Differential gene expression analysis suggests ribosomal protein genes are key blood biomarkers in comorbid PTSD and Alzheimer's Disease

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Abstract: Alzheimer's disease (AD) is a severely debilitating disease that is incurable and affects a large portion of the elderly population. Post-traumatic stress disorder (PTSD) is a mental health condition that is caused by exposure to highly stressful (usually life-threatening) stimuli. Both diseases are highly involved in immune response and neuroinflammatory processes, and studies have indicated that those with PTSD are at increased risk for developing AD later in life. In this study, datasets containing genetic profiles from controls and individuals suffering from either condition were taken from the NIH Gene Expression Omnibus and DEGs present in both were analyzed. 443 significant ≤ 0.05,$|\text{LogFC}| \geq 0.2$ shared DEGs were found, of which 290 were upregulated and 153 downregulated. A protein-protein interaction network was created from these DEGs, which was found to have a significant enrichment p-value. Next, hub genes from the network were calculated using multiple methods. Finally, gene set enrichment analysis (GSEA) was performed and significantly enriched pathways as well as gene ontology terms were compared between the two conditions.

1 Introduction

Alzheimer's disease (AD) is a neurodegenerative disease that primarily effects the elderly population (Kumar et al., 2024). Over 50% of individuals in the United States older than 85 suffer from it, with symptomatic manifestations including, but not limited to: increasing permanent memory loss, severe cognitive dysfunction, social impairment, and death (American Psychiatric Association, 2022). Currently, there is no known method of cure or (significant) prevention for AD, only treatments that delay the inevitable (Passeri et al., 2022).

Post-traumatic stress disorder (PTSD) is a mental disorder that results from significant trauma exposure characterized by recurring flashbacks of the traumatic event, avoidance of stimuli that represent the traumatic event, negative changes in cognition, attention, mood, arousal, and social functioning (American Psychiatric Association, 2022). Lifetime prevalence of PTSD in the United States is around 7.8%, with symptomatic duration varying from 3 months to a lifetime (Kessler, 1995). A person with PTSD is 90% more likely to have another mental disorder than a person without it (Sareen, 2014). Treatments for PTSD include cognitive behavioral therapy, as well as antidepressant and anxiolytic medication (Mansour et al., 2023).

A growing field of research has begun to implicate associations between PTSD and AD. Individuals with PTSD have been shown to have poorer cognitive abilities than neurotypical individuals, with significantly worse performance in tests of working memory, verbal and visuospatial ability, information processing, and executive functioning (Scott et al., 2015). Recent research has found that individuals with PTSD are, on average, of 71% more likely to develop Alzheimer's disease compared to individuals without PTSD (Yaffe et al., 2010a). It has also been found that PTSD treatment in individuals with AD can reduce symptoms of AD alongside those of PTSD (Ruisch et al., 2023).

On a molecular level, causal linkage between AD and PTSD is poorly understood. However, the two conditions share a multitude of biomarkers and known pathways. For example, both diseases are involved in immune activation, neuroinflammation, mitochondrial disruption, and vascular disease (Yaffe et al., 2010b; Justice et al., 2015; Petakh et al., 2024; Roberts et al., 2022). On a protein level, both diseases have been linked to significant changes in c-reactive protein, vascular endothelial growth factor, and neurofilament light (Kuan et al., 2020). PTSD is also shown to be associated with increased amyloid-β (Aβ), a protein that is famous for its role as an essential contributor to the development of AD (Ruisch et al., 2023).

2 Materials and Methods

2.1 Data Collection

Two sets of gene expression profiles, GSE63060 and GSE81761, were downloaded from the open-access Gene Expression Omnibus (GEO) database.

The GSE63060 dataset contained transcription profiles from mRNA within the blood of 104 healthy control samples, 80 mild cognitive impairment (MCI) samples, and 145 AD samples, obtained via the AddNeuroMed Cohort, a biomarker study of AD within various western European countries (Sood et al., 2015). Samples in this dataset were assigned into control or AD groups based on the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) criteria for "possible or probable AD". We excluded the 80 MCI-afflicted samples in this dataset from analysis as they were not related to this study.

