36 (14) | 54 (27) | 49.0/45.4 | MDD | 1.23 | Lower: right superior medial frontal, right orbitofrontal |
| Guo et al. ([Guo et al., 2014](#_ENREF_19)) | 44 (22) | 44 (20) | 27.5/29.4 | MDD | 0.76 | Lower: right inferior temporal, left angular |
| Liu et al. ([C. H. Liu et al., 2014](#_ENREF_40)) | 38 (0) | 19 (0) | 36.2/36.8 | MDD | 1.62 | Lower: bilateral insula |
| Oudega et al. ([Oudega et al., 2014](#_ENREF_47)) | 55 (19) | 23 (11) | 72.3/70.3 | GD | 0.99 | Lower: bilateral inferior frontal, left superior temporal, left middle temporal, left anterior prefrontalGreater: bilateral parietal, left anterior cingulate |
| Watanabe et al. ([Watanabe et al., 2015](#_ENREF_76)) | 29 (16) | 45 (33) | 45.5/41.1 | MDD | 1.03 | Lower: bilateral caudate, left superior temporal, left superior frontal |
| Hagan et al. ([Hagan et al., 2015](#_ENREF_20)) | 109 (28) | 36 (10) | 15.6/15.7 | MDD | NA | Lower: right thalamus |
| Chaney et al. ([Chaney et al., 2014](#_ENREF_9)) | 37 (16) | 46 (18) | 40.3/39.8 | MDD | 0.81 | Lower: left orbitofrontal, left dorsolmedial prefrontal |
| Vasic et al. ([Nenad Vasic et al., 2015](#_ENREF_73)) | 43 (17) | 29 (11) | 37.1/34.5 | MDD | NA | Lower: right cuneus, bilateral parahippocampus, left anterior cingulateGreater: right inferior parietal, right middle temporal, bilateral middle frontal, right medial frontal, right superior frontal, right lentiform nucleus, right caudate |
| Serra-Blasco et al. ([Serra-Blasco et al., 2013](#_ENREF_62)) | 44 (6) | 32 (9) | 48.5/46.0 | MDD | NA | Lower: right superior frontal, bilateral medial frontal, left cingulate, left insula, left inferior frontal, left medial frontal, left parahippocampus, left transverse temporal, left postcentral |
| Arnone et al. ([Arnone et al., 2013](#_ENREF_4)) | 39 (12) | 66 (20) | 36.3/32.1 | MDD | NA | Lower: bilateral hippocampus, bilateral fusiform, bilateral striatum |
| Fang et al. ([Fang et al., 2015](#_ENREF_17)) | 16 (12) | 18 (10) | 59.2/59.1 | MDD | 1.59 | Lower: left inferior frontal, left middle frontal, left parahippocampus, right fusiformGreater: right superior temporal, right postcentral, left cuneus |
| Cai et al. ([Cai et al., 2015](#_ENREF_7)) | 23 (13) | 23 (13) | 30.0/28.2 | UD | NA | Lower: right Inferior frontal, |
| Rodriguez-Gano et al. ([Rodriguez-Cano et al., 2014](#_ENREF_58)) | 32 (12) | 64 (26) | 48.7/46.0 | MDD | NA | Lower: left parahippocampus and hippocampus |
| Kong et al. ([L. Kong et al., 2014](#_ENREF_29)) | 28 (NA) | 28 (NA) | 36.1/32.1 | MDD | 1.41 | Lower: right dorsolateral prefrontal, left middle frontalGreater: left thalamus, right insula |
| Ribeiz et al. ([Ribeiz et al., 2013](#_ENREF_56)) | 30 (7) | 22 (5) | 70.7/70.4 | GD | NA | Lower: bilateral orbitofrontal |
| Ueda et al. ([Ueda et al., 2016](#_ENREF_70)) | 30 (17) | 48 (35) | 44.3/41.2 | MDD | 0.99 | Lower: left temporal pole |
| Lai et al. ([Lai & Wu, 2014](#_ENREF_31)) | 38 (18) | 27 (15) | 36.6/38.3 | MDD | 1.74 | Lower: bilateral superior frontal, left middle frontal, left medial frontal, left insula |
| Liu et al. ([X. Liu et al., 2015](#_ENREF_41)) | 30 (17) | 41 (28) | 44.9/41.2 | MDD | NA | Lower: left orbitofrontal |
| Ma et al. ([Ma et al., 2012](#_ENREF_42)) | 18 (11) | 17 (10) | 27.4/24.2 | MDD | NA | Lower: right middle temporal, bilateral caudate |
| Dannlowski et al. ([Dannlowski et al., 2015](#_ENREF_12)) | 171 (66) | 512 (223) | 38.7/33.5 | MDD | NA | Lower: right parahippocampus, right insula, right orbitofrontal, left lingual, middle cingulate, left superior temporal, bilateral thalamus, left cerebellum |
| Opel et al. ([Opel et al., 2014](#_ENREF_46)) | 85 (31) | 85 (34) | 37.6/37.2 | MDD | NA | Lower: bilateral hippocampus |
| Qi et al. ([Qi et al., 2014](#_ENREF_50)) | 18 (7) | 28 (15) | 31.1/28.6 | MDD | 1.03 | Lower: left insula |
| Redlich et al. ([Redlich et al., 2014](#_ENREF_54)) | 116 (44) | 58 (42) | 37.6/37.8 | UD | 0.8 | Lower: bilateral hippocampus, bilateral fusiform, bilateral lingual, left inferior parietal, cingulate, medial prefrontal, supplementary motor, right middle frontal gyrus, right superior frontal, precuneus, left middle and superior temporal, caudate |
| Stratmann et al. ([Stratmann et al., 2014](#_ENREF_67)) | 132 (56) | 132 (58) | 37.9/37.8 | MDD | NA | Lower: right insula, left superior parietal, bilateral superior temporal, left parahippocampus |
| Wehry et al. ([Wehry et al., 2015](#_ENREF_77)) | 14 (3) | 41 (14) | 14.0/13.0 | MDD | NA | Lower: right superior frontal, Greater: right middle frontal, left precuneus, right thalamus, right caudate, right postcentral, right paracentral |
| Redlich et al. ([Redlich et al., 2016](#_ENREF_55)) | 23 (9) | 21 (10) | 45.7/41.8 | MDD | 1.53 | Lower: anterior cingulate, precuneus, fusiform, lingual, cerebellum, left superior temporal, left middle temporal |

“Lower” and “Greater” separately represent the regions with lower and greater grey matter volumes in MDD patients compared with heathy participants. Abbreviation: MDD: major depressive disorder; UD: unipolar depression; TRD: treatment-refractory depression; RDD: recurrent depressive disorder; MD: melancholic Depression; GD: geriatric depression; NA: not available

**Table S3. Significant gene ontology terms in the first component of partial least squares analysis.**

|  |  |  |  |
| --- | --- | --- | --- |
| GO term ID | GO term | Raw P-value | FDR q-value |
| **PLS1 top-ranked GO enrichment for biological processes** |
| GO:0030001 | metal ion transport | 1.70E-07 | 2.18E-04 |
| GO:0030522 | intracellular receptor signaling pathway | 3.49E-07 | 4.15E-04 |
| GO:0006813 | potassium ion transport | 6.74E-07 | 7.44E-04 |
| GO:0071805 | potassium ion transmembrane transport | 7.09E-07 | 7.30E-04 |
| GO:0071804 | cellular potassium ion transport | 7.09E-07 | 6.85E-04 |
| GO:0034220 | ion transmembrane transport | 1.25E-06 | 1.14E-03 |
| GO:0006325 | chromatin organization | 1.65E-06 | 1.41E-03 |
| GO:0040029 | regulation of gene expression, epigenetic | 1.68E-06 | 1.36E-03 |
| GO:0001580 | detection of chemical stimulus involved in sensory perception of bitter taste | 1.79E-06 | 1.39E-03 |
| GO:0098660 | inorganic ion transmembrane transport | 2.64E-06 | 1.78E-03 |
| GO:0043401 | steroid hormone mediated signaling pathway | 3.88E-06 | 2.40E-03 |
| GO:0098662 | inorganic cation transmembrane transport | 5.20E-06 | 3.09E-03 |
| GO:0050912 | detection of chemical stimulus involved in sensory perception of taste | 7.56E-06 | 4.32E-03 |
| GO:0009755 | hormone-mediated signaling pathway | 1.23E-05 | 6.57E-03 |
| GO:1903507 | negative regulation of nucleic acid-templated transcription | 1.56E-05 | 8.04E-03 |
| GO:1902679 | negative regulation of RNA biosynthetic process | 1.76E-05 | 8.75E-03 |
| GO:0016577 | histone demethylation | 2.05E-05 | 9.92E-03 |
| GO:0055085 | transmembrane transport | 2.96E-05 | 1.39E-02 |
| GO:0036376 | sodium ion export across plasma membrane | 3.16E-05 | 1.40E-02 |
| GO:0006811 | ion transport | 3.18E-05 | 1.36E-02 |
| GO:0045892 | negative regulation of transcription, DNA-templated | 3.47E-05 | 1.45E-02 |
| GO:0098655 | cation transmembrane transport | 4.38E-05 | 1.78E-02 |
| GO:0051253 | negative regulation of RNA metabolic process | 4.98E-05 | 1.92E-02 |
| GO:0016569 | covalent chromatin modification | 4.98E-05 | 1.88E-02 |
| GO:0006482 | protein demethylation | 5.06E-05 | 1.86E-02 |
| GO:0008214 | protein dealkylation | 5.06E-05 | 1.82E-02 |
| GO:0006812 | cation transport | 6.55E-05 | 2.20E-02 |
| GO:0016570 | histone modification | 8.80E-05 | 2.89E-02 |
| **PLS1 down-ranked GO enrichment for biological processes** |
| GO:0002433 | immune response-regulating cell surface receptor signaling pathway involved in phagocytosis | 8.85E-07 | 1.37E-02 |
| GO:0038096 | Fc-gamma receptor signaling pathway involved in phagocytosis | 8.85E-07 | 6.84E-03 |
| GO:0002431 | Fc receptor mediated stimulatory signaling pathway | 9.53E-07 | 4.91E-03 |
| GO:0099177 | regulation of trans-synaptic signaling | 1.95E-06 | 6.02E-03 |
| GO:0038094 | Fc-gamma receptor signaling pathway | 1.97E-06 | 5.07E-03 |
| GO:0044283 | small molecule biosynthetic process | 2.39E-06 | 5.27E-03 |
| GO:0098754 | detoxification | 2.94E-06 | 5.68E-03 |
| GO:0050804 | modulation of chemical synaptic transmission | 3.87E-06 | 5.99E-03 |
| GO:0032940 | secretion by cell | 6.44E-06 | 9.04E-03 |
| GO:0050890 | cognition | 7.61E-06 | 9.80E-03 |
| GO:0042391 | regulation of membrane potential | 8.18E-06 | 9.03E-03 |
| GO:0007611 | learning or memory | 8.78E-06 | 9.05E-03 |
| GO:0006887 | exocytosis | 1.05E-05 | 1.01E-02 |
| GO:0019233 | sensory perception of pain | 1.11E-05 | 1.01E-02 |
| GO:0098916 | anterograde trans-synaptic signaling | 1.14E-05 | 9.79E-03 |
| GO:0007268 | chemical synaptic transmission | 1.14E-05 | 9.28E-03 |
| GO:0099536 | synaptic signaling | 1.41E-05 | 1.09E-02 |
| GO:0099537 | trans-synaptic signaling | 1.41E-05 | 1.04E-02 |
| GO:0060078 | regulation of postsynaptic membrane potential | 1.51E-05 | 1.06E-02 |
| GO:0071248 | cellular response to metal ion | 2.55E-05 | 1.46E-02 |
| GO:0060359 | response to ammonium ion | 4.26E-05 | 2.27E-02 |
| GO:0009410 | response to xenobiotic stimulus | 4.62E-05 | 2.30E-02 |
| GO:0072347 | response to anesthetic | 4.84E-05 | 2.34E-02 |
| GO:0035249 | synaptic transmission, glutamatergic | 5.20E-05 | 2.36E-02 |
| GO:0045055 | regulated exocytosis | 7.03E-05 | 3.02E-02 |
| GO:0031400 | negative regulation of protein modification process | 7.06E-05 | 2.95E-02 |
| GO:0007018 | microtubule-based movement | 9.34E-05 | 3.14E-02 |
| GO:1901617 | organic hydroxy compound biosynthetic process | 9.79E-05 | 3.22E-02 |

