Gene Expression Meta-Analysis of Major Depressive Disorder and Its Relationship with Alzheimer's Disease

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Research

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Abstract

Introduction: Major depressive disorder (MDD) and Alzheimer's disease (AD) are often co-existing in the elderly and have been suggested to share common pathological and physiological links. Understanding the connections between these two diseases could benefit for revealing new possible strategies of early diagnosis and therapeutic intervention.

Methods: we conducted a meta-analysis to identify differentially expressed genes (DEGs) in MDD microarray datasets including 180 MDD and 281 control prefrontal cortex of brain samples. Using identified DEGs, we performed gene ontology (GO), pathway and protein-protein interaction (PPI) analysis.

Results: We identified 1400 DEGs, of which 846 were upregulated and 554 was downregulated in MDD. 198 DEGs were found over-lapping between AD and MDD compared with the previous study on AD. The over-lapping DEGs were particularly enriched in the protein binding of gene ontology and Signal Transduction, Immune System, Metabolism of proteins as for pathways. CDC42 was the most important gene in PPI network which had the most connections with other genes.

Conclusion: Our study shows that MDD and AD share significant common DEGs and pathways and add some new potential perspectives to the comprehensive neurobiologic model between MDD and the development of AD.

Introduction

Major depressive disorder (MDD) is a complex disease with high recurrence rate, high disability rate and high risk of suicide [1–3]; it is characterized by depressed mood, diminished interests, impaired cognitive function and vegetative symptoms, such as disturbed sleep or appetite [4]. The 12-month prevalence in MDD is 6.6% and the lifetime prevalence is 16.2%, and MDD is twice as common in women as in men [5]. Some mechanisms have been indicated in MDD, including underactivity of monoamines [6], reduced levels of brain-derived neurotrophic factor (BDNF)[7], increased pro-inflammatory cytokines[8, 9] and so on, but the neuropathological alterations present in depressive individuals were still unclear. Alzheimer's disease (AD) is the most common neurodegenerative disease, accounting for 60–80% of dementia cases, characterized by gradual memory loss, progressive neurocognitive dysfunction and eventually losing the independency. The pathogenesis of AD is characterized by extracellular aggregates of amyloid β ($A\beta$) plaques and intracellular neurofibrillary tangles made of hyperphosphorylated τ -protein in cortical and limbic areas [10]. Interestingly, MDD and AD often co-exist in the elderly. A systematic review indicated that depression affects about 20–37% AD patients[11]. But the relationship between MDD and AD hasn't reached a consensus. Two main theories have been indicated according to previous clinical-epidemiological studies; the first one is that MDD is a risk factor of AD, and MDD is associated with increased odds of AD, even more than 20 years after diagnosis of MDD [12, 13]. The more serious and the more times MDD occurs, people are more likely to develop AD [14–16]. The second theory is that MDD is

a part of early stage of AD, which means only recent MDD is associated with AD and previous MDD may not lead to increased risk of AD [17–19].

In fact, some limitations in these researches may account for the contradiction between these two theories above. Firstly, the assessment of AD and MDD cannot avoid the influence of subjective factors (such as recall bias) and objective biomarkers for these diseases are lacking [20, 21]. Secondly, although the confounding factors for the risk of AD were adjusted, but the included factors are not the same [22, 23].

The complex relationship between MDD and AD suggests that they may share common neurobiological abnormalities. For example, Butters et al. set up a model which builds a connection between MDD and AD. The model proposed that MDD may cause increased glucocorticoids and generalized ischemia which lead to the damage of specific brain area (hippocampal atrophy and frontostriatal abnormalities) associated with cognitive reserve and finally develop to clinical AD[24]. Moreover, abnormal glucose metabolism (Insulin resistance) [25], inflammation [26], β -amyloid deposition and Tau protein hyperphosphorylation [27], alterations of neurotransmitter[28] and neurotrophic factors (Decreased BDNF)[29] are also proved to play important roles in the connection of MDD and AD.