The GSE81761 dataset contained transcription profiles also from mRNA within the blood of 27 healthy controls and 39 individuals with PTSD, taken from US military service members in the state of Washington who had returned from deployment(Rusch et al., 2015, 2019). Incidence of PTSD within samples in this dataset was determined using the PTSD Checklist-Military version (PCL-M). Individuals with a score of $\geq$50 were placed in the PTSD group and individuals with a score of $\leq$25 were placed in the control group.

2.2 Identification of Differentially Expressed Genes (DEGs)

After the datasets were downloaded, Qlucore Omics Explorer v3.8 (Qlucore AB, Lund, Sweden) was used to visualize and perform significance tests on both datasets. GSE81761 had a total of 17,655 genes while GSE81761 had a total of 22,190. In all, the 15,796 genes shared among both sets were analyzed. Differentially expressed genes (DEGs) were defined as any gene with a $p \leq 0.05$ and a $|\log FC| \geq 0.2$ when testing disease samples against control samples. DEGs with common regulation within both datasets (that is to say, a gene significantly upregulated in both, not a gene was significantly upregulated in one and significantly downregulated in the other) were then identified for further analysis.

2.3 Protein-Protein Interaction (PPI) Network Construction and Hub Gene Identification

To further analyze genetic interplay, the Search Tool for the Retrieval of Interacting Genes (STRING) database (https://string-db.org/) was employed in creating a protein-protein interaction (PPI) network. Cytoscape (v3.10.2), an open-source software used in network data visualization was used to better visualize the PPI network. To identify hub genes, 4 different topological analyses, were performed via the cytoHubba

plugin within Cytoscape (Chin et al., 2014). Genes that were common among the top 10 scores of all four analyses were considered as "hub genes".

2.4 Gene Set Enrichment Analysis (GSEA)

To explore potential biological interactions between PTSD and AD, Gene Set Enrichment Analysis (GSEA) was performed on both datasets. Gene Ontology (GO) enrichment analysis, namely: biological process (BP), molecular function (MF), and cellular component (CC) term analysis, was performed on both datasets, alongside Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis via the open-source online software WebGestalt (Liao et al., 2019).

3 Results

In the PTSD dataset (GSE81761) there were 3,886 DEGs, with 1,519 of them being upregulated genes and 2,367 of them being downregulated genes. In the AD dataset (GSE63060) there were 424 DEGs, with 112 of them being upregulated genes and 312 of them being downregulated genes. Among both datasets, there were 11 common upregulated genes and 157 common downregulated genes (totaling 168), as is shown in Fig 1.

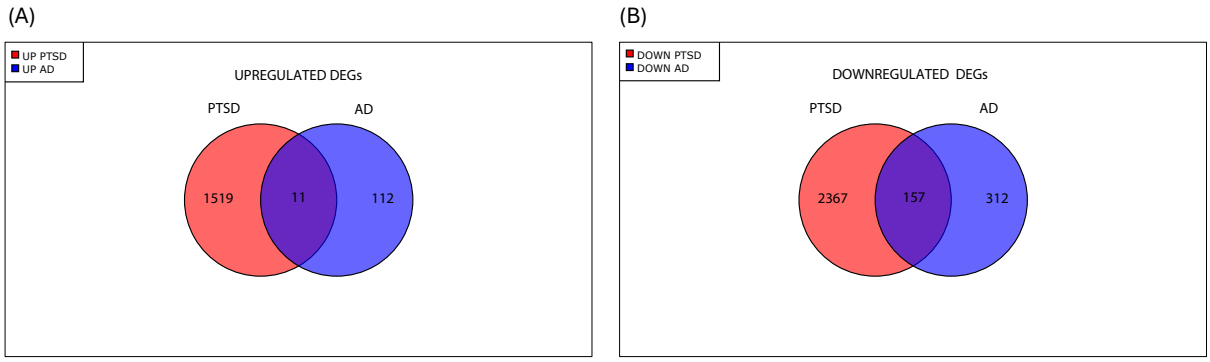

Figure 1: (A) Venn diagram of shared upregulated genes in GSE81761 (red) and GSE63060 (blue). (B) Venn diagram of shared downregulated genes in GSE81761 (red) and GSE63060 (blue).

