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Characterizing Molecular Alterations in Excitatory Neurons of the Entorhinal Cortex in Alzheimer's Disease

Jiahuan He

Shanghai Pinghe High School, Shanghai, China
chloe.he1@icloud.com

Abstract. Alzheimer's disease(AD) is a widespread cognitive disease that has a range of negative impacts on both individuals and society. The entorhinal cortex(EC) often shows the histological alteration in AD in the earliest stage, including the formation of neurofibrillary tangles, amyloid plaque, and neuronal loss. It is highly related to the spatial disorientation symptom, which also occurs early in the progression of AD. The excitatory neurons on EC serve a vital function in memory formation through information transmission and show early vulnerability. Therefore, to characterize molecular alterations in excitatory neurons of the EC in AD and understand their role in disease progression, we created the custom groups of each layer by researching the most expressed gene respectively and used single-nucleus RNA sequencing to profile the EC and its layers. The study revealed significant molecular alterations in excitatory neurons of the entorhinal cortex in Alzheimer's disease, particularly in the deep layers (V/VI), as the superficial layer(layerII and layerIII) had few significantly upregulated genes. We also discovered 4 relevant KEGG pathways through GO analysis of the overlap genes between overall excitatory neurons on EC and those on layer V/VI, which are bacterial invasion of epithelial cells, ECM-receptor interaction, focal adhesion, and PI3K-Akt signaling pathway. In accordance with the previous study, they're all closely related to AD progression. These insights enhance our understanding of the molecular mechanisms underlying early neuronal changes in AD and highlight potential targets for future therapeutic intervention or treatment.

Keywords: Alzheimer’s disease, entorhinal cortex, spatial navigation, excitatory neurons, cytoarchitectonic analysis, sn-RNA sequence analysis

1. Introduction and literature review

Dementia refers to a group of cognitive disorders that harm individuals' ability to remember, think, and make rational decisions [1]. It affects more than 55 million people globally, with nearly 10 million new patients every year. More than 60% of them live in low-and middle-income countries, which can lead to social inequality. As hiring expensive carer is necessary for daily life, dementia cost economies 1.3 trillion US dollars worldwide in 2019. Apart from causing severe neurological harm to individuals, imposing heavy financial burdens and inequality issues on society, dementia is also the seventh leading cause of death among the elderly. To be more specific, Alzheimer's disease (AD) is the most common one among dementia, accounting for around 60~70% of the cases [1].

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According to the Alzheimer's Association, the official death certificates for AD is 121,499 in the year 2019, with an increase of 145% between 2000 and 2019 [2]. All data above shows the significance of preventing, slowing, or curing Alzheimer's disease.

Among various symptoms of AD from depression(9% in the early stage, 98.5% in the late stage) to memory loss(80% in the early stage, 98.5% in the late stage) [3], deficits in spatial navigation are one of the early signs in AD [4]. It imposes significant danger on AD patients and even the whole society. Individuals with AD, of which mostly are aged over 65, are likely to get lost in both unfamiliar and familiar environments [5] and thus encounter mortal peril. Moreover, drivers with AD can greatly increase the risk of severe car accidents [6] and threaten societal safety.

The entorhinal cortex(EC) is a brain structure that is closely related to memory formation, consolidation, and optimization, especially spatial navigation [7]. It is located in the medial temporal lobe [8]. Neurons in the entorhinal cortex send information between the neocortex and hippocampal formation(consists of the major hippocampus subfields CA1-CA3, the dentate gyrus, the subicular complex, and the entorhinal cortex [9]) bi-directionally [10,11]. Research has shown that EC manifests the histological alterations in AD in very early stages, including the formation of neurofibrillary tangles and amyloid plaque [12]. The unique function for spatial orientation is achieved by containing a large number of grid cells, which help build mental maps by firing consistently as an animal moves through an open area, enabling it to understand its position in space by storing and combining information about location, distance, and direction [13]. This research focuses on the excitatory neurons on EC as excitatory neurons are essential for sending information in the memory relevant process and are highly connected with grid cells functionally [14]. As it is defined as a type of neuron that promotes the activation of other neurons by increasing their likelihood of firing an action potential, excitatory neurons play an important role in the brain in promoting the information creation and transmission. Structurally, the entorhinal cortex is a heterogeneous structure [15], containing different proportions of varied types of cells at different places. Therefore, it is vital to have cytoarchitectonic considerations and analyze layers separately.