**Table S4. Significant gene ontology terms in the second component of partial least squares analysis.**

|  |  |  |  |
| --- | --- | --- | --- |
| GO term ID | GO term | Raw P-value | FDR q-value |
| **PLS2 top-ranked GO enrichment for biological processes** |
| GO:0043624 | cellular protein complex disassembly | 5.49E-07 | 8.49E-03 |
| GO:0072655 | establishment of protein localization to mitochondrion | 2.83E-06 | 2.19E-02 |
| GO:0032984 | protein-containing complex disassembly | 4.67E-06 | 2.40E-02 |
| GO:0070126 | mitochondrial translational termination | 5.01E-06 | 1.93E-02 |
| GO:0006415 | translational termination | 5.37E-06 | 1.66E-02 |
| GO:0006091 | generation of precursor metabolites and energy | 5.95E-06 | 1.53E-02 |
| GO:0006839 | mitochondrial transport | 1.03E-05 | 2.27E-02 |
| GO:0022900 | electron transport chain | 1.15E-05 | 2.23E-02 |
| GO:0006626 | protein targeting to mitochondrion | 1.37E-05 | 2.35E-02 |
| GO:0070585 | protein localization to mitochondrion | 1.69E-05 | 2.61E-02 |
| **PLS2 down-ranked GO enrichment for biological processes** |
| GO:0060333 | interferon-gamma-mediated signaling pathway | 9.42E-13 | 1.46E-08 |
| GO:0071310 | cellular response to organic substance | 3.51E-09 | 2.72E-05 |
| GO:0002483 | antigen processing and presentation of endogenous peptide antigen | 6.69E-09 | 2.58E-05 |
| GO:0019885 | antigen processing and presentation of endogenous peptide antigen via MHC class I | 6.69E-09 | 2.07E-05 |
| GO:0007155 | cell adhesion | 9.24E-09 | 2.04E-05 |
| GO:0030155 | regulation of cell adhesion | 1.02E-08 | 1.97E-05 |
| GO:0022610 | biological adhesion | 1.30E-08 | 2.22E-05 |
| GO:0071345 | cellular response to cytokine stimulus | 2.90E-08 | 4.49E-05 |
| GO:0034097 | response to cytokine | 3.16E-08 | 4.44E-05 |
| GO:0098609 | cell-cell adhesion | 4.85E-08 | 5.76E-05 |
| GO:0019883 | antigen processing and presentation of endogenous antigen | 6.58E-07 | 4.84E-04 |
| GO:0002479 | antigen processing and presentation of exogenous peptide antigen via MHC class I, TAP-dependent | 7.32E-07 | 5.15E-04 |
| GO:0043062 | extracellular structure organization | 1.00E-06 | 6.74E-04 |
| GO:0030198 | extracellular matrix organization | 1.14E-06 | 7.36E-04 |
| GO:0050776 | regulation of immune response | 1.41E-06 | 8.08E-04 |
| GO:0034612 | response to tumor necrosis factor | 1.75E-06 | 9.32E-04 |
| GO:0048002 | antigen processing and presentation of peptide antigen | 2.44E-06 | 1.22E-03 |
| GO:0002478 | antigen processing and presentation of exogenous peptide antigen | 2.57E-06 | 1.24E-03 |
| GO:0050920 | regulation of chemotaxis | 2.63E-06 | 1.23E-03 |
| GO:0019884 | antigen processing and presentation of exogenous antigen | 2.70E-06 | 1.23E-03 |
| GO:0019882 | antigen processing and presentation | 3.22E-06 | 1.42E-03 |
| GO:0045785 | positive regulation of cell adhesion | 3.37E-06 | 1.44E-03 |
| GO:0042590 | antigen processing and presentation of exogenous peptide antigen via MHC class I | 4.06E-06 | 1.70E-03 |
| GO:0008016 | regulation of heart contraction | 5.70E-06 | 2.26E-03 |
| GO:0001763 | morphogenesis of a branching structure | 5.78E-06 | 2.23E-03 |
| GO:0098742 | cell-cell adhesion via plasma-membrane adhesion molecules | 8.02E-06 | 2.95E-03 |
| GO:0071356 | cellular response to tumor necrosis factor | 1.11E-05 | 3.66E-03 |
| GO:0061138 | morphogenesis of a branching epithelium | 1.37E-05 | 4.40E-03 |
| GO:0030334 | regulation of cell migration | 1.44E-05 | 4.55E-03 |
| GO:0019221 | cytokine-mediated signaling pathway | 1.48E-05 | 4.57E-03 |
| GO:0071363 | cellular response to growth factor stimulus | 1.60E-05 | 4.86E-03 |
| GO:0045597 | positive regulation of cell differentiation | 1.68E-05 | 5.00E-03 |
| GO:0070848 | response to growth factor | 1.72E-05 | 5.02E-03 |
| GO:0002684 | positive regulation of immune system process | 1.80E-05 | 5.15E-03 |
| GO:0007156 | homophilic cell adhesion via plasma membrane adhesion molecules | 2.29E-05 | 6.43E-03 |
| GO:2000145 | regulation of cell motility | 2.34E-05 | 6.45E-03 |
| GO:0032101 | regulation of response to external stimulus | 2.57E-05 | 6.98E-03 |
| GO:0090257 | regulation of muscle system process | 2.61E-05 | 6.95E-03 |
| GO:0002682 | regulation of immune system process | 2.77E-05 | 7.26E-03 |
| GO:0006954 | inflammatory response | 2.84E-05 | 7.32E-03 |
| GO:0040012 | regulation of locomotion | 2.96E-05 | 7.51E-03 |
| GO:0022407 | regulation of cell-cell adhesion | 3.65E-05 | 8.95E-03 |
| GO:0002475 | antigen processing and presentation via MHC class Ib | 4.74E-05 | 1.13E-02 |
| GO:0001568 | blood vessel development | 5.71E-05 | 1.34E-02 |
| GO:0048729 | tissue morphogenesis | 5.91E-05 | 1.36E-02 |
| GO:0045765 | regulation of angiogenesis | 6.07E-05 | 1.38E-02 |
| GO:0051270 | regulation of cellular component movement | 6.24E-05 | 1.40E-02 |
| GO:0031589 | cell-substrate adhesion | 6.24E-05 | 1.38E-02 |
| GO:1903522 | regulation of blood circulation | 7.11E-05 | 1.53E-02 |
| GO:0070374 | positive regulation of ERK1 and ERK2 cascade | 8.04E-05 | 1.70E-02 |
| GO:0048585 | negative regulation of response to stimulus | 8.79E-05 | 1.84E-02 |
| GO:0007204 | positive regulation of cytosolic calcium ion concentration | 9.87E-05 | 2.01E-02 |