The 168 genes were then used to construct a PPI network (Fig 2). After removing genes separated from the main network, it was found to have 138 nodes (each a gene) and 736 edges. The network had an average node degree of 8.87 and an average local clustering coefficient of 0.443, with an enrichment p-value of $\leq 1 \times 10^{16}$, at a true value that was below the STRING threshold for calculation.

The aforementioned plugin cytoHubba was used for topological analysis. Four different methods, namely:

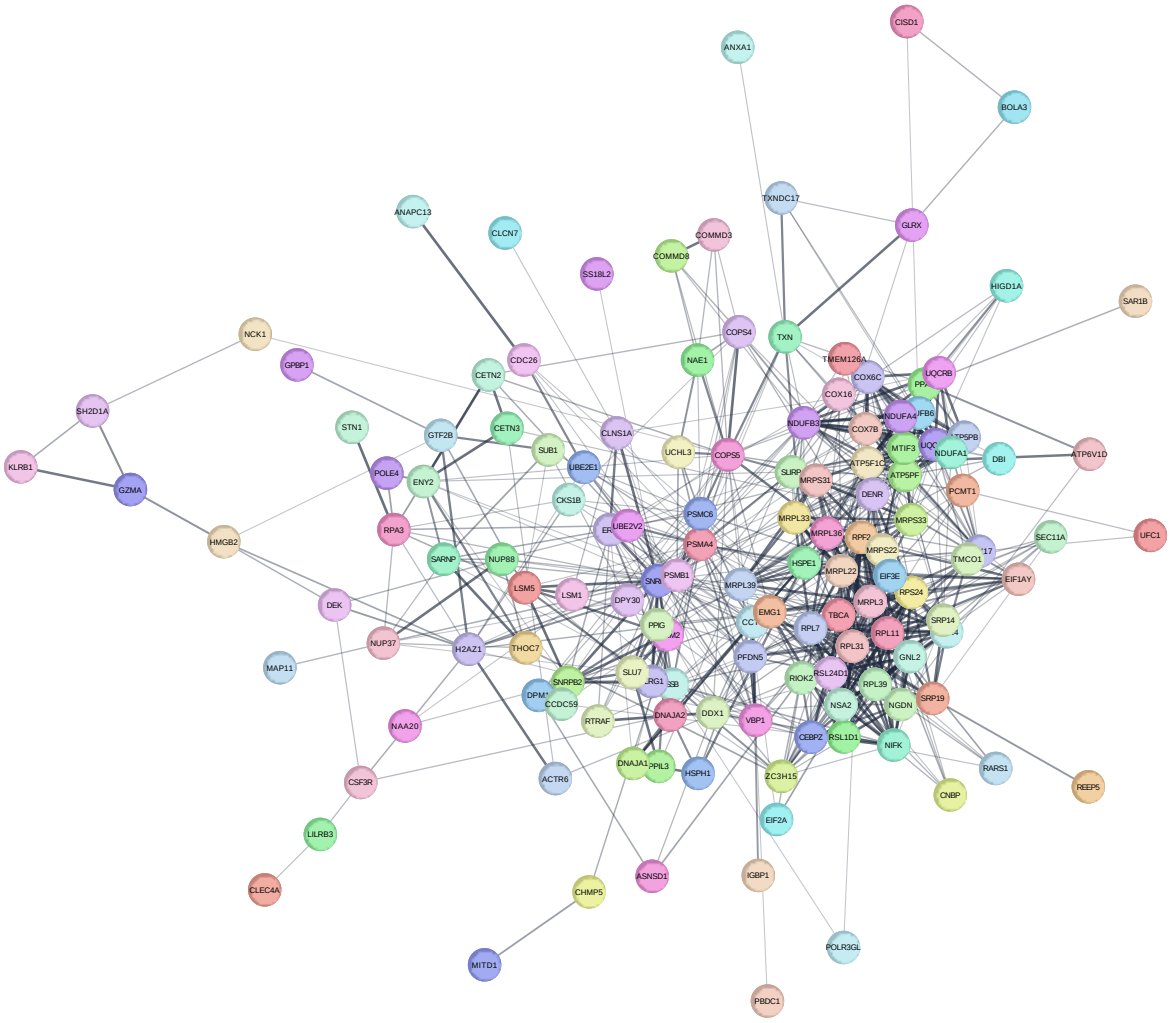

Figure 2: Protein-protein interaction network of DEGs within GSE81761 and GSE63060. Visualization generated by Cytoscape and compressed by a factor of 2 for ease of reading.

Maximal Clique Centrality (MCC), Maximum Neighborhood Component (MNC), Degree, and Closeness, were calculated and the top 10 genes in each were used in creating four unique subnetworks (Fig 3). MRPL3, MRPL22, RPL31, RPL7, and RPL11 were found to be the "hub genes" of the PPI as they met our criteria of being present within each subnetwork. The function and relevance of these genes is further analyzed in the discussion section below.

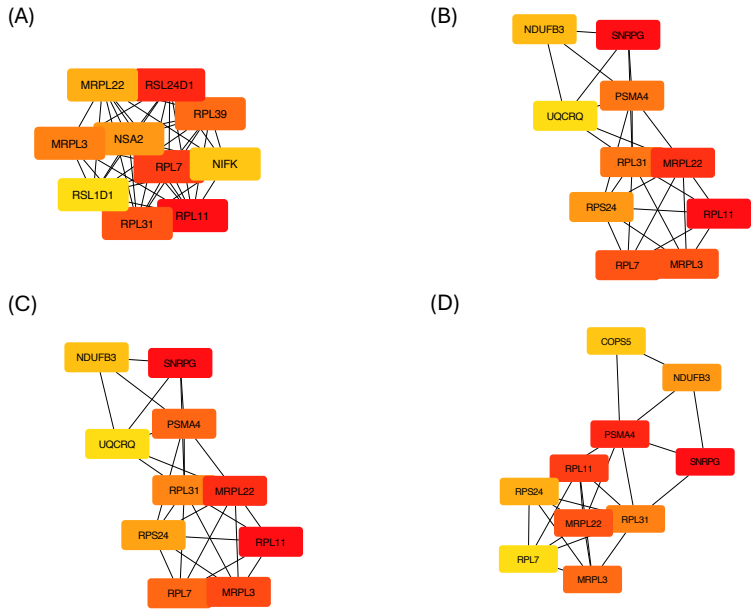

Figure 3: (A) A subnetwork of genes consisting of the top 10 genes as rated by MCC. A darker red color indicates a higher score as rated by the respective method. (B) A subnetwork of genes consisting of the top 10 genes as rated by MNC. (C) A subnetwork of genes consisting of the top 10 genes as rated by Degree. (D) A subnetwork of genes consisting of the top 10 genes as rated by Closeness.

Finally, GSEA was performed on both datasets. The 10 categories with the greatest and least normalized enrichment score (NES) for each term were identified as enriched categories and visualized (see below) via WebGestalt. Categories with an FDR of ≤ 0.05 were considered significant.

In the AD dataset, biological processes and molecular functions associated with metabolism, mitochondrial function, RNA transcription, and protein binding made up the majority of the enriched categories, (Fig. 4A, Fig. 4B). In cellular component analysis, the multiple mitochondrial categories were again strongly enriched, alongside ribosomal ones and a few others (Fig. 4C). Finally, under KEGG pathway analysis, multiple immune signaling pathways, the pathways for multiple infective diseases, cancers, and other (non-AD) neurodegenerative diseases were all enriched (Fig. 4D). Interestingly, across all four groups, ribosome-related categories consistently made up the most negatively enriched term.