There has been massive research on the correlation between dementia and neurons in the entorhinal cortex in monkey or mouse models [11,15]. However, it is unknown how excitatory neurons on the human entorhinal cortex change in Alzheimer's disease at the molecular level. Furthermore, there are no clear research results about the comparison of how excitatory neurons in each layer of the human entorhinal cortex respond to AD. Therefore, this research will mainly focus on the molecular alteration of excitatory neurons in the human entorhinal cortex in Alzheimer's disease and how each layer in the EC responds differently to Alzheimer’s disease.

2. Methodology

2.1. Study samples and dataset information

Samples are extracted from the 10Xgene dataset of single-nuclei RNA sequencing of caudal entorhinal cortex from individuals spanning the neuropathological progression of AD, published by Leng et al. on Nature Neuroscience [15](https://cellxgene.cziscience.com/collections/180bff9c-c8a5-4539-b13b-ddbc00d643e6). Human postmortem brain tissues used in this study were obtained from two sources: the Neurodegenerative Disease Brain Bank (NDBB) at the University of California, San Francisco (UCSF), and the Brazilian BioBank for Aging Studies (BBAS) affiliated with the University of São Paulo [16]. All samples were de-identified prior to receipt to protect donor confidentiality. The brain samples utilized in this research exhibited extensive Alzheimer's disease (AD) pathology. They were specifically chosen to exclude any non-AD pathologies, such as

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Lewy body disease, TDP-43 proteinopathies, primary tauopathies, and cerebrovascular alterations. The researchers utilized standardized protocols and obeyed internationally accepted criteria for neurodegenerative diseases [17,18]. In total, there are 31 cases with 10 cases used for snRNA-seq and 21 Cases used for immunofluorescence validation. The patient samples for snRNA-seq are aged from 50 to 87 years old, with 3 control samples that show no AD pathology. The samples were processed by isolating the nuclei [18]and performing droplet-based single-nucleus RNA-sequencing (snRNA-seq) by the Chromium Single Cell 3′ Reagent Kits v2 from 10X Genomics [15].

2.2. Data analysis

We used Loupe Browser 8.0 to perform differential gene expression analysis between AD patients and the normal and to define entorhinal cortex layers based on gene markers.

There are six layers of the entorhinal cortex, accounting from layer I to layerVI. To investigate the molecular alteration of excitatory neurons on each layer, we chose layerII, layerIII, and layerV/VI to create the custom groups within the dataset through Loupe Browser 8.0. The layer I and layer IV are not included because they both have few neurons [19,20]. The layerV and layerVI were analyzed together since they don't have a clear division or boundary by cytoarchitectonic criteria [21]. Through research and comparison, the genes that express most significantly in each layer respectively were found: CNTN5 for layerII, TRPS1 for layerIII, and FRMPD4 for layerV/VI [21].

The data was filtered by the requirement of a p-value smaller than or equal to 0.01 to ensure statistical significance. The value for log2 fold change is required to be larger than 2. We created volcano plots to show the number of significantly upregulated genes through bioinformatics after converting gene ensemble IDs to gene symbols (using BioTool.fr), (https://www.bioinformatics.com.cn/plot_basic_3_color_volcano_plot_086)

(https://www.biotools.fr/human/ensembl_symbol_converter) and went through GO analysis to further analyze the significant genes and explore how they affect humans macroscopically by Shiny GO 0.80 (http://bioinformatics.sdstate.edu/go/) .