**Table S5. Biological annotations of differential expression genes in major depressive disorder.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Category | ID | Name | p-value | q-value FDR B&H |
|  Molecular Function | GO:0016655 | oxidoreductase activity, acting on NAD(P)H, quinone or similar compound as acceptor | 6.63E-07 | 9.48E-04 |
|  Molecular Function | GO:0050136 | NADH dehydrogenase (quinone) activity | 1.74E-06 | 9.48E-04 |
|  Molecular Function | GO:0008137 | NADH dehydrogenase (ubiquinone) activity | 1.74E-06 | 9.48E-04 |
|  Molecular Function | GO:0003954 | NADH dehydrogenase activity | 1.74E-06 | 9.48E-04 |
|  Molecular Function | GO:0019899 | enzyme binding | 2.46E-06 | 1.07E-03 |
|  Molecular Function | GO:0044877 | protein-containing complex binding | 1.15E-05 | 4.13E-03 |
|  Molecular Function | GO:0015078 | proton transmembrane transporter activity | 1.61E-05 | 4.13E-03 |
|  Molecular Function | GO:0004298 | threonine-type endopeptidase activity | 1.71E-05 | 4.13E-03 |
|  Molecular Function | GO:0070003 | threonine-type peptidase activity | 1.71E-05 | 4.13E-03 |
|  Molecular Function | GO:0008092 | cytoskeletal protein binding | 3.89E-05 | 8.48E-03 |
|  Molecular Function | GO:0005509 | calcium ion binding | 4.99E-05 | 9.90E-03 |
|  Biological Process | GO:0042775 | mitochondrial ATP synthesis coupled electron transport | 2.08E-11 | 1.21E-07 |
|  Biological Process | GO:0022603 | regulation of anatomical structure morphogenesis | 2.89E-11 | 1.21E-07 |
|  Biological Process | GO:0042773 | ATP synthesis coupled electron transport | 5.52E-11 | 1.54E-07 |
|  Biological Process | GO:0009896 | positive regulation of catabolic process | 7.57E-11 | 1.58E-07 |
|  Biological Process | GO:0051130 | positive regulation of cellular component organization | 1.02E-10 | 1.70E-07 |
|  Biological Process | GO:0009894 | regulation of catabolic process | 1.51E-10 | 2.10E-07 |
|  Biological Process | GO:0031329 | regulation of cellular catabolic process | 1.96E-10 | 2.34E-07 |
|  Biological Process | GO:0010498 | proteasomal protein catabolic process | 4.71E-10 | 4.52E-07 |
|  Biological Process | GO:0042176 | regulation of protein catabolic process | 4.86E-10 | 4.52E-07 |
|  Biological Process | GO:0006119 | oxidative phosphorylation | 1.26E-09 | 1.05E-06 |
|  Biological Process | GO:0022904 | respiratory electron transport chain | 2.15E-09 | 1.63E-06 |
|  Biological Process | GO:0045333 | cellular respiration | 2.50E-09 | 1.69E-06 |
|  Biological Process | GO:0009116 | nucleoside metabolic process | 2.63E-09 | 1.69E-06 |
|  Biological Process | GO:0009119 | ribonucleoside metabolic process | 3.65E-09 | 2.09E-06 |
|  Biological Process | GO:0022900 | electron transport chain | 4.41E-09 | 2.09E-06 |
|  Biological Process | GO:1903362 | regulation of cellular protein catabolic process | 4.41E-09 | 2.09E-06 |
|  Biological Process | GO:1901657 | glycosyl compound metabolic process | 4.43E-09 | 2.09E-06 |
|  Biological Process | GO:0043161 | proteasome-mediated ubiquitin-dependent protein catabolic process | 4.52E-09 | 2.09E-06 |
|  Biological Process | GO:0031331 | positive regulation of cellular catabolic process | 4.74E-09 | 2.09E-06 |
|  Biological Process | GO:1903050 | regulation of proteolysis involved in cellular protein catabolic process | 6.99E-09 | 2.92E-06 |
|  Biological Process | GO:0045732 | positive regulation of protein catabolic process | 7.96E-09 | 3.17E-06 |
|  Biological Process | GO:0051347 | positive regulation of transferase activity | 9.30E-09 | 3.51E-06 |
|  Biological Process | GO:0033365 | protein localization to organelle | 9.64E-09 | 3.51E-06 |
|  Biological Process | GO:0043085 | positive regulation of catalytic activity | 1.07E-08 | 3.72E-06 |
|  Biological Process | GO:0051247 | positive regulation of protein metabolic process | 1.20E-08 | 4.02E-06 |
|  Biological Process | GO:0046128 | purine ribonucleoside metabolic process | 1.28E-08 | 4.11E-06 |
|  Biological Process | GO:0009123 | nucleoside monophosphate metabolic process | 1.34E-08 | 4.11E-06 |
|  Biological Process | GO:0055086 | nucleobase-containing small molecule metabolic process | 1.38E-08 | 4.11E-06 |
|  Biological Process | GO:0009057 | macromolecule catabolic process | 1.76E-08 | 4.92E-06 |
|  Biological Process | GO:0042278 | purine nucleoside metabolic process | 1.76E-08 | 4.92E-06 |
|  Biological Process | GO:0006915 | apoptotic process | 1.93E-08 | 5.20E-06 |
|  Biological Process | GO:0044093 | positive regulation of molecular function | 2.06E-08 | 5.38E-06 |
|  Biological Process | GO:0006521 | regulation of cellular amino acid metabolic process | 2.77E-08 | 6.90E-06 |
|  Biological Process | GO:1901566 | organonitrogen compound biosynthetic process | 2.80E-08 | 6.90E-06 |
|  Biological Process | GO:0009141 | nucleoside triphosphate metabolic process | 3.12E-08 | 7.17E-06 |
|  Biological Process | GO:0009205 | purine ribonucleoside triphosphate metabolic process | 3.15E-08 | 7.17E-06 |
|  Biological Process | GO:0009144 | purine nucleoside triphosphate metabolic process | 3.17E-08 | 7.17E-06 |
|  Biological Process | GO:0012501 | programmed cell death | 4.23E-08 | 9.32E-06 |
|  Biological Process | GO:0031175 | neuron projection development | 4.41E-08 | 9.47E-06 |
|  Biological Process | GO:0009161 | ribonucleoside monophosphate metabolic process | 5.05E-08 | 1.06E-05 |
|  Biological Process | GO:0010647 | positive regulation of cell communication | 5.20E-08 | 1.06E-05 |
|  Biological Process | GO:0048666 | neuron development | 5.41E-08 | 1.08E-05 |
|  Biological Process | GO:0030182 | neuron differentiation | 5.93E-08 | 1.15E-05 |
|  Biological Process | GO:0009117 | nucleotide metabolic process | 6.82E-08 | 1.28E-05 |
|  Biological Process | GO:0030163 | protein catabolic process | 6.86E-08 | 1.28E-05 |
|  Biological Process | GO:0006753 | nucleoside phosphate metabolic process | 7.13E-08 | 1.30E-05 |
|  Biological Process | GO:0009199 | ribonucleoside triphosphate metabolic process | 7.42E-08 | 1.32E-05 |
|  Biological Process | GO:0006163 | purine nucleotide metabolic process | 7.60E-08 | 1.33E-05 |
|  Biological Process | GO:0031344 | regulation of cell projection organization | 8.07E-08 | 1.38E-05 |
|  Biological Process | GO:0009167 | purine ribonucleoside monophosphate metabolic process | 8.27E-08 | 1.39E-05 |
|  Biological Process | GO:0019693 | ribose phosphate metabolic process | 8.82E-08 | 1.43E-05 |
|  Biological Process | GO:0038095 | Fc-epsilon receptor signaling pathway | 8.97E-08 | 1.43E-05 |
|  Biological Process | GO:0072521 | purine-containing compound metabolic process | 9.05E-08 | 1.43E-05 |
|  Biological Process | GO:0009126 | purine nucleoside monophosphate metabolic process | 9.29E-08 | 1.43E-05 |
|  Cellular Component | GO:0005739 | mitochondrion | 5.11E-13 | 5.23E-10 |
|  Cellular Component | GO:0043005 | neuron projection | 5.29E-10 | 2.70E-07 |
|  Cellular Component | GO:0044429 | mitochondrial part | 1.74E-09 | 4.47E-07 |
|  Cellular Component | GO:0098796 | membrane protein complex | 2.17E-09 | 4.47E-07 |
|  Cellular Component | GO:0005743 | mitochondrial inner membrane | 2.55E-09 | 4.47E-07 |
|  Cellular Component | GO:0005740 | mitochondrial envelope | 2.83E-09 | 4.47E-07 |
|  Cellular Component | GO:0045202 | synapse | 3.09E-09 | 4.47E-07 |
|  Cellular Component | GO:0019866 | organelle inner membrane | 3.49E-09 | 4.47E-07 |
|  Cellular Component | GO:0031966 | mitochondrial membrane | 4.03E-09 | 4.58E-07 |
|  Cellular Component | GO:0098800 | inner mitochondrial membrane protein complex | 9.04E-09 | 9.25E-07 |
|  Cellular Component | GO:0098798 | mitochondrial protein complex | 1.63E-08 | 1.52E-06 |
|  Cellular Component | GO:0097458 | neuron part | 1.84E-08 | 1.57E-06 |