According to RNA sequencing (RNA-seq), we may find more consistent molecular evidence for MDD and AD. Some studies have collected large RNA-seq from different tissues in several datasets towards MDD or AD and performed meta-analytical procedures to combine them and get larger sample size [30, 31]. A study completed a comprehensive and integrated analysis to explore the biological abnormalities in AD and MDD based on human blood microRNA expression [32]. But no study has done integrated analysis of MDD and AD based on RNA-seq in the human brain.

In the present study, we carried out a meta-analysis with microarray data from human brain tissue to discover differentially expressed genes (DEGs) in MDD and compared these DEGs to AD. We also performed pathway and function enrichment analysis and protein-protein interaction (PPI) network analysis with common-shared DEGs, trying to reveal potential neurobiological links between MDD and AD.

Methods

Data collection and Gene differential expression analysis

We searched NCBI GEO (Gene Expression Omnibus) databases for mRNA expression studies of human brain tissue from patients who were diagnosed with MDD. The inclusion criteria for the studies were listed as follows: (i) used clinically diagnosed MDD; (ii) used brain samples. If a patient had duplicate samples, only one of them was included. The raw CEL files from included studies were loaded into R using 'affy' package. We normalized the datasets using the Robust Multi-array Average (RMA) approach in the affy package. We matched the probesets to Entrez Gene IDs using manufacturer-supplied annotation files, and kept the probeset that had the largest absolute estimated effect size if genes mapped to multiple

probesets. The detection call generated by the affy microarray suite version 5 (MAS5) was applied to remove data that was not reliably detected. Probesets with a chosen percentage of absent calls across all samples were removed. The percentage absent cut-off was set to minimize the P-value of the Anderson-Darling normality test using the 'nortest' R package and give optimum Quantile-Quantile (Q-Q) plots of the z-score from meta-analysis. We removed the bottom 5% of average expression values across samples to reduce expression data noise. We performed meta-analysis using metaUnion R package[31]. The combined effect size across studies was calculated through meta-analysis. DEGs were identified using the combined effect size by 'limma' that was built in the metaUnion package [33]. We then compared DEGs to a previous study on Alzheimer's disease (AD) [31]. All work was conducted in R (3.6.3, R Development Core Team, Vienna, Austria)

Gene Ontology (GO) and pathway enrichment analysis

The online biological tool KOBAS 3.0 (available online: <http://kobas.cbi.pku.edu.cn>) and the "ggplot2" R package (version 3.5.0) were used for the GO function enrichment analysis and KEGG pathway enrichment analysis of the common DEGs between AD and MDD, and four databases were used in the analysis, including KEGG Pathway (available online: <https://www.genome.jp/kegg>), Reactome (available online: <http://www.reactome.org>), BioCyc (available online: <https://biocyc.org/>) and PANTHER (available online: <http://www.pantherdb.org>). Benjamini-Hochberg correction of P value below 0.05 was considered to have statistical significance.

PPI network construction

The STRING online database (available online: <http://string-db.org>) [34] was applied to obtain the PPI information of the DEGs. Cytoscape software (version 3.8.2)[35] was used to construct a PPI relationship network, and the plug-in cytoHubba[36] in Cytoscape was utilized to screen for the top 10 hub genes from the PPI network.

Results

Meta-analysis

Four datasets (GSE12654, GSE53987, GSE54575, GSE92538) from GEO databases[37–40] were included in the meta-analysis with 180 MDD cases and 281 controls. We identified 1400 DEGs from the initial 14577 genes after Bonferroni correction (adjusted P value < 0.05), of which 846 were upregulated and 554 was downregulated. When compared with the previous study on AD, 198 DEGs were found overlapping in both studies. Among 198 common DEGs, 68 were upregulated in both AD and MDD, 41 were downregulated in both, 37 were upregulated in AD but downregulated in MDD, 52 were downregulated in AD but upregulated in MDD.