3. Result

3.1. Analysis of all excitatory neurons on the EC

Differentially expressed genes in the entorhinal cortex are compared between Alzheimer's disease and the normal. We found 1104 significantly upregulated genes in AD with $p < 0.01$. The top 10 upregulated genes are TRAPPC12-AS1, LINC00903, PDC, OXGR1, HEPN1, TGFBI, CDCA7, AP001464.1, AL391987.3, LSAMP-AS1(Fig1). The genes with AC starting and numbers ending, for example, AC112196.1, are not counted as the top 10 upregulated genes as they don't impact the further biological process or KEGG process. There are no downregulated genes from the given dataset.

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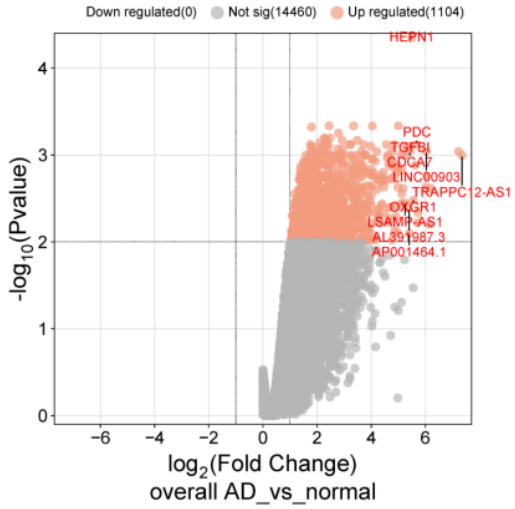

Figure 1. Differential gene expression in excitatory neurons of the human entorhinal cortex, comparing Alzheimer's disease with normal samples; red dots represent significantly upregulated genes (adjusted $p \leq 0.01$, $\log_2 FC \geq 2$), gray dots represent non-significant genes, and the top ten regulated genes are labeled with their symbols

3.2. Analysis for each layer

We used CNTN5 for labeling layerII, TRPS1 for layerIII, FRMPD4 for layerV/VI [23] and got 1288, 767, 7136 number of cells for each layer respectively. We then run differentially expression between the Alzheimer's disease and the normal for each layer. With the filtering of p-value smaller than or equal to 0.01, we found that there are few genes in layerII(0 genes) and layer III(1 genes) that show significant upregulated or downregulated performance. Therefore, the layer analysis mainly focuses on layer V/VI. The top 10 up-regulated genes for layer V/VI are TRAPPC12-AS1, LINC00903, TGFBI, HBB, PDC, LSAMP-AS1, HEPN1, ARHGAP26-AS1, AP001464.1, AP001439.1(Fig2.). The genes with AC starting and numbers ending, for example, AC112196.1 were not counted as the top 10 upregulated genes as they don't impact the further biological process or KEGG process. There are no down-regulated genes for layer V/VI from the given dataset.

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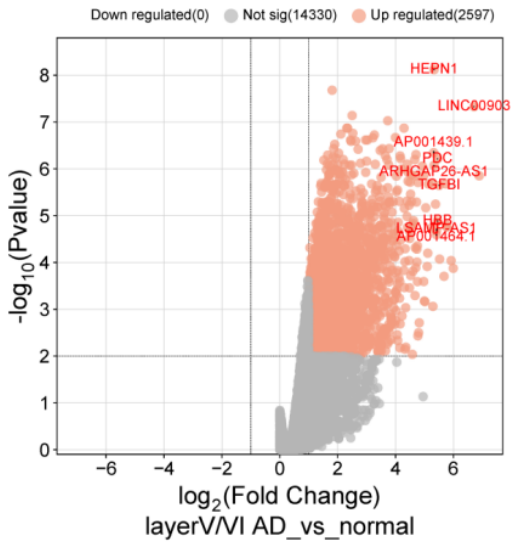

Figure 2. Differential gene expression in excitatory neurons of layers V and VI in the human entorhinal cortex, comparing Alzheimer's disease with normal samples; red dots represent significantly upregulated genes (adjusted $p \leq 0.01$, $\log_2 FC \geq 2$), gray dots represent non-significant genes, and the top ten regulated genes are labeled with their symbols

3.3. Analysis of the overlap genes

There is a great overlap with the differentially expressed genes in layer V/VI and the overall entorhinal cortex, with 1089 genes shown in fig3. We concluded that layerV/VI contributes to most of the overall entorhinal cortex gene change in AD. We thus used 1089 common differential expressed genes for Gene Ontology analysis. We found that the AD upregulated genes are involved in bacterial invasion of epithelial cells, ECM-receptor interaction, focal adhesion, and PI3K-Akt signaling pathway.