**Table S6. The biological annotations of Mod 01.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Category | ID | Name | p-value | q-value FDR B&H |
| Biological Process | GO:0007417 | central nervous system development | 1.84E-07 | 1.20E-03 |
| Biological Process | GO:0007420 | brain development | 4.09E-06 | 1.33E-02 |
| Biological Process | GO:0060322 | head development | 9.16E-06 | 1.99E-02 |
| Biological Process | GO:0090102 | cochlea development | 2.73E-05 | 4.44E-02 |
| Cellular Component | GO:0000788 | nuclear nucleosome | 1.33E-07 | 9.52E-05 |
| Cellular Component | GO:0043025 | neuronal cell body | 8.83E-05 | 1.62E-02 |
| Cellular Component | GO:0044298 | cell body membrane | 9.05E-05 | 1.62E-02 |
| Cellular Component | GO:0032809 | neuronal cell body membrane | 9.05E-05 | 1.62E-02 |
| Cellular Component | GO:0044297 | cell body | 1.68E-04 | 2.34E-02 |
| Cellular Component | GO:0005615 | extracellular space | 1.96E-04 | 2.34E-02 |
| Pathway | 1269754 | G2/M DNA damage checkpoint | 2.83E-07 | 4.97E-04 |
| Pathway | 1309101 | processing of DNA double-strand break ends | 4.68E-07 | 4.97E-04 |
| Pathway | 1470927 | E3 ubiquitin ligases ubiquitinate target proteins | 7.29E-07 | 5.16E-04 |
| Pathway | 1269864 | packaging Of Telomere Ends | 1.36E-06 | 7.21E-04 |
| Pathway | 1269602 | formation of the beta-catenin: TCF transactivating complex | 3.24E-06 | 1.25E-03 |
| Pathway | 1269856 | telomere maintenance | 3.53E-06 | 1.25E-03 |
| Pathway | 1309110 | Nonhomologous End-Joining (NHEJ) | 9.17E-06 | 2.69E-03 |
| Pathway | 1269867 | meiotic synapsis | 1.01E-05 | 2.69E-03 |
| Pathway | 1269855 | deposition of new CENPA-containing nucleosomes at the centromere | 1.52E-05 | 3.09E-03 |
| Pathway | 1269854 | nucleosome assembly | 1.52E-05 | 3.09E-03 |
| Pathway | 1269659 | RNA Polymerase I promoter opening | 1.60E-05 | 3.09E-03 |
| Pathway | 1269753 | G2/M checkpoints | 2.00E-05 | 3.43E-03 |
| Pathway | 1269813 | condensation of prophase chromosomes | 2.10E-05 | 3.43E-03 |
| Pathway | 1269740 | DNA methylation | 2.27E-05 | 3.44E-03 |
| Pathway | 1309098 | recruitment and ATM-mediated phosphorylation of repair and signaling proteins at DNA double strand breaks | 2.46E-05 | 3.48E-03 |
| Pathway | 1309096 | DNA double strand break response | 2.87E-05 | 3.80E-03 |
| Pathway | 1269513 | activated PKN1 stimulates transcription of AR (androgen receptor) regulated genes KLK2 and KLK3 | 3.17E-05 | 3.95E-03 |
| Pathway | 1269853 | chromosome maintenance | 3.78E-05 | 4.26E-03 |
| Pathway | 1269866 | meiotic recombination | 3.81E-05 | 4.26E-03 |
| Pathway | 1269738 | SIRT1 negatively regulates rRNA expression | 4.36E-05 | 4.45E-03 |
| Pathway | 1270429 | DNA damage/telomere stress induced senescence | 4.47E-05 | 4.45E-03 |
| Pathway | 1309100 | HDR through Homologous Recombination (HR) or Single Strand Annealing (SSA) | 4.61E-05 | 4.45E-03 |
| Pathway | 1457808 | protein ubiquitination | 5.60E-05 | 5.16E-03 |
| Pathway | 1269512 | RHO GTPases activate PKNs | 7.34E-05 | 6.49E-03 |
| Pathway | 1309099 | homology directed repair | 8.47E-05 | 7.19E-03 |
| Pathway | 1269735 | PRC2 methylates histones and DNA | 9.21E-05 | 7.52E-03 |
| Pathway | 1269599 | TCF dependent signaling in response to WNT | 1.03E-04 | 8.09E-03 |
| Pathway | 1269742 | Cell Cycle checkpoints | 1.09E-04 | 8.23E-03 |
| Pathway | 1383084 | ERCC6 (CSB) and EHMT2 (G9a) positively regulate rRNA expression | 1.22E-04 | 8.86E-03 |
| Pathway | 1269594 | signaling by Wnt | 1.25E-04 | 8.86E-03 |
| Pathway | 83122 | systemic lupus erythematosus | 1.34E-04 | 9.17E-03 |
| Pathway | 1269865 | Meiosis | 1.42E-04 | 9.44E-03 |
| Pathway | 1270431 | Senescence-Associated Secretory Phenotype (SASP) | 1.48E-04 | 9.54E-03 |
| Pathway | 1269169 | amyloid fiber formation | 1.89E-04 | 1.18E-02 |
| Pathway | 1339126 | B-WICH complex positively regulates rRNA expression | 2.68E-04 | 1.58E-02 |
| Pathway | 1270436 | HDACs deacetylate histones | 2.68E-04 | 1.58E-02 |
| Pathway | PW:0000540 | obesity disease | 3.93E-04 | 2.20E-02 |
| Pathway | 83113 | basal cell carcinoma | 3.94E-04 | 2.20E-02 |
| Pathway | 1339139 | activation of HOX genes during differentiation | 6.99E-04 | 3.62E-02 |
| Pathway | 1339140 | activation of anterior HOX genes in hindbrain development during early embryogenesis | 6.99E-04 | 3.62E-02 |
| Pathway | 1270428 | oxidative stress induced senescence | 6.99E-04 | 3.62E-02 |
| Pathway | 1269662 | RNA Polymerase I chain elongation | 7.36E-04 | 3.72E-02 |
| Pathway | 585563 | alcoholism | 8.30E-04 | 4.10E-02 |
| Pathway | 1309095 | DNA double-strand break repair | 9.62E-04 | 4.64E-02 |

**Table S7. The biological annotations of Mod 02.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Category | ID | Name | p-value | q-value FDR B&H |
| Molecular Function | GO:0004984 | olfactory receptor activity | 6.37E-38 | 5.35E-35 |
| Molecular Function | GO:0004930 | G protein-coupled receptor activity | 6.30E-34 | 2.64E-31 |
| Molecular Function | GO:0004888 | transmembrane signaling receptor activity | 1.39E-22 | 3.88E-20 |
| Molecular Function | GO:0038023 | signaling receptor activity | 2.81E-21 | 5.89E-19 |
| Molecular Function | GO:0060089 | molecular transducer activity | 4.56E-19 | 7.66E-17 |
| Molecular Function | GO:0005549 | odorant binding | 1.05E-11 | 1.47E-09 |
| Molecular Function | GO:0008519 | ammonium transmembrane transporter activity | 4.91E-05 | 5.90E-03 |
| Molecular Function | GO:0070405 | ammonium ion binding | 5.33E-04 | 3.17E-02 |
| Molecular Function | GO:0052852 | very-long-chain-(S)-2-hydroxy-acid oxidase activity | 5.66E-04 | 3.17E-02 |
| Molecular Function | GO:0005427 | proton-dependent oligopeptide secondary active transmembrane transporter activity | 5.66E-04 | 3.17E-02 |
| Molecular Function | GO:0003973 | (S)-2-hydroxy-acid oxidase activity | 5.66E-04 | 3.17E-02 |
| Molecular Function | GO:0052854 | medium-chain-(S)-2-hydroxy-acid oxidase activity | 5.66E-04 | 3.17E-02 |
| Molecular Function | GO:0033041 | sweet taste receptor activity | 5.66E-04 | 3.17E-02 |
| Molecular Function | GO:0052853 | long-chain-(S)-2-hydroxy-long-chain-acid oxidase activity | 5.66E-04 | 3.17E-02 |
| Molecular Function | GO:0015322 | secondary active oligopeptide transmembrane transporter activity | 5.66E-04 | 3.17E-02 |
| Biological Process | GO:0050907 | detection of chemical stimulus involved in sensory perception | 7.73E-40 | 3.07E-36 |
| Biological Process | GO:0007606 | sensory perception of chemical stimulus | 2.42E-38 | 4.80E-35 |
| Biological Process | GO:0050906 | detection of stimulus involved in sensory perception | 1.39E-37 | 1.75E-34 |
| Biological Process | GO:0050911 | detection of chemical stimulus involved in sensory perception of smell | 1.76E-37 | 1.75E-34 |
| Biological Process | GO:0009593 | detection of chemical stimulus | 2.40E-37 | 1.91E-34 |
| Biological Process | GO:0007608 | sensory perception of smell | 3.28E-37 | 2.17E-34 |
| Biological Process | GO:0051606 | detection of stimulus | 9.97E-34 | 5.65E-31 |
| Biological Process | GO:0007600 | sensory perception | 4.61E-31 | 2.29E-28 |
| Biological Process | GO:0007186 | G protein-coupled receptor signaling pathway | 1.48E-24 | 6.54E-22 |
| Biological Process | GO:0050877 | nervous system process | 6.28E-22 | 2.49E-19 |
| Pathway | 83087 | olfactory transduction | 2.56E-39 | 2.15E-36 |
| Pathway | 1269583 | olfactory signaling pathway | 3.16E-37 | 1.32E-34 |
| Pathway | 1269574 | GPCR downstream signaling | 1.14E-23 | 3.18E-21 |
| Pathway | 1269543 | signaling by GPCR | 3.18E-19 | 6.66E-17 |
| Pathway | 1457777 | antimicrobial peptides | 4.75E-09 | 7.97E-07 |
| Pathway | M5885 | ensemble of genes encoding ECM-associated proteins including ECM-affilaited proteins, ECM regulators and secreted factors | 6.68E-09 | 9.34E-07 |
| Pathway | M5889 | ensemble of genes encoding extracellular matrix and extracellular matrix-associated proteins  | 1.77E-06 | 2.12E-04 |
| Pathway | M3468 | genes encoding enzymes and their regulators involved in the remodeling of the extracellular matrix | 5.96E-06 | 6.25E-04 |