Common DEG gene ontology analysis

To provide a detail foundation for exploring and understanding the 198 common DEGs, GO analysis was applied using the “ggplot2” R package and the online biological tool KOBAS 3.0 (available online: <http://kobas.cbi.pku.edu.cn>). Function enrichment analysis identified a total of 67 terms with the 198 common DEGs (Supplementary Table S1). As shown in Fig. 1 and Table 1, the common DEGs were classified into three functional groups, including the biological process group, the cellular component group, and the molecular function group. The GO analysis results showed that the common DEGs were particularly enriched in the protein binding of the molecular function group. All kinds of DEGs including those expressed in the same or different direction in AD or MDD were enriched in the term of protein binding. In cellular component group, the upregulated AD DEGs of common DEGs were significantly enriched in cytosol, while the downregulated DEGs of the both were significantly enriched in membrane.

Table 1

The significantly enriched analysis of common differentially expressed genes between AD and MDD (Top 10 according to corrected P value)

Term	Description	Count	Corrected P-Value
Upregulated in AD and MDD			
GO:0005515	protein binding	49	8.33E-10
GO:0005829	cytosol	26	5.39E-05
GO:0007492	endoderm development	3	0.001585639
GO:0005654	nucleoplasm	19	0.001585639
GO:0005886	plasma membrane	21	0.00322663
GO:0004402	histone acetyltransferase activity	3	0.007297517
GO:0016607	nuclear speck	6	0.007297517
GO:0072378	blood coagulation, fibrin clot formation	2	0.007297517
GO:0032991	protein-containing complex	7	0.008123645
GO:0051056	regulation of small GTPase mediated signal transduction	4	0.008123645
Downregulated in AD and MDD			
GO:0016020	membrane	14	7.04E-06
GO:0090316	positive regulation of intracellular protein transport	2	0.038912445
GO:0043005	neuron projection	4	0.038912445
GO:0017156	calcium-ion regulated exocytosis	2	0.038912445
GO:0005515	protein binding	23	0.038912445
GO:0001958	endochondral ossification	2	0.038912445
GO:0003723	RNA binding	7	0.038912445
GO:0016192	vesicle-mediated transport	3	0.038912445
GO:0043197	dendritic spine	3	0.038937621
GO:0030036	actin cytoskeleton organization	3	0.038937621
Upregulated in AD and downregulated in MDD			
GO:0005515	protein binding	31	8.66E-09

GO, gene ontology; AD, Alzheimer's disease; MDD, Major depressive disorder

Term	Description	Count	Corrected P-Value
GO:0005829	cytosol	18	3.75E-05
GO:0016575	histone deacetylation	3	0.001302985
GO:0003682	chromatin binding	5	0.006910637
GO:0045121	membrane raft	4	0.007068361
GO:0005796	Golgi lumen	3	0.009209301
GO:0005634	nucleus	14	0.009209301
GO:0001825	blastocyst formation	2	0.009209301
GO:0005886	plasma membrane	13	0.009618188
GO:0046872	metal ion binding	9	0.00970618
Downregulated in AD and upregulated in MDD			
GO:0005515	protein binding	33	0.000324068
GO:0102391	decanoate-CoA ligase activity	2	0.013442666
GO:0047676	arachidonate-CoA ligase activity	2	0.013442666
GO:0005759	mitochondrial matrix	5	0.013442666
GO:0004467	long-chain fatty acid-CoA ligase activity	2	0.013442666
GO:0005654	nucleoplasm	14	0.013442666
GO:0008610	lipid biosynthetic process	2	0.013442666
GO:0005886	plasma membrane	16	0.013442666
GO:0003996	acyl-CoA ligase activity	2	0.014315282
GO:0035338	long-chain fatty-acyl-CoA biosynthetic process	2	0.017638685
GO, gene ontology; AD, Alzheimer's disease; MDD, Major depressive disorder			