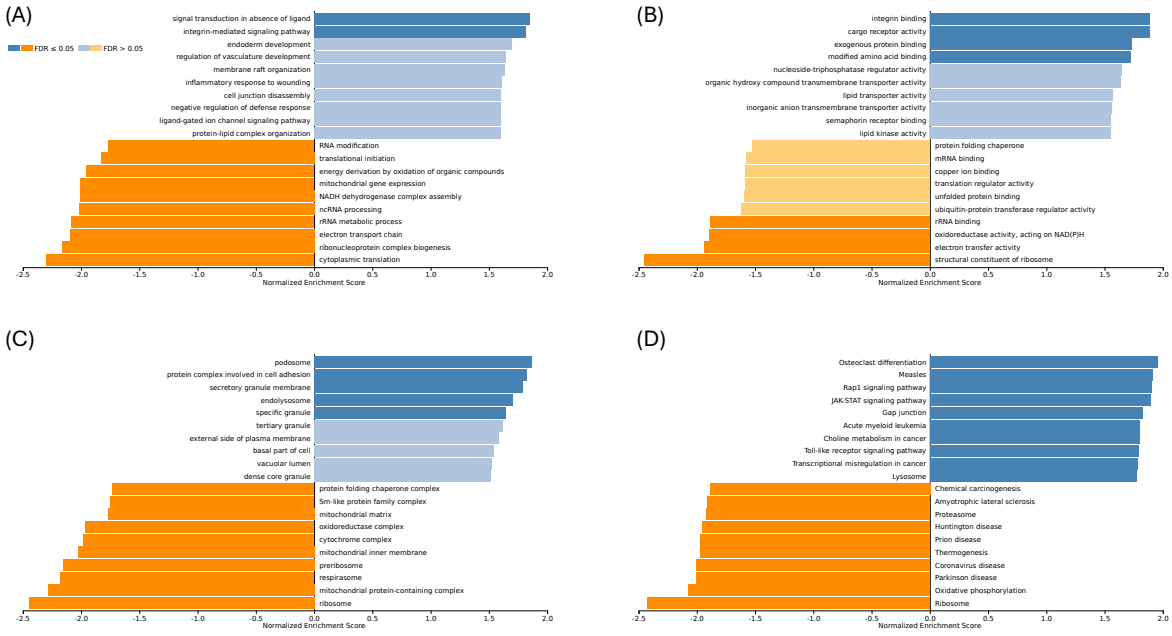

Figure 4: GSEA results for the AD dataset. In orange, the 10 categories in the dataset with the greatest NES. In blue, the 10 categories with the least NES. A darker orange or blue symbolizes statistical significance (FDR$\leq$0.05). (A) 10 greatest and 10 least BP categories as ranked by NES. (B) 10 greatest and 10 least MF categories as ranked by NES. (C) 10 greatest and 10 least CC categories as ranked by NES. (D) 10 greatest and 10 least KEGG pathways as ranked by NES.