**Table S8. The biological annotations of Mod 03.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Category | ID | Name | p-value | q-value FDR B&H |
|  Molecular Function | GO:0023026 | MHC class II protein complex binding | 4.59E-06 | 2.24E-03 |
|  Molecular Function | GO:0023023 | MHC protein complex binding | 9.61E-06 | 2.34E-03 |
|  Molecular Function | GO:0032395 | MHC class II receptor activity | 7.94E-05 | 1.01E-02 |
|  Molecular Function | GO:0042605 | peptide antigen binding | 8.28E-05 | 1.01E-02 |
|  Molecular Function | GO:0044877 | protein-containing complex binding | 1.06E-04 | 1.03E-02 |
|  Molecular Function | GO:0003823 | antigen binding | 2.48E-04 | 2.02E-02 |
|  Molecular Function | GO:0017091 | AU-rich element binding | 6.03E-04 | 4.19E-02 |
|  Biological Process | GO:0002503 | peptide antigen assembly with MHC class II protein complex | 1.94E-11 | 2.80E-08 |
|  Biological Process | GO:0002399 | MHC class II protein complex assembly | 1.94E-11 | 2.80E-08 |
|  Biological Process | GO:0002501 | peptide antigen assembly with MHC protein complex | 1.15E-10 | 8.29E-08 |
|  Biological Process | GO:0002396 | MHC protein complex assembly | 1.15E-10 | 8.29E-08 |
|  Biological Process | GO:0006959 | humoral immune response | 5.66E-06 | 3.26E-03 |
|  Biological Process | GO:0045321 | leukocyte activation | 9.35E-06 | 4.49E-03 |
|  Biological Process | GO:0001775 | cell activation | 3.93E-05 | 1.11E-02 |
|  Biological Process | GO:0098581 | detection of external biotic stimulus | 4.19E-05 | 1.11E-02 |
|  Biological Process | GO:0002505 | antigen processing and presentation of polysaccharide antigen via MHC class II | 5.33E-05 | 1.11E-02 |
|  Biological Process | GO:0071823 | protein-carbohydrate complex subunit organization | 5.33E-05 | 1.11E-02 |
|  Biological Process | GO:0002506 | polysaccharide assembly with MHC class II protein complex | 5.33E-05 | 1.11E-02 |
|  Biological Process | GO:0065006 | protein-carbohydrate complex assembly | 5.33E-05 | 1.11E-02 |
|  Biological Process | GO:0046649 | lymphocyte activation | 6.12E-05 | 1.11E-02 |
|  Biological Process | GO:0042127 | regulation of cell proliferation | 6.26E-05 | 1.11E-02 |
|  Biological Process | GO:0006955 | immune response | 6.27E-05 | 1.11E-02 |
|  Biological Process | GO:0009595 | detection of biotic stimulus | 6.44E-05 | 1.11E-02 |
|  Biological Process | GO:0019886 | antigen processing and presentation of exogenous peptide antigen via MHC class II | 6.53E-05 | 1.11E-02 |
|  Biological Process | GO:0002495 | antigen processing and presentation of peptide antigen via MHC class II | 8.72E-05 | 1.40E-02 |
|  Biological Process | GO:0002504 | antigen processing and presentation of peptide or polysaccharide antigen via MHC class II | 9.22E-05 | 1.40E-02 |
|  Biological Process | GO:0070486 | leukocyte aggregation | 1.02E-04 | 1.47E-02 |
|  Biological Process | GO:0061178 | regulation of insulin secretion involved in cellular response to glucose stimulus | 1.12E-04 | 1.54E-02 |
|  Biological Process | GO:2001179 | regulation of interleukin-10 secretion | 1.31E-04 | 1.71E-02 |
|  Biological Process | GO:0072608 | interleukin-10 secretion | 1.63E-04 | 2.04E-02 |
|  Biological Process | GO:0007159 | leukocyte cell-cell adhesion | 1.92E-04 | 2.17E-02 |
|  Biological Process | GO:0035773 | insulin secretion involved in cellular response to glucose stimulus | 1.95E-04 | 2.17E-02 |
|  Biological Process | GO:0034284 | response to monosaccharide | 1.96E-04 | 2.17E-02 |
|  Biological Process | GO:0002478 | antigen processing and presentation of exogenous peptide antigen | 2.19E-04 | 2.29E-02 |
|  Biological Process | GO:0032633 | interleukin-4 production | 2.23E-04 | 2.29E-02 |
|  Biological Process | GO:0030072 | peptide hormone secretion | 2.31E-04 | 2.29E-02 |
|  Biological Process | GO:0009611 | response to wounding | 2.39E-04 | 2.29E-02 |
|  Biological Process | GO:0090087 | regulation of peptide transport | 2.77E-04 | 2.32E-02 |
|  Biological Process | GO:0007155 | cell adhesion | 2.79E-04 | 2.32E-02 |
|  Biological Process | GO:0019884 | antigen processing and presentation of exogenous antigen | 2.82E-04 | 2.32E-02 |
|  Biological Process | GO:0002790 | peptide secretion | 2.84E-04 | 2.32E-02 |
|  Biological Process | GO:0015833 | peptide transport | 2.96E-04 | 2.32E-02 |
|  Biological Process | GO:0046879 | hormone secretion | 2.96E-04 | 2.32E-02 |
|  Biological Process | GO:0030073 | insulin secretion | 2.99E-04 | 2.32E-02 |
|  Biological Process | GO:0022610 | biological adhesion | 3.14E-04 | 2.32E-02 |
|  Biological Process | GO:0071603 | endothelial cell-cell adhesion | 3.15E-04 | 2.32E-02 |
|  Biological Process | GO:0090276 | regulation of peptide hormone secretion | 3.36E-04 | 2.33E-02 |
|  Biological Process | GO:0042110 | T cell activation | 3.41E-04 | 2.33E-02 |
|  Biological Process | GO:0070489 | T cell aggregation | 3.41E-04 | 2.33E-02 |
|  Biological Process | GO:0071593 | lymphocyte aggregation | 3.47E-04 | 2.33E-02 |
|  Biological Process | GO:0046883 | regulation of hormone secretion | 3.82E-04 | 2.38E-02 |
|  Biological Process | GO:0002791 | regulation of peptide secretion | 3.87E-04 | 2.38E-02 |
|  Biological Process | GO:0009914 | hormone transport | 3.93E-04 | 2.38E-02 |
|  Biological Process | GO:0060333 | interferon-gamma-mediated signaling pathway | 3.96E-04 | 2.38E-02 |
|  Biological Process | GO:0016045 | detection of bacterium | 3.97E-04 | 2.38E-02 |
|  Biological Process | GO:0009743 | response to carbohydrate | 4.09E-04 | 2.40E-02 |
|  Biological Process | GO:0048002 | antigen processing and presentation of peptide antigen | 4.24E-04 | 2.44E-02 |
|  Biological Process | GO:0098543 | detection of other organism | 4.60E-04 | 2.60E-02 |
|  Biological Process | GO:0002252 | immune effector process | 4.86E-04 | 2.69E-02 |
|  Biological Process | GO:0042886 | amide transport | 5.25E-04 | 2.85E-02 |
|  Biological Process | GO:0050673 | epithelial cell proliferation | 6.04E-04 | 3.16E-02 |
|  Biological Process | GO:0002381 | immunoglobulin production involved in immunoglobulin mediated immune response | 6.04E-04 | 3.16E-02 |
|  Biological Process | GO:0050796 | regulation of insulin secretion | 6.16E-04 | 3.17E-02 |
|  Biological Process | GO:0016064 | immunoglobulin mediated immune response | 6.40E-04 | 3.23E-02 |
|  Biological Process | GO:0065003 | protein-containing complex assembly | 6.66E-04 | 3.31E-02 |
|  Biological Process | GO:0032880 | regulation of protein localization | 6.88E-04 | 3.31E-02 |
|  Biological Process | GO:0048103 | somatic stem cell division | 6.89E-04 | 3.31E-02 |
|  Biological Process | GO:0019724 | B cell mediated immunity | 7.14E-04 | 3.37E-02 |
|  Biological Process | GO:0034109 | homotypic cell-cell adhesion | 7.47E-04 | 3.47E-02 |
|  Biological Process | GO:0071638 | negative regulation of monocyte chemotactic protein-1 production | 7.79E-04 | 3.56E-02 |
|  Biological Process | GO:0098609 | cell-cell adhesion | 7.97E-04 | 3.59E-02 |
|  Biological Process | GO:0002437 | inflammatory response to antigenic stimulus | 8.51E-04 | 3.77E-02 |
|  Biological Process | GO:0050776 | regulation of immune response | 8.74E-04 | 3.79E-02 |
|  Biological Process | GO:0046887 | positive regulation of hormone secretion | 8.81E-04 | 3.79E-02 |
|  Biological Process | GO:0060251 | regulation of glial cell proliferation | 9.80E-04 | 4.15E-02 |
|  Biological Process | GO:0014015 | positive regulation of gliogenesis | 1.03E-03 | 4.29E-02 |
|  Biological Process | GO:0001678 | cellular glucose homeostasis | 1.08E-03 | 4.40E-02 |
|  Biological Process | GO:0033591 | response to L-ascorbic acid | 1.09E-03 | 4.40E-02 |
|  Biological Process | GO:0002443 | leukocyte mediated immunity | 1.23E-03 | 4.91E-02 |
|  Cellular Component | GO:0042613 | MHC class II protein complex | 9.74E-10 | 3.28E-07 |
|  Cellular Component | GO:0042611 | MHC protein complex | 3.37E-08 | 5.68E-06 |
|  Cellular Component | GO:0012507 | ER to Golgi transport vesicle membrane | 1.36E-07 | 1.53E-05 |
|  Cellular Component | GO:0030134 | COPII-coated ER to Golgi transport vesicle | 8.09E-07 | 6.81E-05 |
|  Cellular Component | GO:0030662 | coated vesicle membrane | 9.14E-06 | 6.16E-04 |
|  Cellular Component | GO:0098852 | lytic vacuole membrane | 3.45E-05 | 1.40E-03 |
|  Cellular Component | GO:0005765 | lysosomal membrane | 3.45E-05 | 1.40E-03 |
|  Cellular Component | GO:0000323 | lytic vacuole | 3.75E-05 | 1.40E-03 |
|  Cellular Component | GO:0005764 | lysosome | 3.75E-05 | 1.40E-03 |
|  Cellular Component | GO:0098553 | lumenal side of endoplasmic reticulum membrane | 5.43E-05 | 1.66E-03 |
|  Cellular Component | GO:0071556 | integral component of lumenal side of endoplasmic reticulum membrane | 5.43E-05 | 1.66E-03 |
|  Cellular Component | GO:0030135 | coated vesicle | 6.62E-05 | 1.86E-03 |
|  Cellular Component | GO:0098576 | lumenal side of membrane | 9.14E-05 | 2.37E-03 |
|  Cellular Component | GO:0045334 | clathrin-coated endocytic vesicle | 1.34E-04 | 3.03E-03 |
|  Cellular Component | GO:0031902 | late endosome membrane | 1.35E-04 | 3.03E-03 |
|  Cellular Component | GO:0030658 | transport vesicle membrane | 1.54E-04 | 3.24E-03 |
|  Cellular Component | GO:0005770 | late endosome | 2.30E-04 | 4.56E-03 |
|  Cellular Component | GO:0030665 | clathrin-coated vesicle membrane | 3.42E-04 | 6.39E-03 |
|  Cellular Component | GO:0030669 | clathrin-coated endocytic vesicle membrane | 4.68E-04 | 8.30E-03 |
|  Cellular Component | GO:0005912 | adherens junction | 8.03E-04 | 1.35E-02 |
|  Cellular Component | GO:0070161 | anchoring junction | 1.10E-03 | 1.76E-02 |
|  Cellular Component | GO:0030136 | clathrin-coated vesicle | 1.17E-03 | 1.80E-02 |
|  Cellular Component | GO:0098552 | side of membrane | 1.23E-03 | 1.80E-02 |
|  Cellular Component | GO:0031410 | cytoplasmic vesicle | 1.80E-03 | 2.47E-02 |
|  Cellular Component | GO:0097708 | intracellular vesicle | 1.83E-03 | 2.47E-02 |
|  Cellular Component | GO:0005924 | cell-substrate adherens junction | 2.48E-03 | 3.22E-02 |
|  Cellular Component | GO:0030055 | cell-substrate junction | 2.70E-03 | 3.37E-02 |
|  Cellular Component | GO:0032588 | trans-Golgi network membrane | 2.97E-03 | 3.58E-02 |
|  Cellular Component | GO:0031616 | spindle pole centrosome | 3.85E-03 | 4.28E-02 |
|  Cellular Component | GO:0005615 | extracellular space | 3.90E-03 | 4.28E-02 |
|  Cellular Component | GO:0005774 | vacuolar membrane | 3.94E-03 | 4.28E-02 |
|  Cellular Component | GO:0030659 | cytoplasmic vesicle membrane | 4.19E-03 | 4.42E-02 |
|  Cellular Component | GO:0005771 | multivesicular body | 4.49E-03 | 4.59E-02 |
|  Cellular Component | GO:0044437 | vacuolar part | 4.93E-03 | 4.88E-02 |
| Pathway | 83122 | systemic lupus erythematosus | 1.60E-08 | 8.96E-06 |
| Pathway | 172846 | staphylococcus aureus infection | 2.14E-08 | 8.96E-06 |
| Pathway | 128760 | intestinal immune network for IgA production | 1.70E-07 | 4.28E-05 |
| Pathway | 83120 | asthma | 2.05E-07 | 4.28E-05 |
| Pathway | 83123 | allograft rejection | 7.31E-07 | 1.22E-04 |
| Pathway | 83124 | graft-versus-host disease | 1.17E-06 | 1.63E-04 |
| Pathway | 83095 | Type I diabetes mellitus | 1.56E-06 | 1.87E-04 |
| Pathway | 83074 | antigen processing and presentation | 3.92E-06 | 4.10E-04 |
| Pathway | 169642 | toxoplasmosis | 5.17E-06 | 4.59E-04 |
| Pathway | 83121 | autoimmune thyroid disease | 5.48E-06 | 4.59E-04 |
| Pathway | 125138 | viral myocarditis | 1.03E-05 | 7.86E-04 |
| Pathway | 1458885 | Th1 and Th2 cell differentiation | 1.29E-05 | 8.96E-04 |
| Pathway | 842771 | Inflammatory bowel disease (IBD) | 1.82E-05 | 1.09E-03 |
| Pathway | 83078 | hematopoietic cell lineage | 1.82E-05 | 1.09E-03 |
| Pathway | 1269174 | translocation of ZAP-70 to Immunological synapse | 3.23E-05 | 1.80E-03 |
| Pathway | 144181 | leishmaniasis | 3.54E-05 | 1.85E-03 |
| Pathway | 153910 | phagosome | 4.95E-05 | 2.44E-03 |
| Pathway | 1269173 | phosphorylation of CD3 and TCR zeta chains | 5.47E-05 | 2.54E-03 |
| Pathway | 1269182 | PD-1 signaling | 6.42E-05 | 2.83E-03 |
| Pathway | 200309 | rheumatoid arthritis | 1.15E-04 | 4.82E-03 |
| Pathway | PW:0000204 | Notch signaling | 2.12E-04 | 8.15E-03 |
| Pathway | PW:0000459 | apelin signaling | 2.14E-04 | 8.15E-03 |
| Pathway | 1269175 | generation of second messenger molecules | 2.37E-04 | 8.44E-03 |
| Pathway | 1269200 | MHC class II antigen presentation | 2.42E-04 | 8.44E-03 |
| Pathway | P00045 | Notch signaling pathway | 2.64E-04 | 8.84E-03 |
| Pathway | 1469482 | Th17 cell differentiation | 2.98E-04 | 9.59E-03 |
| Pathway | 1269855 | deposition of new CENPA-containing nucleosomes at the centromere | 3.86E-04 | 1.15E-02 |
| Pathway | 1269854 | nucleosome assembly | 3.86E-04 | 1.15E-02 |
| Pathway | 137910 | CXCR4-mediated signaling events | 4.65E-04 | 1.34E-02 |
| Pathway | 217173 | influenza A | 6.80E-04 | 1.90E-02 |
| Pathway | 213780 | tuberculosis | 8.32E-04 | 2.25E-02 |
| Pathway | 1269499 | nuclear signaling by ERBB4 | 1.20E-03 | 3.11E-02 |
| Pathway | 1269314 | interferon gamma signaling | 1.23E-03 | 3.11E-02 |
| Pathway | 83069 | Cell adhesion molecules (CAMs) | 1.48E-03 | 3.18E-02 |
| Pathway | 1268883 | signaling by NOTCH1 in cancer | 1.48E-03 | 3.18E-02 |
| Pathway | 1268891 | constitutive signaling by NOTCH1 HD+PEST domain mutants | 1.48E-03 | 3.18E-02 |
| Pathway | 1268889 | constitutive signaling by NOTCH1 PEST domain mutants | 1.48E-03 | 3.18E-02 |
| Pathway | 1268890 | signaling by NOTCH1 HD+PEST domain mutants in cancer | 1.48E-03 | 3.18E-02 |
| Pathway | 1268888 | signaling by NOTCH1 PEST domain mutants in cancer | 1.48E-03 | 3.18E-02 |
| Pathway | 1269176 | downstream TCR signaling | 1.84E-03 | 3.85E-02 |
| Pathway | 1269536 | activated NOTCH1 transmits signal to the nucleus | 2.27E-03 | 4.63E-02 |
| Pathway | 1269853 | chromosome maintenance | 2.46E-03 | 4.89E-02 |