Signaling pathway enrichment analysis

The online biological tool KOBAS 3.0 (available online: <http://kobas.cbi.pku.edu.cn>) and the “ggplot2” R package were used in the KEGG pathway enrichment analysis of the DEGs, and four databases were used in this analysis, including “KEGG Pathway,” “Reactome,” “BioCyc,” and “PANTHER.” Fig. 2A showed the top 20 out of 209 significantly enriched pathways of the 198 common DEGs. DEGs were highly clustered in Signal Transduction, Metabolism, Immune System and Metabolism of proteins. As shown in Table 2 and Fig. 2B-E, further analysis indicated that the common DEGs upregulated in both AD and MDD were enriched in Signaling by Rho GTPases and Extracellular matrix organization (Fig. 2B), while the common

DEGs downregulated in both AD and MDD were mainly enriched in Vesicle-mediated transport and Membrane Trafficking (Fig. 2C). DEGs upregulated in AD but downregulated in MDD were enriched in Signal Transduction and Signaling by NOTCH (Fig. 2D), while those downregulated in AD but upregulated in MDD were mainly enriched in Fatty acyl-CoA biosynthesis (Fig. 2E).

Table 2
Pathway enrichment analysis of common DEGs function between AD and MDD (Top 10 according to corrected P value)

Pathway	Description	Gene count	Corrected P-Value
Upregulated in AD and MDD			
Reactome: R-HSA-194315	Signaling by Rho GTPases	6	0.018442363
Reactome: R-HSA-1474244	Extracellular matrix organization	5	0.018442363
KEGG PATHWAY: hsa05135	Yersinia infection	4	0.018442363
Reactome: R-HSA-194840	Rho GTPase cycle	4	0.018442363
KEGG PATHWAY: hsa04510	Focal adhesion	4	0.031147141
KEGG PATHWAY: hsa05205	Proteoglycans in cancer	4	0.031147141
Reactome: R-HSA-162582	Signal Transduction	13	0.037450463
Downregulated in AD and MDD			
Reactome: R-HSA-199991	Membrane Trafficking	5	0.026215978
Reactome: R-HSA-5653656	Vesicle-mediated transport	5	0.026215978
Reactome: R-HSA-195721	Signaling by WNT	4	0.026215978
Reactome: R-HSA-5663205	Infectious disease	4	0.026215978
Reactome: R-HSA-453279	Mitotic G1-G1/S phases	3	0.026215978
KEGG PATHWAY: hsa04310	Wnt signaling pathway	3	0.026215978
PANTHER: P00013	Cell cycle	2	0.026215978
Reactome: R-HSA-3238698	WNT ligand biogenesis and trafficking	2	0.026215978

AD, Alzheimer's disease; MDD, Major depressive disorder

Pathway	Description	Gene count	Corrected P-Value
PANTHER: P05916	Opioid prodynorphin pathway	2	0.026215978
PANTHER: P05917	Opioid proopiomelanocortin pathway	2	0.026215978
Upregulated in AD and downregulated in MDD			
Reactome: R-HSA-162582	Signal Transduction	10	0.019960248
Reactome: R-HSA-157118	Signaling by NOTCH	4	0.019960248
Reactome: R-HSA-1912420	Pre-NOTCH Processing in Golgi	2	0.019960248
Reactome: R-HSA-1643685	Disease	6	0.027088245
PANTHER: P00026	Heterotrimeric G-protein signaling pathway-Gi alpha and Gs alpha mediated pathway	3	0.027088245
Reactome: R-HSA-350054	Notch-HLH transcription pathway	2	0.027088245
Reactome: R-HSA-9006934	Signaling by Receptor Tyrosine Kinases	4	0.035127599
KEGG PATHWAY: hsa05166	Human T-cell leukemia virus 1 infection	3	0.035127599
Reactome: R-HSA-2894858	Signaling by NOTCH1 HD + PEST Domain Mutants in Cancer	2	0.035127599
Reactome: R-HSA-2644606	Constitutive Signaling by NOTCH1 PEST Domain Mutants	2	0.035127599
Downregulated in AD and upregulated in MDD			
Reactome: R-HSA-75105	Fatty acyl-CoA biosynthesis	3	0.005506403
KEGG PATHWAY: hsa04920	Adipocytokine signaling pathway	3	0.01140614
BioCyc: PWY-7049	icosapentaenoate biosynthesis II (metazoa)	2	0.01140614
BioCyc: PWY-6000	gamma-linolenate biosynthesis	2	0.01140614