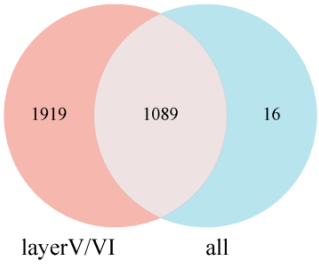

Figure 3. Venn diagram of differentially upregulated genes in excitatory neurons comparing layer V/VI with the overall entorhinal cortex in Alzheimer's disease; the dark pink area shows genes unique to layer V/VI, the blue area shows genes unique to the overall cortex, and the light pink area shows the overlap (adjusted $p \leq 0.01$, $\log_2 FC \geq 2$)

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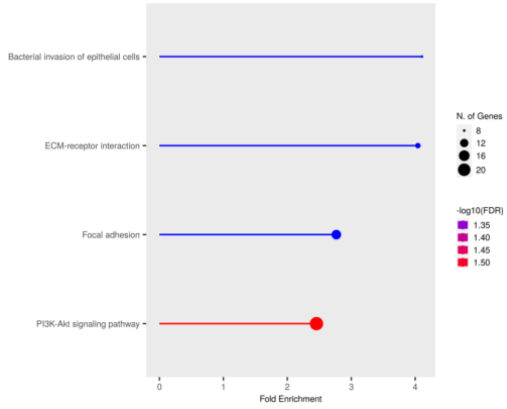

Figure 4. Bar plot of KEGG pathway enrichment analysis for the overlapping genes: the x-axis shows fold enrichment, and the size of the circle atop each bar represents the number of genes enriched in the corresponding pathway

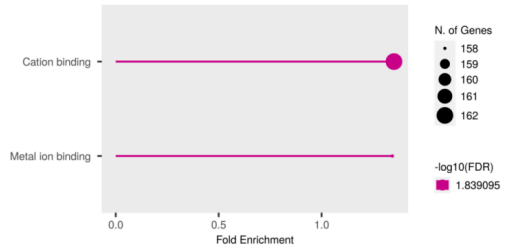

Figure 5. Gene Ontology (GO) enrichment analysis for cellular component terms of the overlapping genes presented as a bubble chart, where the x-axis represents fold enrichment and circle size corresponds to the number of genes enriched per term

4. Discussion

4.1. The KEGG pathways and their relevance to AD pathology

The first pathway, bacterial invasion of epithelial cells, shown in the Fig4. is relevant to body inflammation reaction and that supports neuroinflammation theory of Alzheimer's disease [22]. Inspecting the individual gene found that CTNNA1 [23], DOCK1 [24], FN1 [25], CTNNA3 [26], ITGA5 [27] ITGB1 [28], RHOG [29], CAV3 [30] are associated with Alzheimer's disease.

The rest of the pathways all have a close relationship with the AD pathology. ECM, also known as extracellular matrix, is a complex network of structural macromolecules secreted by cells [31,32]. It plays an essential role in maintaining cell morphology and structure [33], and it is also highly relevant to nerve cells' survival, differentiation, development, and migration [32]. ECM-receptor interactions lead to the progression of AD through harming cell signaling pathways, which may exacerbate neuronal damage and contribute to the accumulation of pathological proteins like amyloid-beta, and fostering neuroinflammation [34]. These interactions could result in the alteration of the intercellular environment in the brain and further neuronal damage as observed in common AD pathology.