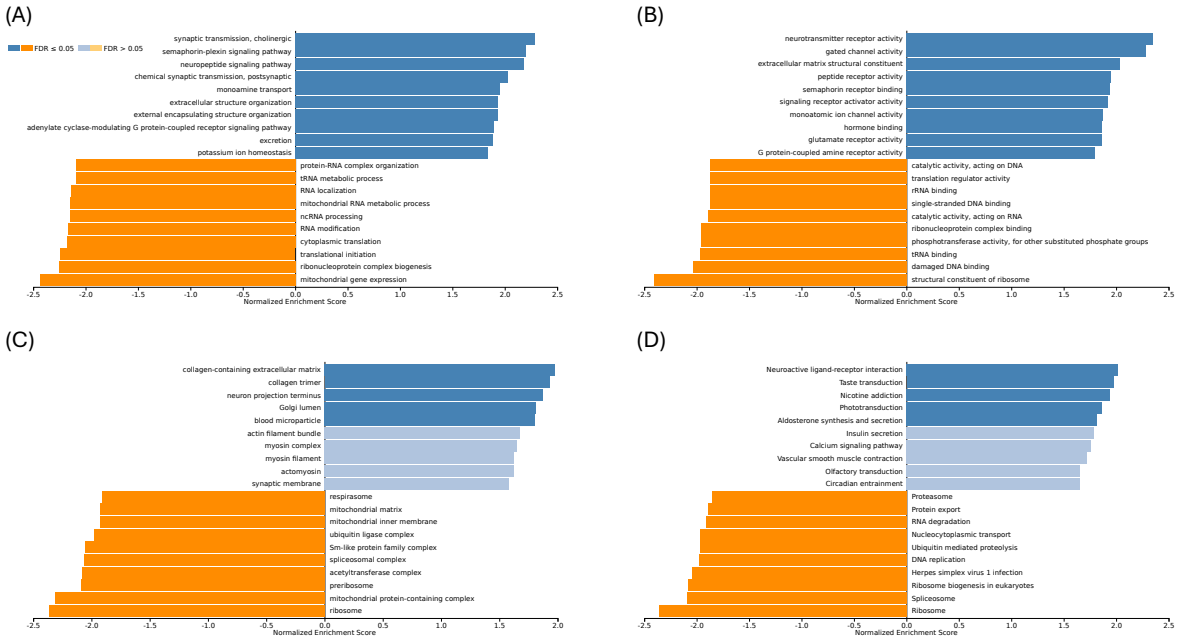

Figure 5: GSEA results for the PTSD dataset. In orange, the 10 categories dataset with the greatest NES. In blue, the 10 categories with the least NES. A darker orange or blue symbolizes statistical significance (FDR≤0.05). (A) 10 greatest and 10 least BP categories as ranked by NES. (B) 10 greatest and 10 least MF categories as ranked by NES. (C) 10 greatest and 10 least CC categories as ranked by NES. (D) 10 greatest and 10 least KEGG pathways as ranked by NES.

In the PTSD dataset, biological processes and molecular functions associated with cell signaling, neurotransmission, RNA processing, and mitochondrial function made up the majority of the categories (Fig. 5A, Fig. 5B). In cellular component analysis, categories involved with the ribosome, neurons, mitochondria, and intracellular collagen were significantly enriched (Fig 5C). In KEGG pathway analysis, steroidal, hormonal, ribosomal, and RNA-related pathways were enriched, alongside those for nicotine addiction and herpes simplex virus (Fig. 5D).

4 Discussion

As previously mentioned, there is an interesting linkage between PTSD and AD incidence. Not only does PTSD produce mild AD-like cognitive defects in many patients, but it increases the risk of developing AD in the future by a very large margin (Prieto et al., 2023). Current theories point to the role of chronic stress and immune dysregulation as potential explanations, but more in-depth analysis is needed (Justice et al., 2015). This study sought to do so by bringing more insight into the molecular relationship between the two.

Through PPI network topology analysis, we identified 5 "hub genes" that may play a role in AD-PTSD genetic interplay, as biomarkers or even possible effects. Interestingly, all 5 genes were ribosomal proteins, with 2 being members of the MRPL family and 3 being members of the RPL family. Below, we analyze existing research on the role of both gene families in the pathology of AD and PTSD.

MRPL3 and MRPL22 encode mitochondrial ribosomal proteins, which are proteins that translate mitochondrial genes to produce proteins within the mitochondria. Both of these genes were downregulated in either dataset, and downregulation of mitochondrial translation processes is known to be a sign of mitochondrial dysfunction (Pearce et al., 2013). A large body of research currently supports the theory that mitochondrial dysfunction plays a significant role in AD neurodegeneration (Bhatia et al., 2022; Ashleigh et al., 2023). Mitochondrial dysfunction has also been implicated in PTSD, though its role is likely less central (Pinna et al., 2023). Similarly, dysfunctional mitochondrial ribosomal proteins themselves have been implicated in AD (see Del Giudice et al., 2022), though we could find no literature examining their role in PTSD. Finally, in support of this, multiple mitochondrial ribosomal proteins, including MRPL22, have previously been shown to be altered in the blood of AD patients, much like what was found in this analysis (Shigemizu et al., 2020). As such, the above two mitochondrial ribosomal proteins, among others, may serve as possible biomarkers of PTSD-AD interaction.