AD, Alzheimer's disease; MDD, Major depressive disorder

Pathway	Description	Gene count	Corrected P-Value
BioCyc: PWY-5143	fatty acid activation	2	0.01140614
BioCyc: PWY-7592	arachidonate biosynthesis III (metazoa)	2	0.01140614
Reactome: R-HSA-74160	Gene expression (Transcription)	8	0.011975211
KEGG PATHWAY: hsa00061	Fatty acid biosynthesis	2	0.011975211
BioCyc: PWY66-391	fatty acid beta-oxidation (peroxisome)	2	0.011975211
BioCyc: PWY66-387	fatty acid alpha-oxidation	2	0.011975211
AD, Alzheimer's disease; MDD, Major depressive disorder			

Protein-protein interaction network analysis

To identify the core genes that are involved in AD and MDD from the interaction level, Cytoscape software and the online database STRING (available online: <https://string-db.org/>) were used. A total of 107 DEGs of the 198 common DEGs were filtered into the PPI network, which contained 107 nodes/genes and 143 edges, but 91 of the 198 DEGs were not filtered into the PPI network complex (Fig. 3A). Among the 107 nodes, the top 10 hub nodes screened by cytoHubba and ranked by Maximal Clique Centrality (MCC) scores were shown in Table 3. Only one node (CDC42) had more than 10 connections/interactions. Combined with the findings in pathway analysis, a total of 6 hub genes belonged to Signal Transduction pathway including CDC42 which had the most connections with other genes. The subnetwork in Fig. 3B was constructed by nodes/genes belonging to Signal Transduction pathway, 22 of the 107 common DEGs were filtered into the subnetwork, consisting 22 nodes/genes and 34 edges. Half of the 22 genes were upregulated in both AD and MDD, and 18 of 22 genes (except PRKCQ, GNAO1, CDC42 and TAC3) were upregulated in AD.

Table 3
The hub node genes in the PPI network ranked by MCC method.

Rank	Name	AD	MDD	Score
1	CDC42	Downregulated	Downregulated	39
2	RHOJ	Upregulated	Upregulated	20
3	RHOT1	Upregulated	Upregulated	19
4	BPTF	Upregulated	Upregulated	10
5	GNAI2	Upregulated	Downregulated	9
6	ARHGEF12	Upregulated	Upregulated	8
6	ARAP1	Upregulated	Downregulated	8
6	ACLY	Downregulated	Upregulated	8
9	ABCA1	Upregulated	Upregulated	7
9	VAMP2	Downregulated	Downregulated	7
MCC, Maximal Clique Centrality; AD, Alzheimer's disease; MDD, Major depressive disorder				

Discussion

We used an approach of meta-analysis and identified 1400 DEGs in MDD by integrating 461 independent samples from four microarray gene expression datasets; only 671 DEGs were included in all four datasets. It's possible that there are potential interesting genes which haven't been identified because they are not being measured in each previous study. Among the top 30 DEGs, 11 are not included in all datasets. A recent meta-analysis using GWAS data of 135,458 major depression cases and 344,901 controls identified 44 significantly associated genomic regions for MDD[41]. Only 5 of the genes in or near the 4 SNP were identified in the 1400 DEGs of MDD in our study, including ZNF445(chr_44287760_I), RSR1(rs7430565), MLF1(rs7430565), LINC01231(rs1354115) and CCDC68(rs1833288). However, none of the GWAS genes were present in the 198 over-lapping DEGs of AD and MDD. It's probably because the expression data from seven MDD cohorts used in the meta-analysis of GWAS study were all from blood but not brain tissue.