**Table S9. The biological annotations of Mod 04.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Category | ID | Name | p-value | q-value FDR B&H |
|  Biological Process | GO:0015980 | energy derivation by oxidation of organic compounds | 6.25E-06 | 4.40E-02 |
|  Biological Process | GO:0007005 | mitochondrion organization | 1.47E-05 | 4.48E-02 |
|  Biological Process | GO:0006091 | generation of precursor metabolites and energy | 1.91E-05 | 4.48E-02 |
|  Cellular Component | GO:0005739 | mitochondrion | 5.71E-15 | 4.79E-12 |
|  Cellular Component | GO:0044429 | mitochondrial part | 3.07E-13 | 1.29E-10 |
|  Cellular Component | GO:0005759 | mitochondrial matrix | 1.55E-09 | 4.32E-07 |
|  Cellular Component | GO:0005740 | mitochondrial envelope | 9.02E-09 | 1.63E-06 |
|  Cellular Component | GO:0031966 | mitochondrial membrane | 9.73E-09 | 1.63E-06 |
|  Cellular Component | GO:0031967 | organelle envelope | 2.31E-08 | 3.23E-06 |
|  Cellular Component | GO:0031975 | envelope | 2.97E-08 | 3.56E-06 |
|  Cellular Component | GO:0019866 | organelle inner membrane | 1.70E-07 | 1.78E-05 |
|  Cellular Component | GO:0005743 | mitochondrial inner membrane | 5.80E-07 | 5.41E-05 |
|  Cellular Component | GO:0044455 | mitochondrial membrane part | 1.51E-06 | 1.27E-04 |
|  Cellular Component | GO:0005762 | mitochondrial large ribosomal subunit | 1.31E-04 | 9.18E-03 |
|  Cellular Component | GO:0000315 | organellar large ribosomal subunit | 1.31E-04 | 9.18E-03 |
|  Cellular Component | GO:0098798 | mitochondrial protein complex | 1.84E-04 | 1.19E-02 |
|  Cellular Component | GO:0098800 | inner mitochondrial membrane protein complex | 5.43E-04 | 3.26E-02 |
|  Cellular Component | GO:1990204 | oxidoreductase complex | 8.10E-04 | 4.53E-02 |
|  Cellular Component | GO:0070469 | respiratory chain | 1.04E-03 | 4.78E-02 |
|  Cellular Component | GO:0045273 | respiratory chain complex II | 1.20E-03 | 4.78E-02 |
|  Cellular Component | GO:0005749 | mitochondrial respiratory chain complex II, succinate dehydrogenase complex (ubiquinone) | 1.20E-03 | 4.78E-02 |
|  Cellular Component | GO:0045283 | fumarate reductase complex | 1.20E-03 | 4.78E-02 |
|  Cellular Component | GO:0045281 | succinate dehydrogenase complex | 1.20E-03 | 4.78E-02 |
|  Cellular Component | GO:0045257 | succinate dehydrogenase complex (ubiquinone) | 1.20E-03 | 4.78E-02 |
|  Cellular Component | GO:0043209 | myelin sheath | 1.29E-03 | 4.92E-02 |
| Pathway | 835393 | superpathway of conversion of glucose to acetyl CoA and entry into the TCA cycle | 9.67E-06 | 1.34E-02 |
| Pathway | 1270121 | The citric acid (TCA) cycle and respiratory electron transport | 1.19E-05 | 1.34E-02 |
| Pathway | M16991 | skeletal muscle hypertrophy is regulated via AKT/mTOR pathway | 1.75E-05 | 1.34E-02 |
| Pathway | M15371 | electron transport reaction in mitochondria | 4.53E-05 | 2.18E-02 |
| Pathway | 83058 | autophagy - animal | 6.12E-05 | 2.18E-02 |
| Pathway | 82927 | citrate cycle (TCA cycle) | 7.41E-05 | 2.18E-02 |
| Pathway | SMP00057 | citric acid cycle | 7.43E-05 | 2.18E-02 |
| Pathway | 138068 | signaling events mediated by stem cell factor receptor (c-Kit) | 8.53E-05 | 2.18E-02 |
| Pathway | PW:0000034 | oxidative phosphorylation | 8.53E-05 | 2.18E-02 |
| Pathway | 1270125 | citric acid cycle (TCA cycle) | 1.11E-04 | 2.56E-02 |
| Pathway | 413348 | citrate cycle, second carbon oxidation, 2-oxoglutarate => oxaloacetate | 1.32E-04 | 2.76E-02 |
| Pathway | 1270127 | respiratory electron transport, ATP synthesis by chemiosmotic coupling, and heat production by uncoupling proteins. | 1.45E-04 | 2.79E-02 |