RPL7, RPL11, and RPL31 all belong to the large family of genes that encode ribosomal proteins, proteins that perform translation of nuclear DNA into proteins. A large body of research supports the theory that ribosomal proteins are blood biomarkers in AD, as well as immune activation (Shigemizu et al., 2020; Wang et al., 2023; Feng et al., 2024; Zhang et al., 2024). RPL7, RPL11, and RPL31 levels have all been shown to be significantly altered (downregulated) in multiple studies of AD (Shigemizu et al., 2020; Garcia-Esparcia et al., 2017). In terms of PTSD, at least one study has found that ribosomal protein genes are similarly downregulated in stress response, and one other study has found evidence that RPL7 and RPL11 underly Parkinson's-PTSD interaction, but research is otherwise limited (Hemmings et al., 2022; Zhang et al., 2023). For that reason, RPL7, RPL11, and RPL31 and are also possible biomarkers of comorbid PTSD-AD, though further research, especially surrounding the role of ribosomal proteins in PTSD, is needed.

The role of ribosomal and mitochondrial processes in PTSD-AD interaction was further affirmed by our GSEA results, which showed various significantly enriched categories related to the ribosome, the mitochondria, and their respective functions. Among both PTSD and AD GSEA results, ribosome- and mitochondria-related categories make up the majority of the significantly downregulated categories. Furthermore, the single most downregulated BP, MF, CC, and KEGG terms for PTSD were found to be "mitochondrial gene expression", "structural constituent of ribosome", "ribosome", and "Ribosome", respectively. Similarly, the most downregulated BP, MF, CC, and KEGG terms for AD were "cytoplasmic translation", "structural

constituent of ribosome", "ribosome", and "Ribosome". These results clearly indicate that reduction in ribosome related processes was highly present in both datasets, which is largely consistent with our PPI findings.

With that said, our research methodology was still subject to limitations. Primarily, research in this study was solely performed in silico, and was not verified by our own physical experimentation. Furthermore, the genes within both of the datasets used in our DEG identification had a very low fold change among compared groups, which led us to identifying DEGs by |LogFC| of only $\geq$0.2. Equal LogFC cutoffs have previously been used in other studies analyzing peripheral blood in AD cases (Shigemizu et al., 2020; Garcia-Esparcia et al., 2017). We hypothesize that this is due to the fact that the data comes from patient blood, where the genetic effects of neurological disease may be less present. Finally, diagnosis for both AD and PTSD (which was used to create the datasets we used) can be complex and somewhat subjective. For example, the DSM-IV criteria for "possible or probable AD" requires some form of memory impairment, which is considered outdated. In the case of the two studies we obtained our data from, samples were grouped solely based upon doctor or patient observations, as opposed to more concrete tests. This fact may have allowed for incorrect groupings, which could have had an effect on this study's results. Because of these limitations, and the nature of the scientific process, further research on the findings of this study is needed before any definitive conclusions are drawn.

5 Conclusion

Both Alzheimer's disease and PTSD are dauntingly strange diseases with complex biological etiologies and effects. Incidences of comorbidity indicate linkage between them, yet the exact reason for this linkage is unknown. This study sought to uncover that linkage through analyzing common DEGs among datasets for both diseases, and in doing so we uncovered five key genes: MRPL3, MRPL22, RPL31, RPL7, RPL11. All of these genes happen to code for ribosomal proteins (with two encoding mitochondrial ribosomal proteins), indicating that ribosomal and mitochondrial processes may underpin PTSD-AD interaction. In support of this, our GSEA results revealed that ribosomal and mitochondrial processes were significantly dysregulated in both diseases. These results may support the hypothesis that ribosomal and mitochondrial processes are important in the linkage between PTSD and Alzheimer's, and that ribosomal proteins may be key biomarkers in comorbidity cases between the two.

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