Compared to previous study of AD[31], 198 DEGs were over-lapping in prefrontal cortex of both MDD and AD, 109 DEGs are consistently upregulated or downregulated. This result was different from the study of human blood microRNA expression comparison[32]. In the study of microRNA expression, all seven common differentially expressed microRNAs were up-regulated in patients with MDD and down-regulated in patients with AD. When comparing the 198 DEGs and the 43 DEGs regulated by the 7 microRNAs based on the DIANA database, only 3 DEGs (ANKS1A, PKN2, PRKCQ) were shared in common. As for AD patients, ANKS1A and PKN2 were both upregulated in prefrontal cortex and blood, while PRKCQ was

downregulated in prefrontal cortex but upregulated in blood. PRKCQ is involved in platelet activation[42]. Inyushin et al. revealed that A β peptide is massively released to the blood upon the activation/aggregation of platelets, so platelet hyper-activation has been conclusively shown to be an aspect of AD, which may explain the increasing of PRKCQ in blood sample of AD cases[43]. PRKCQ is also associated with axon guidance[44]. Zhang et al. proved that axon-guidance molecules play an important role in guiding growth cones to form synapses and are involved in the pathogenesis of AD by regulating the levels of A β and hyperphosphorylation of tau through various signaling pathways[45], which may explain the decreasing of PRKCQ in brain sample of AD cases.

However, these 3 DEGs were all upregulated in prefrontal cortex but downregulated in blood in MDD patients. To better understand MDD, various pathophysiological mechanisms have been proposed, including changes in monoaminergic neurotransmission, imbalance of excitatory and inhibitory signaling in the brain, hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis, and abnormalities in normal neurogenesis, which indicated the significant role of signal transduction in MDD [44]. PKN2[46] and PRKCQ[47] have been proved to be involved in the pathway of signal transduction. Moreover, PRKCQ is related to axon guidance[44] and ANKS1A is associated with neuron remodeling[48], which are specific for brain. So it maybe account for the different expression between brain and blood.

Another possible explanation is that human prefrontal cortex has different regions and expression pattern is different in different regions (including rostral prefrontal cortex, dorsolateral prefrontal cortex, ventrolateral prefrontal cortex, medial prefrontal cortex and orbitofrontal prefrontal cortex). Here we combined them together, so it's likely that the 198 DEGs don't show specific expression pattern (for instance all genes upregulated in AD and downregulated in MDD) in AD and MDD.

Functional enrichment analysis identified 67 GO terms and 209 KEGG terms associated to the 198 common DEGs in both AD and MDD. And the most significantly enriched GO term is protein binding (one of the molecular function) which may be corresponded with the highly enriched KEGG terms named Signal Transduction, Metabolism of proteins and Immune System. A recent study found that [49] the inflammasome becomes activated when the microglia cells sense the aggregated amyloid- β , and the activation of inflammasome and subsequent caspase 1 cleavage contribute to disease development and progression. It builds up a connection between Immune System and protein binding. Similarly, another study[50] indicated that systemic inflammation can activate microglial TLR4, NLRP3 inflammasome, and complement in the brain, leading to neuroinflammation, A β accumulation, synapse loss and neurodegeneration, and targeting the molecular mechanisms underlying the TLR-complement-NLRP3 inflammasome signaling pathways can be a preventive and therapeutic approach for AD. It combined the signal transduction, immune system and metabolism of proteins together. That's to say, no matter MDD is the risk factor or prodrome of AD, MDD may affect Immune system and signal transduction like the studies implied above and contribute to aggregation of amyloid- β (One of the important molecular pathology of AD).