**Table S10. The biological annotations of Mod 05.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Category | ID | Name | p-value | q-value FDR B&H |
|  Molecular Function | GO:0008227 | G protein-coupled amine receptor activity | 6.71E-05 | 2.81E-02 |
|  Molecular Function | GO:0030594 | neurotransmitter receptor activity | 2.19E-04 | 3.76E-02 |
|  Molecular Function | GO:0004969 | histamine receptor activity | 2.69E-04 | 3.76E-02 |
|  Molecular Function | GO:0070405 | ammonium ion binding | 3.69E-04 | 3.86E-02 |
|  Biological Process | GO:0043269 | regulation of ion transport | 2.69E-05 | 2.50E-02 |
|  Biological Process | GO:1903792 | negative regulation of anion transport | 3.12E-05 | 2.50E-02 |
|  Biological Process | GO:0006811 | ion transport | 4.50E-05 | 2.50E-02 |
|  Biological Process | GO:0034767 | positive regulation of ion transmembrane transport | 4.89E-05 | 2.50E-02 |
|  Biological Process | GO:0034764 | positive regulation of transmembrane transport | 6.51E-05 | 2.50E-02 |
|  Biological Process | GO:0051241 | negative regulation of multicellular organismal process | 7.87E-05 | 2.50E-02 |
|  Biological Process | GO:0001936 | regulation of endothelial cell proliferation | 8.12E-05 | 2.50E-02 |
|  Biological Process | GO:0050918 | positive chemotaxis | 1.20E-04 | 2.82E-02 |
|  Biological Process | GO:0008015 | blood circulation | 1.33E-04 | 2.82E-02 |
|  Biological Process | GO:0003013 | circulatory system process | 1.39E-04 | 2.82E-02 |
|  Biological Process | GO:0032891 | negative regulation of organic acid transport | 1.45E-04 | 2.82E-02 |
|  Biological Process | GO:0001935 | endothelial cell proliferation | 1.80E-04 | 2.82E-02 |
|  Biological Process | GO:1900133 | regulation of renin secretion into blood stream | 1.81E-04 | 2.82E-02 |
|  Biological Process | GO:0009628 | response to abiotic stimulus | 1.83E-04 | 2.82E-02 |
|  Biological Process | GO:0043270 | positive regulation of ion transport | 2.19E-04 | 3.13E-02 |
|  Biological Process | GO:0003018 | vascular process in circulatory system | 2.33E-04 | 3.13E-02 |
|  Biological Process | GO:0006812 | cation transport | 2.46E-04 | 3.13E-02 |
|  Biological Process | GO:0014063 | negative regulation of serotonin secretion | 2.70E-04 | 3.24E-02 |
|  Biological Process | GO:0098655 | cation transmembrane transport | 3.05E-04 | 3.46E-02 |
|  Biological Process | GO:0060429 | epithelium development | 3.64E-04 | 3.54E-02 |
|  Biological Process | GO:0032414 | positive regulation of ion transmembrane transporter activity | 3.71E-04 | 3.54E-02 |
|  Biological Process | GO:0002001 | renin secretion into blood stream | 3.77E-04 | 3.54E-02 |
|  Biological Process | GO:0061138 | morphogenesis of a branching epithelium | 3.77E-04 | 3.54E-02 |
|  Biological Process | GO:0050678 | regulation of epithelial cell proliferation | 4.76E-04 | 3.86E-02 |
|  Biological Process | GO:0001999 | renal response to blood flow involved in circulatory renin-angiotensin regulation of systemic arterial blood pressure | 5.02E-04 | 3.86E-02 |
|  Biological Process | GO:0051048 | negative regulation of secretion | 5.11E-04 | 3.86E-02 |
|  Biological Process | GO:0071526 | semaphorin-plexin signaling pathway | 5.34E-04 | 3.86E-02 |
|  Biological Process | GO:0001763 | morphogenesis of a branching structure | 5.46E-04 | 3.86E-02 |
|  Biological Process | GO:0032411 | positive regulation of transporter activity | 5.84E-04 | 3.86E-02 |
|  Biological Process | GO:0051924 | regulation of calcium ion transport | 6.23E-04 | 3.86E-02 |
|  Biological Process | GO:0048265 | response to pain | 6.24E-04 | 3.86E-02 |
|  Biological Process | GO:0007268 | chemical synaptic transmission | 6.33E-04 | 3.86E-02 |
|  Biological Process | GO:0098916 | anterograde trans-synaptic signaling | 6.33E-04 | 3.86E-02 |
|  Biological Process | GO:0099537 | trans-synaptic signaling | 6.33E-04 | 3.86E-02 |
|  Biological Process | GO:0043010 | camera-type eye development | 6.34E-04 | 3.86E-02 |
|  Biological Process | GO:0014050 | negative regulation of glutamate secretion | 6.43E-04 | 3.86E-02 |
|  Biological Process | GO:0033555 | multicellular organismal response to stress | 6.90E-04 | 3.98E-02 |
|  Biological Process | GO:0099536 | synaptic signaling | 7.01E-04 | 3.98E-02 |
|  Biological Process | GO:0034765 | regulation of ion transmembrane transport | 7.43E-04 | 4.11E-02 |
|  Biological Process | GO:0014062 | regulation of serotonin secretion | 8.02E-04 | 4.22E-02 |
|  Biological Process | GO:0014052 | regulation of gamma-aminobutyric acid secretion | 8.02E-04 | 4.22E-02 |
|  Biological Process | GO:0000904 | cell morphogenesis involved in differentiation | 8.97E-04 | 4.44E-02 |
|  Biological Process | GO:0050880 | regulation of blood vessel size | 9.42E-04 | 4.44E-02 |
|  Biological Process | GO:0030517 | negative regulation of axon extension | 9.51E-04 | 4.44E-02 |
|  Biological Process | GO:2001259 | positive regulation of cation channel activity | 9.51E-04 | 4.44E-02 |
|  Biological Process | GO:0034762 | regulation of transmembrane transport | 9.55E-04 | 4.44E-02 |
|  Biological Process | GO:0035150 | regulation of tube size | 9.66E-04 | 4.44E-02 |
|  Biological Process | GO:0048640 | negative regulation of developmental growth | 1.05E-03 | 4.62E-02 |
|  Biological Process | GO:0009314 | response to radiation | 1.05E-03 | 4.62E-02 |
| Pathway | 1269553 | amine ligand-binding receptors | 4.89E-05 | 2.64E-02 |
| Pathway | 1269557 | histamine receptors | 1.32E-04 | 3.55E-02 |

**Table S11. Biological annotations of proteins mediating the relationship between the transcriptomal signatures and grey volume changes in major depressive disorder.**