Focal adhesion (FA) proteins form intracellular complexes that facilitate integrin-mediated communication between the extracellular matrix and the actin cytoskeleton, which are crucial for regulating various physiological processes in cells, including the cell cycle [35]. Focal adhesions

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involve integrin receptors, which are proteins that help cells adhere to their surroundings and transmit signals [36]. Aβ protein, which can lead to one of AD's most common trait amyloid plaque, binds to various integrins, including α5/β1, α2/β1, and αv/β1 [37], impacting neuronal health in different ways. While some integrin interactions with Aβ have protective effects, such as preventing Aβ aggregation or reducing neurotoxicity [38,39], others contribute to neurotoxicity. For example, Aβ binding to integrins can activate downstream signaling pathways, like focal adhesion kinase (FAK) and Paxillin [40], leading to harmful effects on neurons. Apart from that, integrins are also involved in synaptic plasticity and neuronal excitability. Disruption of integrin functions can lead to defective long-term potentiation (LTP) [41], a process crucial for learning and memory. The interaction between Aβ and integrins may disrupt normal signaling, leading to neurotoxicity and contributing to the progression of Alzheimer's disease [36,37,40,42].

PI3K-AKT, full name as the phosphatidylinositol 3-kinase/Akt signaling axis, is seen as the most essential and challenging pathway in the progression of Alzheimer's disease. First of all, by eliminating the suppressive effect of this pathway on GSK-3β, accumulated Aβ prevents the propagation of the PI3K/Akt signaling axis and increases the activity of this protein kinase(GSK-3β)in the neurons. Apart from that, Aβ oligomers could also directly stimulate GSK-3β in neurons and NSCs, in which the activated GSK-3β will eventually improve the apoptotic signals and diminish the survival capacity of the cells [43]. It will also indirectly improve hyper-phosphorylation of Tau, one of the most common traits of AD [44]. Furthermore, the PI3K-AKT pathway is also related to AD in altered insulin signaling, autophagy, oxidative stress, and neuroinflammation [45].

4.2. Layer analysis

From the given dataset, we found that layer V/VI showed more significant genes compared to layer II and layer III. The EC inputs to the hippocampus arise primarily from the superficial layers (II and III), while the deep layers (layers V and VI) receive projections from the hippocampal and transmit signals to various downstream targets, including the neocortex [46,47]. LayerII and layerIII have been receiving massive attention with their specific changes in the Alzheimer's disease as they seem as the main entryways for much of the cortical information to be processed by the hippocampal formation [12].

The great number of significantly upregulated genes in the deep layers of the entorhinal cortex and its large overlap with the overall excitatory neurons showed its potential importance in disease development and neural degeneration, especially in the occurrence of spatial orientation. It aligns with the evidence that layerVI contains a relatively high proportion of excitatory neurons, which respond to stimulation of the hippocampal output circuit [47].

The significant genes are also relevant to 4 main pathways, which are proven to be essential in AD progression by massive research papers. All shown above suggests that the deep layers of the entorhinal cortex significantly contribute to the pathological process and should also be considered in terms of developing treatment methods.

4.3. Limitations

There were several limitations in this study. Firstly, the treatment history of patient samples was not annotated, and therefore, was not considered in the analysis. However, advanced treatments such as Lecanemab — an antibody medication that decreases β-amyloid protein build-up in the brain, may influence patients' prognosis significantly and thus treatment history should be taken into consideration in future studies. Apart from that, there was a limited sample size from the dataset we

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used. With only 10 patients' snRNA-seq data, it limited the universality of our findings. Therefore, a larger study population should be employed to achieve more thorough and reliable conclusions. Thirdly, there was no analysis for different Braak stages of the disease, which is an important factor in disease progression and may show us more precise results. Last but not the least, it's important to note that the 10 patient samples from used dataset are all male. The gender bias may limit the applicability of the results to male Alzheimer's Disease patients specifically. To get more thorough and comprehensive results, future research should aim to include more gender-balanced samples.

5. Conclusion

In conclusion, the study showed the significant upregulated activity of excitatory neurons on the entorhinal cortex, especially the deep layers, revealing the potential importance of the deep layers of the entorhinal cortex to Alzheimer's disease, especially for spatial navigation ability, and found 4 relevant KEGG pathways through analysis of single-nuclei RNA sequencing with potential clinical utility.

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