Our results show that the Reactome term named Rho GTPase cycle significantly enriched in AD and MDD. On the one hand, protein aggregation is a hallmark of diverse neurodegenerative diseases like AD, and a study has implied that signaling from the RHO GTPase and the ROCK1 and LIMK1 kinases controls cofilin-1 activity to remodel actin and modulate aggregate entry[51]. On the other hand, depression induces structural and functional synaptic plasticity in brain reward circuits, and Rho GTPase-related genes, which are known regulators of synaptic structure), revealed a sustained reduction in RAS-related C3 botulinum toxin substrate 1 (Rac1, one of Rho GTPase-related genes) expression in the nucleus accumbens after chronic social defeat stress[52]. These findings reveal great value of Rho GTPase in AD and MDD. The mechanical property of extracellular matrix and cell-supporting substrates is known to modulate neuronal growth, differentiation, extension and branching[53], and AD is associated with reduced brain tissue stiffness[54]. We can see that the term named Extracellular matrix organization is also upregulated in AD and MDD, which may suggest that MDD may change the hardness of local brain tissue and finally evolve into AD. Extracellular vesicles, specifically exosomes, have been demonstrated to participate in mediating inflammatory response[55] and Tau propagation[56] in brain. And Vesicle-mediated transport is downregulated in both two, which provides possible insights between AD and MDD in another aspects. In protein-protein interaction network, CDC42 is the most important one which is also proved to be participated in 9 of top 10 significantly enriched pathways. In previous study, CDC42 has been proven to involve in dendritic cell migration[57] and dendritic spine morphogenesis[58]. The dendritic spine could pave the way to the identification of novel biomarkers to monitor synaptic loss in AD[59]. Moreover, CDC42 is associated with ephrin receptor signaling pathway. Adam et al. found that the Eph/ephrin system has been implicated in pathological settings of Alzheimer's disease[60], and Vargas et al. suggested that the activation of the Ephrin-A4/c-Abl axis would explain the synaptic spine alterations found in AD[61]. These findings above indicate the important role of CDC42 in the process of AD.

A limitation of this study is that MDD is probably not a unitary disease, but rather a heterogeneous syndrome which means different MDD patients could have different neurophysiological changes[62], but the expression data of MDD we could acquire didn't take this issue into account, so it may explain the relatively lack of connections among the 198 DEGs. In other words, different types of MDD may be associated with AD in different pathways. That's why we've got some DEGs that are not closely related. And some potential connections between AD and MDD are stated above. What's more, in this study we only analyzed gene expression data in prefrontal cortex, it's necessary to include more areas of brain and compare the different expression patterns among different areas, which may help us understand this question in a more general view.

In conclusion, our meta-analysis is the first study to make connections between MDD and AD with the expression data of brain tissue. Our results add some new potential perspectives to the comprehensive neurobiological model between MDD and the development of AD, mainly including the "trilogy" (change of signal transduction, the binding of amyloid β , inflammatory response), the reducing stiffness of brain tissue, and Vesicle-mediated transport disorder.

Abbreviations

MDD

Major depressive disorder

AD

Alzheimer's disease

DEGs

differentially expressed genes

GO

Gene Ontology

PPI

protein protein interaction

Declarations

- Ethics approval and consent to participate

Ethics approval, consent to participate are not applicable.

- Consent for publication

Consent for publication is not applicable.

- Availability of data and materials

All the four datasets of major depressive disorder in this article are available in the GEO public databases[37-40].

GSE12654: <https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE12654>

GSE53987: <https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE53987>

GSE54575: <https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE54575>

GSE92538: <https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE92538>

The data of AD analysed during this study are included in this published article and its Supplementary Table S2[31].

- Competing interests

The authors declare no competing financial interests.

- Funding

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- Authors' contributions

Ruihan Wang contributed substantially to conception and design, acquisition of data. Quan Zheng contributed a lot to analysis of data by using R packages. Interpretation of data is finished by Jinghao Duan and Wang Ruihan. Xueping Chen revised it critically for important intellectual content and gave final approval of the version to be published.

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Figures

Figure 1

GO analysis of 198 common DEGs between AD and MDD. The DEGs were classified into three functional groups, including biological process, cellular component and molecular function. Significant enriched GO terms of common DEGs based on their functions. P-Value was corrected with Benjamini-Hochberg. DEGs, differentially expressed genes; GO, gene ontology; AD, Alzheimer's disease; MDD, Major depressive disorder.

Figure 2

Scatter plot of enriched pathways statistics. Rich factor is the ratio of the differentially expressed gene number to the total gene number in a certain pathway. The color and size of the dots represent the range of the P-value and the number of DEGs mapped to the indicated pathways, respectively. Top 20 enriched pathways are shown in the figure. A