|  |  |  |  |
| --- | --- | --- | --- |
| GO items | Description | Observed gene count | q-value FDR |
| GO.0044281 | small molecule metabolic process | 142 | 5.85E-11 |
| GO.0007399 | nervous system development | 133 | 1.05E-10 |
| GO.0051641 | cellular localization | 138 | 1.05E-10 |
| GO.1902578 | single-organism localization | 176 | 6.75E-10 |
| GO.0006793 | phosphorus metabolic process | 122 | 1.59E-09 |
| GO.0006796 | phosphate-containing compound metabolic process | 118 | 6.28E-09 |
| GO.0034613 | cellular protein localization | 84 | 4.31E-08 |
| GO.0044765 | single-organism transport | 161 | 4.31E-08 |
| GO.0055114 | oxidation-reduction process | 77 | 4.31E-08 |
| GO.0006091 | generation of precursor metabolites and energy | 44 | 4.56E-08 |
| GO.0044710 | single-organism metabolic process | 213 | 4.84E-08 |
| GO.0051128 | regulation of cellular component organization | 130 | 4.84E-08 |
| GO.0022607 | cellular component assembly | 114 | 5.83E-08 |
| GO.0009056 | catabolic process | 112 | 6.76E-08 |
| GO.1901564 | organonitrogen compound metabolic process | 105 | 6.84E-08 |
| GO.0051179 | localization | 216 | 6.93E-08 |
| GO.0051234 | establishment of localization | 186 | 6.93E-08 |
| GO.0016043 | cellular component organization | 232 | 7.92E-08 |
| GO.0033036 | macromolecule localization | 123 | 1.21E-07 |
| GO.0006810 | transport | 180 | 1.44E-07 |
| GO.0008104 | protein localization | 107 | 1.89E-07 |
| GO.0071822 | protein complex subunit organization | 95 | 1.89E-07 |
| GO.0019637 | organophosphate metabolic process | 64 | 1.90E-07 |
| GO.1901575 | organic substance catabolic process | 99 | 1.90E-07 |
| GO.0045184 | establishment of protein localization | 89 | 2.58E-07 |
| GO.1902580 | single-organism cellular localization | 66 | 2.58E-07 |
| GO.0051649 | establishment of localization in cell | 109 | 2.84E-07 |
| GO.0022008 | neurogenesis | 93 | 2.95E-07 |
| GO.0015980 | energy derivation by oxidation of organic compounds | 37 | 3.84E-07 |
| GO.0048699 | generation of neurons | 89 | 4.53E-07 |
| GO.0051049 | regulation of transport | 107 | 4.95E-07 |
| GO.0065008 | regulation of biological quality | 160 | 5.93E-07 |
| GO.0016192 | vesicle-mediated transport | 79 | 1.04E-06 |
| GO.0009060 | aerobic respiration | 14 | 1.32E-06 |
| GO.0032879 | regulation of localization | 129 | 1.41E-06 |
| GO.0048731 | system development | 180 | 2.03E-06 |
| GO.0044085 | cellular component biogenesis | 114 | 3.66E-06 |
| GO.0006101 | citrate metabolic process | 11 | 4.15E-06 |
| GO.0060627 | regulation of vesicle-mediated transport | 38 | 4.85E-06 |
| GO.0060341 | regulation of cellular localization | 79 | 4.92E-06 |
| GO.0044712 | single-organism catabolic process | 64 | 5.92E-06 |
| GO.0050804 | modulation of synaptic transmission | 29 | 6.46E-06 |
| GO.0006099 | tricarboxylic acid cycle | 10 | 1.08E-05 |
| GO.0051960 | regulation of nervous system development | 53 | 1.08E-05 |
| GO.0044087 | regulation of cellular component biogenesis | 51 | 1.47E-05 |
| GO.0015031 | protein transport | 79 | 1.51E-05 |
| GO.0006886 | intracellular protein transport | 55 | 1.73E-05 |
| GO.0006753 | nucleoside phosphate metabolic process | 41 | 2.13E-05 |
| GO.0045333 | cellular respiration | 23 | 2.43E-05 |
| GO.0055086 | nucleobase-containing small molecule metabolic process | 43 | 2.55E-05 |
| GO.0030036 | actin cytoskeleton organization | 36 | 2.64E-05 |
| GO.0010975 | regulation of neuron projection development | 33 | 2.79E-05 |
| GO.0044248 | cellular catabolic process | 87 | 4.09E-05 |
| GO.0065003 | macromolecular complex assembly | 75 | 4.19E-05 |
| GO.0009117 | nucleotide metabolic process | 40 | 4.60E-05 |
| GO.0050803 | regulation of synapse structure or activity | 25 | 4.76E-05 |
| GO.0060284 | regulation of cell development | 55 | 5.44E-05 |
| GO.0071702 | organic substance transport | 105 | 6.88E-05 |
| GO.0007268 | synaptic transmission | 44 | 0.000173 |
| GO.0006461 | protein complex assembly | 63 | 0.000182 |
| GO.0017157 | regulation of exocytosis | 20 | 0.000182 |
| GO.0030029 | actin filament-based process | 36 | 0.000182 |
| GO.0048856 | anatomical structure development | 191 | 0.000182 |
| GO.0070271 | protein complex biogenesis | 63 | 0.000182 |
| GO.0007275 | multicellular organismal development | 190 | 0.000189 |
| GO.0009894 | regulation of catabolic process | 56 | 0.000202 |
| GO.0010646 | regulation of cell communication | 142 | 0.000212 |
| GO.0046907 | intracellular transport | 78 | 0.000252 |
| GO.0060322 | head development | 50 | 0.000278 |
| GO.0010243 | response to organonitrogen compound | 54 | 0.000286 |
| GO.0030168 | platelet activation | 25 | 0.000286 |
| GO.0006457 | protein folding | 23 | 0.000293 |
| GO.0050767 | regulation of neurogenesis | 44 | 0.000313 |
| GO.0046903 | secretion | 44 | 0.000324 |
| GO.0031329 | regulation of cellular catabolic process | 50 | 0.000333 |
| GO.0007417 | central nervous system development | 57 | 0.000347 |
| GO.0051130 | positive regulation of cellular component organization | 70 | 0.000462 |
| GO.1901698 | response to nitrogen compound | 57 | 0.000462 |
| GO.0048167 | regulation of synaptic plasticity | 17 | 0.000464 |
| GO.0051259 | protein oligomerization | 34 | 0.000519 |
| GO.0007596 | blood coagulation | 41 | 0.000524 |
| GO.0061024 | membrane organization | 57 | 0.000526 |
| GO.0031344 | regulation of cell projection organization | 36 | 0.000575 |
| GO.0016310 | phosphorylation | 66 | 0.000675 |
| GO.0044708 | single-organism behavior | 33 | 0.000803 |
| GO.0007420 | brain development | 46 | 0.000864 |
| GO.0030182 | neuron differentiation | 61 | 0.000909 |
| GO.1901699 | cellular response to nitrogen compound | 40 | 0.000909 |
| GO.0022604 | regulation of cell morphogenesis | 37 | 0.000921 |
| GO.0032940 | secretion by cell | 37 | 0.000998 |
| GO.0070887 | cellular response to chemical stimulus | 116 | 0.000998 |
| GO.0044767 | single-organism developmental process | 205 | 0.00102 |
| GO.0031175 | neuron projection development | 46 | 0.00111 |
| GO.0044763 | single-organism cellular process | 389 | 0.00111 |
| GO.1903530 | regulation of secretion by cell | 43 | 0.00111 |
| GO.0032502 | developmental process | 206 | 0.00114 |
| GO.0010256 | endomembrane system organization | 34 | 0.00127 |
| GO.0007010 | cytoskeleton organization | 53 | 0.00129 |
| GO.0051640 | organelle localization | 30 | 0.00131 |
| GO.0043933 | macromolecular complex subunit organization | 108 | 0.00142 |
| GO.0007409 | axonogenesis | 37 | 0.00145 |
| GO.0061564 | axon development | 38 | 0.00145 |
| GO.0071417 | cellular response to organonitrogen compound | 37 | 0.00145 |
| GO.0009161 | ribonucleoside monophosphate metabolic process | 21 | 0.00158 |
| GO.0048666 | neuron development | 52 | 0.0016 |
| GO.0023051 | regulation of signaling | 131 | 0.00167 |
| GO.0007154 | cell communication | 218 | 0.00179 |
| GO.0007269 | neurotransmitter secretion | 15 | 0.00179 |
| GO.0007610 | behavior | 38 | 0.00179 |
| GO.0009167 | purine ribonucleoside monophosphate metabolic process | 20 | 0.00179 |
| GO.0045664 | regulation of neuron differentiation | 36 | 0.00179 |
| GO.0072521 | purine-containing compound metabolic process | 30 | 0.00179 |
| GO.0006605 | protein targeting | 33 | 0.00189 |
| GO.0019693 | ribose phosphate metabolic process | 28 | 0.00189 |
| GO.0010976 | positive regulation of neuron projection development | 21 | 0.00195 |
| GO.0051129 | negative regulation of cellular component organization | 40 | 0.00197 |
| GO.0006836 | neurotransmitter transport | 17 | 0.00225 |
| GO.0042391 | regulation of membrane potential | 25 | 0.0023 |
| GO.0001505 | regulation of neurotransmitter levels | 17 | 0.00241 |
| GO.0044699 | single-organism process | 402 | 0.00241 |
| GO.1902582 | single-organism intracellular transport | 66 | 0.00266 |
| GO.0009259 | ribonucleotide metabolic process | 27 | 0.00279 |
| GO.0009150 | purine ribonucleotide metabolic process | 26 | 0.00308 |
| GO.0006163 | purine nucleotide metabolic process | 27 | 0.00327 |
| GO.0050878 | regulation of body fluid levels | 45 | 0.00327 |
| GO.0009896 | positive regulation of catabolic process | 35 | 0.00338 |
| GO.0046128 | purine ribonucleoside metabolic process | 24 | 0.00341 |
| GO.0045109 | intermediate filament organization | 6 | 0.00349 |
| GO.0051962 | positive regulation of nervous system development | 32 | 0.00349 |
| GO.0007626 | locomotory behavior | 20 | 0.00351 |
| GO.0044711 | single-organism biosynthetic process | 73 | 0.00357 |
| GO.0031331 | positive regulation of cellular catabolic process | 32 | 0.00372 |
| GO.0050896 | response to stimulus | 279 | 0.00372 |
| GO.0044282 | small molecule catabolic process | 23 | 0.00374 |
| GO.0006629 | lipid metabolic process | 62 | 0.00394 |
| GO.0006887 | exocytosis | 25 | 0.00394 |
| GO.1903362 | regulation of cellular protein catabolic process | 26 | 0.00394 |
| GO.1901566 | organonitrogen compound biosynthetic process | 57 | 0.00398 |
| GO.0010033 | response to organic substance | 119 | 0.00415 |
| GO.0043043 | peptide biosynthetic process | 29 | 0.00415 |
| GO.0008286 | insulin receptor signaling pathway | 17 | 0.00417 |
| GO.0006811 | ion transport | 65 | 0.0042 |
| GO.0043603 | cellular amide metabolic process | 41 | 0.0042 |
| GO.1903050 | regulation of proteolysis involved in cellular protein catabolic process | 25 | 0.0042 |
| GO.0014047 | glutamate secretion | 7 | 0.00421 |
| GO.0009719 | response to endogenous stimulus | 76 | 0.00471 |
| GO.0042176 | regulation of protein catabolic process | 32 | 0.00471 |
| GO.0043434 | response to peptide hormone | 32 | 0.00471 |
| GO.0009119 | ribonucleoside metabolic process | 25 | 0.00485 |
| GO.0007005 | mitochondrion organization | 31 | 0.00489 |

Note: Top 150 GO items were listed here.

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**Figure S1. Relationship between MDD-related transcriptome signatures and differential expression genes in the postmortem tissues of MDD.**

We found negative correlation between abnormal transcriptions of genes in anterior cingulate cortex and PLS1 weights (A and B) and positive correlation between abnormal transcriptions of genes in dorsolateral prefrontal cortex and PLS1 weights (C and D). Aberrations: ACC: anterior cingulate cortex; dlPFC: dorsolateral prefrontal cortex.